Evidence tables- Patient information

Study	Pier 2008 Country: Australia Qualitative study- Interviews
Aim	To identify health and mental health information needs of people with coronary heart disease (CHD), with and without co-morbid depression.
Population	N=14. Age range: 50-64 years : 4 patients 65-79 years: 8 patients ≥80 years: 2 patients Highest education level Primary school: 2 patients High school: 6 patients Tertiary: 6 patients Major depressive episode: Current: 5 patients Prior history: 3 patients None: 6 patients Diabetes: Type 1: 1 patient Type 2: 1 patient None: 12 patients Selection: Two GP's searched their patient databases to identify potentially eligible patients who met one or more of the study's criteria for CHD: MI, CABG, angioplasty or angina (confirmed through testing). The GP's posted letters to the identified participants informing them of the study and asking them to contact the research officer if they wished to participate. Of theses patients, 20 consented to participate. Four later withdrew (reasons not provided), leaving a total of 16 participants (14 men and 2 women). However, as prominent themes emerged from interviews with the first 14 participants, the remaining two men were advised that their participation was no longer required.
Method of gaining views	1) MINI (The Mini international Neuropsychiatric Interview) – A brief structured clinical interview to assess 16 Axis 1 disorders from the Diagnostic and statistical manual of mental disorders and the International classification of diseases and one personality disorder. It included questions to differentiate disorders of organic origin or those due to alcohol or drug use. 2) Interviews –deigned to obtain qualitative data. It was conducted in a private room and took about 40 mins to complete. The interviews were semi-structured, in that the interviewers were guided by a series of open-ended questions supplemented by spontaneous probes.

	Information was requested about patient's current access to health information and the type of information they would find useful to help them manage their heart health, including their physiological and psychological well being. The interviewers encouraged participants to talk freely about the subject matter but redirected participants who deviated from the purpose of the interviews. Participants completed the clinical diagnostic review (MINI) by telephone after giving informed consent. On a separate day each patient met with two investigators to complete individual semi-structured interviews. All semi-structured interviews were performed in a standardised manner, audio taped, transcribed verbatim after removal of identifying information.
Data analysis	Analysis conducted by an independent investigator using the thematic approach. Subsequent examination of the analysis by two other authors verified occurrence of the key themes identified.
Findings	Eight participants had a current diagnosis or prior history of major depression as assessed by the MINI. All participants endorsed the view that further provision of health information would be useful in helping them manage their CHD or psychological well being. Four common themes of information topics emerged from the data categorised as: psychosocial; physical activity; medical; and information for family. **Psychosocial:** Six participants indicated that information on depression would be useful for themselves or other with CHD, particularly information about how to recognise and manage depressive symptoms and about the relationship between depressive symptoms and physical health. Patients also suggested provision of information about particular strategies for managing depression, such as positive self-statements and a log book to record activities to stay motivated. **Social isolation:** Five patients expressed the view that social connectedness is important, either in helping them to manage depressive symptoms or to gain support and understanding about their medical condition from other people with CHD. Several patients in this group indicated the need for information on how to establish social networks and access social and support groups. **Anger:** 4 patients wanted more information on anger and anger management. Patients suggested that information about how to identify precipitating symptoms of anger and anger management would be useful. **Physical activity:** 4 participants reported a need for information on physical activity. Patients reported a need for information on how to safely reintroduce physical activity and exercise options after a cardiac event. **Medical information:** 9 patients reported a need for medical information. Medical information grouped in to 2 areas: Symptoms and prognosis and Surgery. Symptoms and prognosis: Patients wanted information about symptoms that might occur, rather than only those that will occur; disease progression; prognosis; prevention of further cardiac events; and survival rates. Surgery: 4 patients reported a need for more information before and after surgical intervention. They wanted procedural information to inform them of exactly what would happen during the operation and what to expect when waking from anesthesia. **Information for family:** 9 patients reported that information for family members and spouses would be useful. Patients wanted information pertaining to the psychological aspects of the illness, such a s how the patient might react emotionally to an adverse cardiac event or medical procedure.
Comments	Baseline data reported. Methods well described.

Study	Weetch 2003. Country: UK Qualitative study: Questionnaire
Aim	The study intended to determine the level of satisfaction of patients with the amount and quality of information that they receive. It was intended that the results would enable the nursing staff to review practice in relation to the provision of the appropriate level, type and quality of information and education given to patients with angina.
Population	N=16. The population to be studied were patients suffering from angina who had been hospitalised in the coronary care ward. A convenience sample was taken of those admitted during the time allocated to carry out the study. All patients discharged from the ward with a diagnosis of angina during the study were asked to participate.. The average age of the respondents was 59.7 years, with a age range of 40 to 78. Some 60% of the respondents were male and 40% were female.
Method of gaining views	The patients were given a letter of explanation, together with a questionnaire and a stamped return envelope. No further details reported.
Data analysis	Results analysed quantitatively and qualitative themes identified. No further details reported
Findings	30 patients were identified as having been discharged with a diagnosis of angina during a 3 month period and were issued with a questionnaire of which 16 were returned (53.3%). 7 of theses correspondents had previously been hospitalised with an MI; 8 had angina but no previous MI. One respondent denied all knowledge of having angina and returned a blank questionnaire. The results showed a very high level of satisfaction with the overall standard of care. The results showed a wide variation of responses with satisfaction slightly above mid-point. Specifically, 73% felt that they needed more information about the effect of angina on their daily activities. They wanted to know more about the causes of angina, its treatment, their medication, and in particular the effect it will have on their daily activities. Most participants agreed that nurses gave them the opportunity to ask questions; however, many particularly those who had not had an MI, wanted more written and verbal information. Another significant finding was the lack of satisfaction with the information that patients had received from health care professionals working in primary care settings.
Comments	Little baseline data given. The role of the researcher was not described. Almost no methodology described so results could be unreliable. Results not well reported.

Study	Karlik 1990. Country USA Cross-sectional- Questionnaire
Aim	To compare the learning needs of patients as rated both by patients diagnosed with coronary artery disease who experienced angina pectoris and by nurses who care for them.
Population	N=15 in- patients (11 men and 4 were women) .n=15 out-patients (9 were men and 6 women) with angina pectoris and n=15 nurses The age of the in-patients ranged from 26-70 years. The age of the out-patients ranged from 41-70 years. The educational level of the subjects in both samples was almost identical. Of the inpatients, 8 had a high school diploma while the remaining 7 obtained at least one college degree. Of the post-discharge patients, 9 had a high school diploma while the remaining 6 had obtained at least one college degree. Selection of patients: To identify patients experiencing angina, in-patients admitted to an acute-care hospital for a cardiac catheterisation were initially accessed through the admitting office. When the patient was admitted to the hospital, one of the investigators reviewed the chart to determine the patient's eligibility for the study. Criteria for a subject selection consisted of patients who had a primary diagnosis of CAD and who had experienced angina; did not have a history of an MI, open heart surgery, or coronary angioplasty. Patients were approached for voluntary participation either before or after a cardiac catheterisation. To obtain subjects for the post-discharge group, the medical records of all patients who underwent a cardiac catheterisation in the hospital within 3 to 6 months of the study were reviewed. The same criteria used for in-patient inclusion was used with addition that the patients had to be medically, rather than surgically, managed for their angina post-catheterisation.
Method of gaining views	Instruments used were: 1. The Cardiac Patient Learning Need Inventory (CPLNI) a 43 item instrument originally designed to measure learning needs of post MI patients. Patients and nurses respond to a 5 point scale ranging from 'not important' (1) through 'very important'. The items on the CPLNI were grouped in to 8 categories: 1) introduction to CCU. 2) Cardiovascular anatomy and physiology. 3) psychologic concerns (feelings, emotions and stress control). 4) Risk factors. 5) Information about medications. 6) Dietary information. 7) Physical activity information. 8) Miscellaneous information. Each category contained 4 to 7 items. 2. The Educator Preference Tool was developed from the same list of items as those on the CPLNI. This instrument was designed primarily to explore the cardiac patients perceptions of nurses as teachers Patients were instructed to indicate who (nurse, physician, pharmacist, dietician or other) they believed would be able to teach them cardiac information. 3. The Health Information Scale (HIS) was designed to measure cardiac patient's intentions to follow a medical regimen in different situations, including home, work, sports, recreational and social settings. The 5 actions (diet, activity, stress control, smoking cessation and medication) were behaviours identified in the literature as usually included in the medical regimen of patients with ischemic heart disease. The HIS administered in this study was a 20 item, 5 point Likert-type scale ranging from 'unlikely' (1) through 'likely' (5). 4. The Health Behaviour Scale (HBS) is a 20 item, 5 point Likert-type scale that measures cardiac patient's actual adherence to medical regimen. In the present study HBS was administered to the post-discharge patients with angina.

Data analysis	For each of the 8 CPLNI categories means were generated for individuals and then for each patients group. For each of the 8 information categories the percentage of in- patients and post discharge patients indicating a preference in the Educator Preference Tool was generated. For each of the 5 subscales on the HIS and HBS, means were generated for individuals and for patients groups.
Findings	**CPLNI** With the exception of the mean obtained for post discharge patients on the psychologic category, patients considered all the informational categories important. When the categories were ranked by inpatient rankings, the categories of risk factors and medications emerged as the most important to learn and the categories of introduction to the hospital unit and diet emerged as the least important to learn. The category of risk factors emerged as the most important to learn and the category of medications emerged as the second most important to learn when ranked by post discharge patients. Information category: Inpatients ; Post-discharge patients Introduction to hospital unit: 4.21 ; 4.34 Anatomy and Physiology: 4.32 ; 4.31 Psychologic: 4.28 ; 3.97 Risk factors: 4.42; 4.65 Medications: 4.42; 4.65 Diet: 4.21; 4.34 Activity: 4.36; 4.25 Miscellaneous: 4.22; 4.20 **Educator Preference Tool** A greater percentage of patients expressed a preference for physicians alone, rather than for nurses alone, to teach them all 8 informational categories. Nurses received the highest percentage by patients in the category of introduction to the hospital unit and the lowest percentage in the categories of risk factors and activity. No patients believed the nurse alone could teach them dietary information. Physicians received the highest percentage by patients in the category of activity and the lowest percentage in the category of diet. Combining the percentages of nurses alone and nurses with others, patients still preferred physicians to teach them all informational categories except introduction to hospital unit. Percentage of patients expressing 'Who can teach' information categories Information category: Nurses alone (%); Nurses with others (%); Physicians alone (%); others (%) Introduction to hospital unit: 34% ; 24%; 41%; 1% Anatomy and Physiology: 5%; 20%; 73%; 2% Psychologic: 12%; 32%; 50%; 6% Risk factors: 1%; 15%; 79%; 5% Medications: 3%; 28% 55%; 14% Diet: 0%; 20%; 23%; 57% Activity: 1%; 12%; 87%; 0%

	Miscellaneous: 13%; 24%; 61%; 2% **HIS and HBS** The results of these 2 scales are not relevant to the question hence not reported.
Comments	Validated instruments used. Role of researcher not well described. Mean values reported but not Standard deviation. The study could have used qualitative approach. This is a cross-sectional study design.

Study	McGillion 2004. Country: Canada Qualitative study- Focus groups
Aim	The aim of the study was to determine the self-management learning needs of chronic stable angina patients living at home in order to inform the content of a future chronic stable angina self-management programme.
Population	N=8 (chronic stable angina patients) The study targeted both chronic stable angina patients and clinicians. Eligible chronic stable angina patients: a) had stable angina symptoms for at least 6 months, b) were experiencing either class I, II, or III angina, c) had a medical diagnosis of CAD confirmed either by imaging or angiography. The patients were recruited from two outpatient clinics and the cardiovascular rehabilitation centre at the study site. The age of the eight patients ranged from 44 to 70 years, and one had post-secondary education. These two women and 6 men lived with angina from 6 months to 10 years. Three participants worked full time, one part-time, 2 were retired and 2 were on disability pay due to their chronic stable angina symptoms. Eligible clinicians were, a) registered nurses, nurse practitioners, or physicians practicing in the field of cardiology and b)at a university-affiliated teaching hospital.
Method of gaining views	Four groups were held in the same classroom setting at a major university-affiliated, teaching hospital and included two for clinicians (n=6,n=5) and two for chronic stable angina patients (n=5,n=3) [since views of clinicians are not relevant to the question, the results for the clinicians will not be reported in the review]. Each session lasted approximately lasted approximately 1 ½ hours and all sessions consisted of semi-structured group interviews moderated by the Principal investigator. A set of 3 questions was developed for both the angina patients groups and the clinician groups to generate thinking and discussion about the day to day problems that angina patients face in relation to their symptoms and their corresponding self-management learning needs. The Principal investigator acted as the moderator, and an independent assistant moderator took field notes. At the end of each group, a summary of the results was read back to the participants, enabling them to verify key issues.
Data analysis	All focus groups were audio-taped and then transcribed in full. Braden's Self-Help model was the conceptual framework used to guide the transcript-based analysis. Analysis was ongoing once the first focus group was conducted. Axial coding and constant comparison were used to derive key themes in the data to be subsumed under the antecedents of Braden's and Kruger's model. The frequency, extensiveness, intensity, and specificity of participant's comments were of central importance for the two investigators who reduced the data in to these themes and then selected illustrative quotes. The results were thematized under the antecedents of Braden's Self-Help Model : Perceived Severity of illness Uncertainty Limitation
Findings	Note: As we are looking at information needs of patients in this review, we will not be reporting the information requirements as stated by the

	clinicians in the study. Results according to the antecedent constructs of Braden's Self-Help Model: **Perceived Severity of Illness:** The patients identified that education on interpreting angina symptoms was a high priority. The patients felt that they have great difficulty knowing when they are experiencing angina versus some other type of pain symptom. The following are examples of typical patient comments: *''My main issue is trying to determine when it is angina that I'm having versus some musculoskeletal kind of pain''.* *''The one thing that's going for the rest of your life is angina and learning to identify that you're having it''.* *''I'm constantly trying to figure out if its angina I'm having or not''.* Patients also expressed experiencing difficulty in deciding when they should speak to a health professional about their condition. *''I guess in my life, I've been trained to tough it out and not be a baby-at times I'm also unsure if there is a problem, so I go on ignoring it, and I just hate being a bother to busy people''.* Patients also had difficulty deciding to seek help, even when they were certain they were having a crisis that was beyond their capacity to manage at home. The decision to go to the ER was often put on hold because patients doubted their own judgement, and the ER was seen as a burden. A typical remark was: *''When I'm in trouble, going to the ER just seems like such an added burden, I hate it, they put you through so much-all those tests and it's so chaotic-and I know I have trouble, but I'm never entirely certain that I really have to go''* Another major contribution to indecision about emergency assistance was found to be confusion about how ambulance services and tertiary care centres are organised. A common question raised was why patients are often taken to a hospital where they had not been cared for previously. *'' My major question is when I have a major emergency and I call, or my wife calls, for an ambulance, why I am not brought to (name of the hospital), the paramedics just say that 'we will get turned away''-but that's where all my chart and information is. This makes no sense, so I want to put off going, even when I really have to''.* **Uncertainty:** The majority of patients stated they were taking a minimum of four medications and that they did not know the purpose of most of these medications. Patients were also overwhelmed and confused about medication schedules, especially when they were taking several and had to take them at various times during the day: *''I have so many pills and I don't know what I'm taking the pills for, I always get confused and I'm not sure if I'm taking them right.''* *''I'm on a ton of medication, it's so hard to get it right, I need help with this''.* Both patients felt that they were confused about exercise, specifically about acceptable duration and frequency: *''I really need help with not knowing if I push myself too hard when I exercise. Sometimes I think it's better if I just sit on the couch and not do anything at all. I know I have a heart condition, but at the same time, I don't know what I should be doing and what I shouldn't. I have a gut sense of what I should be doing, but at the same time I don't know if I'm doing it right. I don't find that there's anybody to watch over me''.*

	Limitation: Accepting both the physical and social limitations imposed by angina was repeatedly identified as a difficult issue for angina patients. Data suggested that patients dealing with angina related limitations needed a forum in which to discuss the difficulties of identifying safe activity limits: *''It's good to talk about it. It's a question of being realistic with yourself as you can be in terms of what you are facing, what the limitations are, then you begin to adjust to that. Getting it out has helped me''.* Patients expressed a need for help in dealing with their anxiety. Most reported great anxiety about having to constantly anticipate subsequent angina episodes; this was constantly tied with the fear of MI and death: *''Sometimes I go in to a level of anxiety where I become concerned that maybe it's going to progress to another attack. So sometimes I think that level of anxiety may in itself bring on another attack, and I kind of think about what chemically is happening inside my body because of that second level of anxiety and what it may be doing''.* Patients felt very stressed about having to manage angina in their lives, and felt that they were ill-equipped to deal with the day-to-day stressed that sometimes exacerbated their angina: *''I never know what to eat, so that becomes a concern, because I stress myself off every time I look at a cookie''.* Several suggestions on how to deal with emotional responses and triggers were generated; the most popular were teaching guided imagery and progressive muscle relaxation as means to alleviate anxiety, stress and general tension. Additional findings: The majority of patients expressed a need for a programme wherein they could learn to develop their chronic stable angina self-management skills. A one patients said: *''From my perspective, because angina is the one thing that says with you, that you have to manage forever, I think reinforcement of how to manage everything to do with that is important, and that's why I would go in to a programme like this''.*
Comments	Baseline data of patients reported. Methodology well described. Researcher role well described.

Methodology checklist: qualitative studies[1]

Study identification *Include author, title, reference, year of publication*	**Pier C, Shandley KA, Fisher JL et al. Identifying the health and mental health information needs of people with coronary heart disease, with and without depression. *Med J Aust.* 2008; 188(12 Suppl):S142-S144.**
Guidance topic: Stable Angina	**Key research question/aim:** What are the information needs of patients with stable angina regarding their condition and its management?
Checklist completed by: Sharangini	

Section 1: theoretical approach		
1.1 Is a qualitative approach appropriate? *For example:* • Does the research question seek to understand processes or structures, or illuminate subjective experiences or meanings? • Could a quantitative approach better have addressed the research question?	☒ Appropriate ☐ Inappropriate ☐ Not sure	Comments: To identify health and mental health information needs of people with coronary heart disease would need a qualitative approach.
1.2 Is the study clear in what it seeks to do? *For example:* • Is the purpose of the study discussed – aims/objectives/research question(s)? • Is there adequate/appropriate reference to the literature? • Are underpinning values/assumptions/theory discussed?	☒ Clear ☐ Unclear ☐ Mixed	Comments: To identify the health and mental health information needs of people with coronary heart disease, with and without co-morbid depression.

[1] This checklist is based on checklists in:

Spencer L. Ritchie J, Lewis J, Dillon L (2003) Quality in qualitative evaluation: a framework for assessing research evidence. London: Government Chief Social Researcher's Office. Available from: www.strategy.gov.uk/downloads/su/qual/downloads/qqe_rep.pdf

Public Health Resource Unit England (2006) Critical Appraisal Skills Programme (CASP) – making sense of evidence: 10 questions to help you make sense of qualitative research . Available from: www.phru.nhs.uk/Doc_Links/Qualitative%20Appraisal%20Tool.pdf

National Training and Research Appraisal Group (NTRAG); contact: www.ntrag.co.uk

British Sociological Association (BSA); contact: www.britsoc.co.uk

Section 2: study design		
2.1 How defensible/rigorous is the research design/methodology? *For example:* • Is the design appropriate to the research question? • Is a rationale given for using a qualitative approach? • Are there clear accounts of the rationale/justification for the sampling, data collection and data analysis techniques used? • Is the selection of cases/sampling strategy theoretically justified?	☒ Defensible ☐ Not defensible ☐ Not sure	Comments: Design appropriate for the research question.

Section 3: data collection		
3.1 How well was the data collection carried out? *For example:* • Are the data collection methods clearly described? • Were the appropriate data collected to address the research question? • Was the data collection and record keeping systematic?	☒ Appropriate ☐ Inappropriate ☐ Not sure/ inadequately reported	Comments: Semi-structured interviews, audio-taped, transcribed verbatim after removal of identifying information.

Section 4: validity		
4.1 Is the role of the researcher clearly described? *For example:* • Has the relationship between the researcher and the participants been adequately considered? • Does the paper describe how the research was explained and presented to the participants?	☒ Clear ☐ Unclear ☐ Not described	Comments: The interviewers guided the interviews and encouraged participants to talk freely about the subject matter but redirected participants who deviated from the purpose of the interviews.
4.2 Is the context clearly described? *For example:* • Are the characteristics of the participants and settings clearly defined? • Were observations made in a sufficient variety of circumstances? • Was context bias considered?	☒ Clear ☐ Unclear ☐ Not sure	Comments: Patients recruited form GP practices. Characteristics of patients reported.
4.3 Were the methods reliable? *For example:* • Were data collected by more than one method? • Is there justification for triangulation, or for not triangulating? • Do the methods investigate what they claim to?	☒ Reliable ☐ Unreliable ☐ Not sure	Comments: Data collected by only one method: Audio taping of semi-structured interviews.

Section 5: analysis		
5.1 Is the data analysis sufficiently rigorous? *For example:* • Is the procedure explicit – is it clear how the data were analysed to arrive at the results? • How systematic is the analysis – is the procedure reliable/dependable? • Is it clear how the themes and concepts were derived from the data?	☒ Rigorous ☐ Not rigorous ☐ Not sure/not reported	Comments: Data analysed by an independent investigator using the thematic approach.
5.2 Are the data 'rich'? *For example:* • How well are the contexts of the data described? • Has the diversity of perspective and content been explored? • How well have the detail and depth been demonstrated? • Are responses compared and contrasted across groups/sites?	☐ Rich ☐ Poor ☒ Not sure/not reported	Comments: Responses not compared across groups.
5.3 Is the analysis reliable? *For example:* • Did more than one researcher theme and code transcripts/data? • If so, how were differences resolved? • Did participants feed back on the transcripts/data? (if possible and relevant) • Were negative/discrepant results addressed or ignored?	☒ Reliable ☐ Unreliable ☐ Not sure/not reported	Comments: Analysis conducted an independent investigator; subsequent examination of the analysis was done by two additional investigators.
5.4 Are the findings convincing? *For example:* • Are the findings clearly presented? • Are the findings internally coherent? • Are extracts from the original data included? • Are the data appropriately referenced? • Is the reporting clear and coherent?	☒ Convincing ☐ Not convincing ☐ Not sure	Comments: Well supported themes with quotations presented.
5.5 Are the findings relevant to the aims of the study?	☒ Relevant ☐ Irrelevant ☐ Partially relevant	Comments: Findings are descriptive of the information needs of the patients.

5.6 Are the conclusions adequate? *For example:* • How clear are the links between data, interpretation and conclusions? • Are the conclusions plausible and coherent? • Have alternative explanations been explored and discounted? • Does this study enhance understanding of the research subject? • Are the implications of the research clearly defined? • Is there adequate discussion of any limitations encountered?	☒ Adequate ☐ Inadequate ☐ Not sure	Comments: see narrative

Section 6: ethics		
6.1 How clear and coherent is the reporting of ethical considerations? *For example,* • Have ethical issues been taken into consideration? • Are ethical issues discussed adequately – do they address consent and anonymity? • Have the consequences of the research been considered; for example, raising expectations, changing behaviour? • Was the study approved by an ethics committee?	☒ Clear ☐ Not clear ☐ Not sure/not reported	Comments: Study approved by the Monash University Human Research and Ethics Committee.

Study identification *Include author, title, reference, year of publication*	**Weetch RM. Patient satisfaction with information received after a diagnosis of angina. *Prof Nurse.* 2003; 19(3):150-153.**
Guidance topic: Stable angina	**Key research question/aim:** What are the information needs of patients with stable angina regarding their condition and its management?
Checklist completed by: Sharangini	

Section 1: theoretical approach		
1.1 Is a qualitative approach appropriate? *For example:* • Does the research question seek to understand processes or structures, or illuminate subjective experiences or meanings? • Could a quantitative approach better have addressed the research question?	☒ Appropriate ☐ Inappropriate ☐ Not sure	Comments: Descriptive study of patient information needs requires qualitative approach.
1.2 Is the study clear in what it seeks to do? *For example:* • Is the purpose of the study discussed – aims/objectives/research question(s)? • Is there adequate/appropriate reference to the literature? • Are underpinning values/assumptions/theory discussed?	☒ Clear ☐ Unclear ☐ Mixed	Comments: Aim: To determine the level of satisfaction of patients with the amount and quality of information that they receive.

Section 2: study design		
2.1 How defensible/rigorous is the research design/methodology? *For example:* • Is the design appropriate to the research question? • Is a rationale given for using a qualitative approach? • Are there clear accounts of the rationale/justification for the sampling, data collection and data analysis techniques used? • Is the selection of cases/sampling strategy theoretically justified?	☒ Defensible ☐ Not defensible ☐ Not sure	Comments: The design is appropriate to the research question. The authors state that to measure a subjective reaction a qualitative approach is needed.

Section 3: data collection		
3.1 How well was the data collection carried out? *For example:* • Are the data collection methods clearly described? • Were the appropriate data collected to address the research question? • Was the data collection and record keeping systematic?	☐ Appropriate ☐ Inappropriate ☒ Not sure/ inadequately reported	Comments: Data was collected by questionnaires. Appropriate data was collected addressed the research question. But additional details about data collection/questionnaires not reported.

Section 4: validity		
4.1 Is the role of the researcher clearly described? *For example:* • Has the relationship between the researcher and the participants been adequately considered? • Does the paper describe how the research was explained and presented to the participants?	☐ Clear ☐ Unclear ☒ Not described	Comments: Role of the researcher not well described. The participants were given a letter of explanation, together with a questionnaire and a stamped addressed return envelope.
4.2 Is the context clearly described? *For example:* • Are the characteristics of the participants and settings clearly defined? • Were observations made in a sufficient variety of circumstances? • Was context bias considered?	☐ Clear ☐ Unclear ☒ Not sure	Comments: The population were patients suffering from angina who had been hospitalised in the coronary care ward. Characteristics of participants not well reported. There was no discussion of context bias.
4.3 Were the methods reliable? *For example:* • Were data collected by more than one method? • Is there justification for triangulation, or for not triangulating? • Do the methods investigate what they claim to?	☐ Reliable ☐ Unreliable ☒ Not sure	Comments: Only one method was used – Questionnaire.

Section 5: analysis		
5.1 Is the data analysis sufficiently rigorous? *For example:* • Is the procedure explicit – is it clear how the data were analysed to arrive at the results? • How systematic is the analysis – is the procedure reliable/dependable? • Is it clear how the themes and concepts were derived from the data?	☐ Rigorous ☐ Not rigorous ☒ Not sure/not reported	Comments: No details given on the method of analysis used. The study reports that both quantitative and qualitative themes were identified.
5.2 Are the data 'rich'? *For example:* • How well are the contexts of the data described? • Has the diversity of perspective and content been explored? • How well have the detail and depth been demonstrated? • Are responses compared and contrasted across groups/sites?	☐ Rich ☒ Poor ☐ Not sure/not reported	Comments: Contexts of the data not well reported. The responses were compared between patients who had previous MI and those who had angina.
5.3 Is the analysis reliable? *For example:* • Did more than one researcher theme and code transcripts/data? • If so, how were differences resolved? • Did participants feed back on the transcripts/data? (if possible and relevant) • Were negative/discrepant results addressed or ignored?	☐ Reliable ☐ Unreliable ☒ Not sure/not reported	Comments: Not details of analysis reported, hence difficult to consider the results to be reliable.
5.4 Are the findings convincing? *For example:* • Are the findings clearly presented? • Are the findings internally coherent? • Are extracts from the original data included? • Are the data appropriately referenced? • Is the reporting clear and coherent?	☐ Convincing ☒ Not convincing ☐ Not sure	Comments: Very brief description of the results reported. No quotes from participants/patients reported.
5.5 Are the findings relevant to the aims of the study?	☒ Relevant ☐ Irrelevant ☐ Partially relevant	Comments: The study also reported the type and amount of information needs stated by participants in the group.

5.6 Are the conclusions adequate? *For example:* • How clear are the links between data, interpretation and conclusions? • Are the conclusions plausible and coherent? • Have alternative explanations been explored and discounted? • Does this study enhance understanding of the research subject? • Are the implications of the research clearly defined? • Is there adequate discussion of any limitations encountered?	☒ Adequate ☐ Inadequate ☐ Not sure	Comments: The results of the study indicated that patients want more information. There was no discussion regarding the limitations of the study. But the authors state that 'statistically a further study is needed to confirm the findings of this study'.

Section 6: ethics		
6.1 How clear and coherent is the reporting of ethical considerations? *For example,* • Have ethical issues been taken into consideration? • Are ethical issues discussed adequately – do they address consent and anonymity? • Have the consequences of the research been considered; for example, raising expectations, changing behaviour? • Was the study approved by an ethics committee?	☒ Clear ☐ Not clear ☐ Not sure/not reported	Comments: Permission for the study was obtained from the local ethics committee.

Study identification *Include author, title, reference, year of publication*	**Karlik BA, Yarcheski A, Braun J et al. Learning needs of patients with angina: an extension study. *J Cardiovasc Nurs.* 1990; 4(2):70-82.**
Guidance topic: Stable Angina	**Key research question/aim:** What are the information needs of patients with stable angina regarding their condition and its management?
Checklist completed by: Sharangini	

Section 1: theoretical approach		
1.1 Is a qualitative approach appropriate? *For example:* • Does the research question seek to understand processes or structures, or illuminate subjective experiences or meanings? • Could a quantitative approach better have addressed the research question?	☒ Appropriate ☐ Inappropriate ☐ Not sure	Comments: Descriptive study of learning needs of patients requires qualitative approach.
1.2 Is the study clear in what it seeks to do? *For example:* • Is the purpose of the study discussed – aims/objectives/research question(s)? • Is there adequate/appropriate reference to the literature? • Are underpinning values/assumptions/theory discussed?	☒ Clear ☐ Unclear ☐ Mixed	Comments: Aim : To compare the learning needs of patients with angina with ratings by the patients themselves and the nurses who care for them.

Section 2: study design		
2.1 How defensible/rigorous is the research design/methodology? *For example:* • Is the design appropriate to the research question? • Is a rationale given for using a qualitative approach? • Are there clear accounts of the rationale/justification for the sampling, data collection and data analysis techniques used? • Is the selection of cases/sampling strategy theoretically justified?	☒ Defensible ☐ Not defensible ☐ Not sure	Comments: Design is appropriate to the research question.

Section 3: data collection		
3.1 How well was the data collection carried out? *For example:* • Are the data collection methods clearly described? • Were the appropriate data collected to address the research question? • Was the data collection and record keeping systematic?	☒ Appropriate ☐ Inappropriate ☐ Not sure/ inadequately reported	Comments: Data collected by validated learning needs instruments.

Section 4: validity		
4.1 Is the role of the researcher clearly described? *For example:* • Has the relationship between the researcher and the participants been adequately considered? • Does the paper describe how the research was explained and presented to the participants?	☐ Clear ☐ Unclear ☒ Not described	Comments: Role of the researcher not well described.
4.2 Is the context clearly described? *For example:* • Are the characteristics of the participants and settings clearly defined? • Were observations made in a sufficient variety of circumstances? • Was context bias considered?	☐ Clear ☐ Unclear ☒ Not sure	Comments: Patients were recruited from an acute care hospital where patients were admitted for a cardiac catheterisation. Characteristics of patients not well reported.
4.3 Were the methods reliable? *For example:* • Were data collected by more than one method? • Is there justification for triangulation, or for not triangulating? • Do the methods investigate what they claim to?	☒ Reliable ☐ Unreliable ☐ Not sure	Comments: Only one method was used- Validated learning instruments.

Section 5: analysis		
5.1 Is the data analysis sufficiently rigorous? *For example:* • Is the procedure explicit – is it clear how the data were analysed to arrive at the results? • How systematic is the analysis – is the procedure reliable/dependable? • Is it clear how the themes and concepts were derived from the data?	☐ Rigorous ☒ Not rigorous ☐ Not sure/not reported	Comments: Qualitative method sued. Means values reported but not standard deviation.
5.2 Are the data 'rich'? *For example:* • How well are the contexts of the data described? • Has the diversity of perspective and content been explored? • How well have the detail and depth been demonstrated? • Are responses compared and contrasted across groups/sites?	☐ Rich ☐ Poor ☒ Not sure/not reported	Comments: Only questions in the learning needs instruments considered. Limited range of information categories in the learning needs instruments.
5.3 Is the analysis reliable? *For example:* • Did more than one researcher theme and code transcripts/data? • If so, how were differences resolved? • Did participants feed back on the transcripts/data? (if possible and relevant) • Were negative/discrepant results addressed or ignored?	☐ Reliable ☐ Unreliable ☒ Not sure/not reported	Comments: No details on data analysis reported.
5.4 Are the findings convincing? *For example:* • Are the findings clearly presented? • Are the findings internally coherent? • Are extracts from the original data included? • Are the data appropriately referenced? • Is the reporting clear and coherent?	☐ Convincing ☐ Not convincing ☒ Not sure	Comments: Mean values and description of the data reported.
5.5 Are the findings relevant to the aims of the study?	☒ Relevant ☐ Irrelevant ☐ Partially relevant	Comments: Study reports the preferred information categories by the patients and preference of educator.

5.6 Are the conclusions adequate? *For example:* • How clear are the links between data, interpretation and conclusions? • Are the conclusions plausible and coherent? • Have alternative explanations been explored and discounted? • Does this study enhance understanding of the research subject? • Are the implications of the research clearly defined? • Is there adequate discussion of any limitations encountered?	☒ Adequate ☐ Inadequate ☐ Not sure	Comments: Authors state the limitations of the study: small sample size, limited range of responses on the Likert scale. Further research as reported in the study: Use of a more sensitive instrument so that subtle differences in beliefs might be more readily detected and reliabilities might be increased.

Section 6: ethics		
6.1 How clear and coherent is the reporting of ethical considerations? *For example,* • Have ethical issues been taken into consideration? • Are ethical issues discussed adequately – do they address consent and anonymity? • Have the consequences of the research been considered; for example, raising expectations, changing behaviour? • Was the study approved by an ethics committee?	☒ Clear ☐ Not clear ☐ Not sure/not reported	Comments: Approval by Institutional Review Board.

Study identification *Include author, title, reference, year of publication*	**McGillion MH, Watt-Watson JH, Kim J et al. Learning by heart: a focused group study to determine the self-management learning needs of chronic stable angina patients. *Can J Cardiovasc Nurs.* 2004; 14(2):12-22.**
Guidance topic: Stable angina	**Key research question/aim:** What are the information needs of patients with stable angina regarding their condition and its management?
Checklist completed by: Sharangini	

Section 1: theoretical approach		
1.1 Is a qualitative approach appropriate? *For example:* • Does the research question seek to understand processes or structures, or illuminate subjective experiences or meanings? • Could a quantitative approach better have addressed the research question?	☒ Appropriate ☐ Inappropriate ☐ Not sure	Comments: Descriptive study of patient learning needs requires a qualitative approach.
1.2 Is the study clear in what it seeks to do? *For example:* • Is the purpose of the study discussed – aims/objectives/research question(s)? • Is there adequate/appropriate reference to the literature? • Are underpinning values/assumptions/theory discussed?	☒ Clear ☐ Unclear ☐ Mixed	The purpose of the study was to determine the self-management learning needs of chronic stable angina patients living at home.

Section 2: study design		
2.1 How defensible/rigorous is the research design/methodology? *For example:* • Is the design appropriate to the research question? • Is a rationale given for using a qualitative approach? • Are there clear accounts of the rationale/justification for the sampling, data collection and data analysis techniques used? • Is the selection of cases/sampling strategy theoretically justified?	☒ Defensible ☐ Not defensible ☐ Not sure	Comments: The study design is appropriate to the research question. The authors give the rationale for using focus groups in the study ‘’Focus groups foster the ‘collective voice’, rather than individual voices, allowing for more free expression of ideas from participants who may otherwise feel constrained or pressured by the researcher in a one-to-one interview situation’’.

Section 3: data collection		
3.1 How well was the data collection carried out? *For example:* • Are the data collection methods clearly described? • Were the appropriate data collected to address the research question? • Was the data collection and record keeping systematic?	☒ Appropriate ☐ Inappropriate ☐ Not sure/ inadequately reported	Comments: Focus groups were held in a classroom setting and semi-structures interviews moderated by the Principal investigator. An independent assistant moderator took field notes and all focus groups were audio taped. .

Section 4: validity		
4.1 Is the role of the researcher clearly described? *For example:* • Has the relationship between the researcher and the participants been adequately considered? • Does the paper describe how the research was explained and presented to the participants?	☒ Clear ☐ Unclear ☐ Not described	Comments: The Principal investigator explained the procedure to the focus groups and also moderated the semi-structured interviews.
4.2 Is the context clearly described? *For example:* • Are the characteristics of the participants and settings clearly defined? • Were observations made in a sufficient variety of circumstances? • Was context bias considered?	☒ Clear ☐ Unclear ☐ Not sure	Comments: Participants recruited from two outpatient clinics and the cardiovascular rehabilitation centre at the study site. Characteristics of participants reported. There was no discussion of context bias.
4.3 Were the methods reliable? *For example:* • Were data collected by more than one method? • Is there justification for triangulation, or for not triangulating? • Do the methods investigate what they claim to?	☒ Reliable ☐ Unreliable ☐ Not sure	Comments: Data only collected by one method-audio taping of the semi-structured interviews and then transcribed in full.

Section 5: analysis		
5.1 Is the data analysis sufficiently rigorous? *For example:* • Is the procedure explicit – is it clear how the data were analysed to arrive at the results? • How systematic is the analysis – is the procedure reliable/dependable? • Is it clear how the themes and concepts were derived from the data?	☒ Rigorous ☐ Not rigorous ☐ Not sure/not reported	Comments: Branden's Self-Help Model was the conceptual framework and was used to guide the transcript based analysis.
5.2 Are the data 'rich'? *For example:* • How well are the contexts of the data described? • Has the diversity of perspective and content been explored? • How well have the detail and depth been demonstrated? • Are responses compared and contrasted across groups/sites?	☐ Rich ☐ Poor ☒ Not sure/not reported	Comments: Responses not compared between groups. The authors report that, as no new themes emerged during the second patient group in relation to the first, the investigators determined the data saturation had been reached and that interviewing the absent individuals at a later date was unnecessary.
5.3 Is the analysis reliable? *For example:* • Did more than one researcher theme and code transcripts/data? • If so, how were differences resolved? • Did participants feed back on the transcripts/data? (if possible and relevant) • Were negative/discrepant results addressed or ignored?	☒ Reliable ☐ Unreliable ☐ Not sure/not reported	Comments: Two researchers reduced the data in to themes and then selected key illustrative quotes. At the end of each focus group session, a summary of the results was read back to the participants, enabling them to verify key issues.
5.4 Are the findings convincing? *For example:* • Are the findings clearly presented? • Are the findings internally coherent? • Are extracts from the original data included? • Are the data appropriately referenced? • Is the reporting clear and coherent?	☒ Convincing ☐ Not convincing ☐ Not sure	Comments: Well supported themes with quotations presented.
5.5 Are the findings relevant to the aims of the study?	☒ Relevant ☐ Irrelevant ☐ Partially relevant	Comments: Findings are descriptive of the learning needs of the participants.

5.6 Are the conclusions adequate? *For example:* • How clear are the links between data, interpretation and conclusions? • Are the conclusions plausible and coherent? • Have alternative explanations been explored and discounted? • Does this study enhance understanding of the research subject? • Are the implications of the research clearly defined? • Is there adequate discussion of any limitations encountered?	☒ Adequate ☐ Inadequate ☐ Not sure	Comments: The study reports the limitations of the study: Use of purposive sampling, which may limit transferability of findings; use of focus groups may create an artificial setting. Further research defined: Include broad range of professionals (beyond nursing and medicine) in order to obtain a wider perspective on the self-management learning needs of chronic stable angina patients.

Section 6: ethics		
6.1 How clear and coherent is the reporting of ethical considerations? *For example,* • Have ethical issues been taken into consideration? • Are ethical issues discussed adequately – do they address consent and anonymity? • Have the consequences of the research been considered; for example, raising expectations, changing behaviour? • Was the study approved by an ethics committee?	☒ Clear ☐ Not clear ☐ Not sure/not reported	Comments: Approval from Ethical review boards of a Canadian University and University-affiliated hospital.

Evidence Extractions

Question: What is the clinical /cost effectiveness of short acting drugs for the management of angina?

Grading: 1+	Well-conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias

Atterhog JH;Ekelund LG;Melin AL;

Effect of nifedipine on exercise tolerance in patients with angina pectoris

Ref ID 2760

1975 Feb 28

Study Type	Randomised Controlled Trial	**Funding**	No sources of funding are reported

Number of participant	RCT with crossover design N=10 Swedish study
Inclusion/Exclusion Criteria	Not specified
Patient Characteristics	Males aged between 44-69 years (average 57.3 years) with a classic history of angina pectoris of effort (mean 3.3 years duration) and stable angina documented for at least 4months. 7/10 had had at least one infarct but not during previous year. No participant had heart failure, hypertension, intermittent claudication, rhythm disturbances or conduction defects.
Recruitment	The trial was conducted in Sweden
Setting	Unclear
Interventions/ Test/ Factor being investigated	10 mg nifedipine capsule kept in the mouth and chewed (sublingual administration) identical placebo capsule
Comparisons	Nifedipine vs placebo
Length of Study/ Follow-up	There were 4 tests (approx 1hr) in 2 wks after entering the study.Randomisation was to wk1 stepwise load test (repeated 2 days later) and wk 2 continuously increasing load test (repeated 2 days later), or vice versa, and to order of treatment within tests
Outcome measures studied	Relevant outcomes: Total work time, total workload, workload at breakpoint. Others: Number of loads, highest load, heart rate at breakpoint, systolic blood pressure at breakpoint, patient reported symptoms (questionnaire) at breakpoint, adverse events
Results	No primary/secondary outcomes noted. No standard deviations were given for the mean values reported, only approximate p-values. Relevant outcomes (recorded for both a stepwise and continuous increasing load): Total work time, total work, estimated workload at breakpoint. Breakpoint is the time at which each participant stopped exercising because of chest pain. No details are reported on baseline therapy No details of a wash out period are given. Patients performed tests at the same time of day on each occasion. Food intake was standardised and smoking not permitted before the test. Stepwise test : Using a electrically braked bicycle with the participant in the sitting position and increasing loads every six minutes Continuous test : Using a electrically braked bicycle with the participant in the sitting position for a 2 minute warm up, then increasing load continuously and linearly at a predetermined individual rate (nifedipine mean rate of increase = 80 kpm/min/min, placebo mean rate of increase = 79kpm/min/min, p=non significant) For stepwise load test: Total work time Nifedipine = 22.0 minutes, Placebo = 16.8 minutes

Mean difference = 5.2
p<0.02

Total work
Nifedipine = 10976 kpm, Placebo = 7291 kpm
Mean difference = 3685 kpm
p<0.01

Estimated workload at breakpoint
Nifedipine = 722 kpm/min, Placebo = 578 kpm/min
Mean difference = 146kpm/min
p<0.01

For continuous load test:
Total work time
Nifedipine = 12.9 minutes, Placebo = 11.8 minutes
Mean difference = 1.1 minutes
p<0.05

Total work
Nifedipine = 6225 kpm, Placebo = 5079 kpm
Mean difference = 1146 kpm
p<0.0025

Estimated Workload at breakpoint
Nifedipine = 978 kpm/min, Placebo = 866 kpm/min
Mean difference = 112 kpm/min
p<0.05

Safety and adverse effects

No safety issues are reported in the trial. Patients spontaneously reported a feeling of "heat in the face" at an average 14 minutes after 11 of 20 administrations of nifedipine.

Does the study answer the question?

Yes this study helps answer the key question, although the sample size is small.

This double blind, randomised cross over trial examined the effect of short acting (sublingual) nifedipine compared to placebo in 10 males with angina who underwent two types of exercise testing (with stepwise and continuous load increases) within a two week period. Exercise testing began 30 minutes after adminstration of treatment and stopped when chest pain prevented the participant from continuing. In both tests nifedipine significantly improved exercise performance (total work time, total workload and estimated workload at breakpoint) compared to placebo.

These results suggest that prophylatic use of short acting nifedipine is more effective than placebo in improving exercise duration and workload undertaken 30 minutes after administration .

Effect due to factor in study?

See GRADE

Consistency of results with other studies?

Not applicable

Directly applicable to guideline population?

See GRADE

Internal Validity

Selection and performance bias

Marra S;Paolillo V;Baduini G;Spadaccini F;Angelino PF;

Acute effects of chewable nifedipine on hemodynamic responses to upright exercise in patients with prior myocardial infarction and effort angina

Ref ID 2409

1983 Jan

Study Type Randomised Controlled Trial

Funding No study funding details are reported

Number of participant	Double blind RCT with crossover design N=10 Italian study
Inclusion/Exclusion Criteria	Not stated
Patient Characteristics	10 males (age range 37 - 59, mean 49.4) with stable angina and a MI within previous 3 months. 7/10 had ischaemic ST segment changes during exercise. None had heart failure, mitral regurgitation, ventricular arrythmia above Lown grade 3, chronotropic incompetence or effort hypotension. All participants underwent coronary angiography as well as right and left coronary catheterisation forty days prior to trial commencement. Exercise test 1 was performed 48hrs later. Exercise test 2 was within the next 40 days to establish the stability and threshold of angina. Patients were hospitalised and for a week before testing were limited to GTN treatment only (wash out). Beta blockers were stopped 5 days prior to the trial drug administration (wash out). An exercise test was performed 20-25 minutes after each drug's administration. Both tests performed at the same time of day 24 hours apart.
Recruitment	Not specified
Setting	Hospital
Interventions/ Test/ Factor being investigated	20mg sublingual nifedipine (2 pills chewed and held in the mouth for 10 minutes before ingestion) identical placebo pills
Comparisons	Sublingual nifedipine vs sublingual placebo
Length of Study/ Follow-up	Patients were followed for 40 days prior to trial drug administration and during exercise tests following trial drug administration on 2 subsequent days.
Outcome measures studied	Mean work capacity (minutes of exercise) at angina threshold Maximal work capacity (minutes of exercise) at maximal exercise level
Results	No outcomes were noted as being primary or secondary. Mean work capacity (minutes of exercise) at angina threshold Nifedipine group = 8.80 SD 2.89 Placebo group = 6.70 SD 2.67 p = 0.001 Maximal work capacity (minutes of exercise) at maximal exercise level Nifedipine group =10.00 SD 3.06 Placebo group = 7.70 SD 2.75 p = 0.001
Safety and adverse effects	None are reported
Does the study answer the question?	Yes this study helps answer the key question. This double blind, randomised cross over trial examined the effect of short acting (sublingual) nifedipine compared to placebo in 10 males with angina who had had an MI within the previous 3 months and recent cardiac catheterisation. Participants underwent two baseline exercise tests prior to administration of nifedipine/placebo, then had one test 20-25 minutes after administration of each drug on subsequent days. Exercise tests were stopped either at the appearance of grade 3 or 4 angina or when ischaemic ST segment changes became evident. If only one of these two signs was present the exercise was continued until fatigue or dysnoea appeared. Nifedipine significantly improved exercise performance (mean work capacity at angina threshold and maximal work capacity at maximal exercise level) compared to placebo. These results suggest that prophylatic use of short acting nifedipine is more effective than placebo in improving exercise work capacity 25 minutes after administration .
Effect due to factor in study?	See GRADE

Consistency of results with other studies?	Not applicable
Directly applicable to guideline population?	See GRADE
Internal Validity	Selection bias

Mooss AN;Mohiuddin SM;Hilleman DE;Sketch MH;

A comparison of sublingual nifedipine versus nitroglycerin in the treatment of acute angina pectoris

Ref ID 1631 1989 Jul

Study Type Randomised Controlled Trial **Funding** No details provided

Number of participant	Single blind RCT with crossover design for non responders to treatment US study n=13 nifedipine n = 6, GTN n = 7 4 of the nifedipine group crossed over to GTN after 4 minutes
Inclusion/Exclusion Criteria	Inclusion criteria : Men or women aged 19-70 years who developed typical anginal pain with or without electrocardiographic changes during diagnostic Bruce treadmill exercise testing were eligible to participate. Exclusion criteria: Patients with significant pulmonary, peripheral vascular or orthopaedic disease. Patients who had had MI or who had undergone CABG in the previous 6 wks. Patients taking nitrates, BBs, digoxin or CCBs.
Patient Characteristics	All study participants had 70% or more stenosis in one or more coronary arteries. GTN n = 7 6 males , 1 female mean age 54 +/- 9 yrs 5 of 7 had> 1mm ST segment depression on ECG during Bruce treadmill test Mean pain intensity rating prior to treatment 7.6 +/- 1.1 Nifedipine n = 6 5 males, 2 females mean age 56 +/- 12 years 6 of 6 had> 1mm ST segment depression on ECG during Bruce treadmill test Mean pain intensity rating prior to treatment 7.8 +/- 0.8 (not significantly different to GTN group)
Recruitment	No details provided
Setting	Unclear
Interventions/ Test/ Factor being investigated	0.4mg tablet GTN given sublingually 10mg liquid nifedipine syringed from a nifedipine capsule and given sublingually
Comparisons	SL GTN tabletvs SL nifedipine liquid
Length of Study/ Follow-up	Patients were followed for four minutes after receiving their randomised drug. Those who had <50% reduction in pain intensity were crossed over to the alternate therapy and followed for another 2 minutes.
Outcome measures studied	No primary or secondary outcomes are detailed Relevant outcomes: No pts with complete pain resolution at 2 mins and 4 mins, Mean pain intensity rating at 2 mins and 4 mins, No pts with complete pain resolution at 2 mins after cross over therapy
Results	No pts with pain at 0 mins GTN = 7/7 Nifedipine = 6/6

	Mean pain intensity rating at 0 mins GTN = 7.6 +/- 1.1 Nifedipine = 7.8 +/- 0.8 mean pain intensity rating at 2 mins GTN = 1.0 +/- 1.7 Nifedipine = 7.3 +/- 2.1 mean pain intensity rating at 4 mins GTN = 0.4 +/- 0.8 Nifedipine = 6.0 +/- 1.7 No pts with complete pain resolution at 4 mins GTN = 5/7 Nifedipine = 0/6 No pts with complete pain resolution at 2 mins GTN = 5/7 Nifedipine = 0/6 No pts with complete pain resolution at 2 mins after cross over therapy Nifedipine crossed to GTN = 4/4 GTN crossed to nifedipine = 0
Safety and adverse effects	Adverse reactions attributable to nifedipine and nitroglycerin were negligible. No patients complained of side effects following nifedipine alone. Two of the nifedipine patients complained of flushing following GTN administration and one of these patients developed a headache. One of the seven patients who received GTN alone complained of headache.
Does the study answer the question?	Yes this study helps answer the key clinical question, although the study is small This RCT compared the effect of SL GTN to SL nifedipine for the relief of anginal pain caused by treadmill exercise. 13 patients with stable angina participated.At 2 minutes post treatment, there was a significant number of participants with 100% pain relief and lower mean pain intensity in the GTN group.Mean pain intensity was lower for the two remaining participants with pain at 4 minutes. However, the number of participants with 100% pain relief and mean pain intensity in the SL nifedipine group had not changed significantly from baseline. By four minutes only 2 of 6 partipants in the SL nifedipine group had >50% reduction in mean pain intensity. These results suggest that 0.4mg SL GTN decreases anginal pain and terminates anginal attacks more quickly than 10mg SL nifedipine.
Effect due to factor in study?	See GRADE
Consistency of results with other studies?	Not applicable
Directly applicable to guideline population?	See GRADE
Internal Validity	Selection bias

Grading: 1- Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias*

Pupita G;Mazzara D;Centanni M;Rimatori C;Ferretti GF;Dessi FP;Russo P;Rappelli A;

Ischemia in collateral-dependent myocardium: effects of nifedipine and diltiazem in man

Ref ID 1198 1993 Jul

Study Type Randomised Controlled Trial **Funding** Details are not reported

Number of participant
Single blind RCT with crossover design
N=9
Italian study

Inclusion/Exclusion Criteria
Inclusion criteria :
1) Chronic stable angina without changes in symptoms in previous 3 months
2) Presence of >=1 completely blocked coronary arteries filled by collateral circulation arising from angiographically normal coronary arteries
3) No stenosis in remaining vessels
4) Normal global and segmental left ventricular wall motion
5) Positive exercise test off therapy.
All patients were in sinus rhythm and had normal resting ST segment level
None had heart failure, cardiomyopathy, valvular disease or were taking digitalis

Patient Characteristics
9 consecutively recruited males
Aged 52 to 69 (mean 60+/- 5 years)
4 with left anterior descending artery occlusion, 5 with right coronary artery occlusion (1 with additional circumflex artery occlusion and 1 with additional first obtuse marginal branch artery occlusion)
Ejection fraction range 62% to 72%
7 with normal ECG, 1 with flat Tw V4-V6, 1 with negative Tw V1-V2
Duration of symptom onset range 0.9 to 14 years
3 with occasional effort angina, 2 with effort angina, 3 with effort/variable threshold angina, 1 with effort/variable threshold/rest angina,
CCS angina class - 3 with no score, 3 with score II, 3 with score III

All patients were in sinus rhythm and had normal resting ST segment level
None had heart failure, cardiomyopathy, valvular disease or were taking digitalis

Recruitment
Details are not reported

Setting
Details are not reported

Interventions/ Test/ Factor being investigated
10mg of sublingual nifedipine
120mg of oral diltiazem
0.5mg of sublingual nitroglycerin

Comparisons
Nifedipine vs no treatment
Nifedipine vs nitroglycerin

Nifedipine vs diltiazem
Diltiazem vs no treatment
Nitroglycerin vs no treatment
Diltiazem vs nitroglycerin

Length of Study/ Follow-up
Patients were involved in the study for a duration of approximately 24 Days.
Assessments were made at the start and end of this period ("off therapy") and three times directly following administration of drugs

Outcome measures studied
Outcomes are not classed as primary or secondary.
Relevant outcome :
Mean exercise time to 1mm ST depression (secs)

Results
Protocol

Washout periods
>= 2 days for CCBs and Oral nitrates

>= 4 days for BBs

Washout as appropriate, followed by a baseline exercise test, then with 2 day intervals between each and according to randomisation sequence
1) exercise test 5 minutes after 10mg of sublingual nifedipine
2) exercise test 1 hr after 120mg of oral diltiazem
3) exercise test 5 minutes after 0.5mg of sublingual nitroglycerin
A second "off therapy" exercise test performed within the subsequent 2 weeks

Mean exercise time to 1mm ST depression (secs)

Off therapy = 430 +/- 176 s
Nifedipine = 576 +/- 205 s
Nitroglycerin = 666 +/- 76 s

Nifedipine vs off therapy (no treatment) p< 0.01
Nifedipine vs nitroglycerin p=0.09

Safety and adverse effects

Details are not reported

Does the study answer the question?

Yes this study helps answer the key question, although the sample size is small.

This single blind, randomised cross over trial examined the effects of sublingual nifedipine, oral diltiazem and sublingual nitroglycerin in 10 males with stable angina who underwent exercise testing "off therapy" at baseline and 2wks after the last drug administration and "on therapy" testing after administration of each drug. Haemodynamic and exercise test outcomes were collected. Nifedipine significantly increased the mean exercise time to 1mm ST depression compared to no treatment. However, there was no significant difference in this parameter when nifedipine and nitroglycerin were compared.

These results suggest that prophylatic use of short acting nifedipine is more effective than no treatment in improving exercise duration before angina onset but that there is no significant difference in exercise time before angina onset between nifedipine and nitroglycerin

Effect due to factor in study?

See GRADE

Consistency of results with other studies?

Not applicable

Directly applicable to guideline population?

See GRADE

Internal Validity

Selection bias

Ryden L;Schaffrath R;

Buccal versus sublingual nitroglycerin administration in the treatment of angina pectoris: a multicentre study

Ref ID 1867

1987 Sep

Study Type Randomised Controlled Trial

Funding No details are reported

Number of participant

Open RCT with cross over design
N=126
Swedish study

Inclusion/Exclusion Criteria

Inclusion criteria
Patients with stable exercise-induced angina demonstrated by a typical case history and exercise test in 80% of patients or by a well documented, long duration case history of exercise induced chest pain relieved by rest (20%).

Exclusion criteria:
Concomitant diseases that could affect angina adversly (eg anaemia)

	A history of myocardial infarction within the previous 4 weeks
Patient Characteristics	All patients had at least a 6 month history of stable angina with a minimum of 5 attacks/wk Mean age 61+/- 8 years (range 38-82) Male 80% Dental prosthesis 35% All were on stable chronic treatment for angina BB only - 37% CCB only- 18% BB and CCB - 40% LAN only - 3% Dipyridamole - 2% LAN with or without other drugs - 76%
Recruitment	Patients were recruited from 11 participating hospitals according to a protocol
Setting	Hospital outpatient clinics in Sweden
Interventions/ Test/ Factor being investigated	2.5mg or 5mg buccal GTN tablet for the treatment or prophylaxis of angina (tablet held in the cheek for 15 minutes 1) after the relief of angina, 2) after stopping an activity inducing pain or 3) following cessation of activity, when taken prophylactically prior to activity starting.) 0.25mg or 0.5mg sublingual GTN tablet used for treatment or prophylaxis of angina (the patients' standard treatment)
Comparisons	Buccal GTN vs Sublingual GTN
Length of Study/ Follow-up	Patients participated for 6 weeks. All patients received training on use of buccal GTN and their dose was titrated over 2 weeks, then they were randomised to 2 wks buccal , then 2wks sublingual GTN or vice versa
Outcome measures studied	Primary and seondary outcomes are not specified." Relevant outcomes: Total number of treated anginal attacks, pain severity, prevention of expected attack
Results	During the study background medications were kept constant. Off therapy" data are not reported. Outcomes recorded in patient diaries and from 2 questionnaires administered at wk 4 and 6 Total number of treated anginal attacks during treatment Buccal GTN = 1381 SL GTN = 1978 p<0.01 Pain severity (read from graph) Buccal GTN Mild = 35% Moderate = 43% Severe = 22% Sublingual GTN Mild = 35% Moderate = 45% Severe = 20% p= non-significant Prevention of expected attack SL GTN = 532/806 (66%) Buccal GTN = 687/929 (74%) p<0.05
Safety and adverse effects	4 patients were withdrawn from the study due to side effects of buccal GTN (headache 3 patients, flushing 1 patient) Side effects reported following active enquiry Headache Buccal GTN = 30% Sublingual GTN =27%

p = non significant

Dizziness
Buccal GTN = 6%
Sublingual GTN =11%
p = non significant

Flush
Buccal GTN = 11%
Sublingual GTN =15%
p = non significant

Smarting sensation in mouth
Buccal GTN = 64%
Sublingual GTN =40%
p <0.05

Does the study answer the question?

This study does not provide high quality data with which to answer the question. It is a poorly reported, open label, cross over RCT of 113 stable angina patients who took buccal and sublingual GTN for the treatment and prevention of angina. Off therapy data were not recorded, some results were narratively described rather than being tabulated, and results were often dichotomised or categorised where a mean value (with SD) would have been more informative. As such, results should be interpreted cautiously.

Significantly fewer anginal attacks occurred and were treated during the buccal GTN period than in the SL GTN period. The severity of pain associated with attacks was similar in each group. Prophylactic buccal GTN prevented significantly more expected angina attacks when compared to prophylactic use of SL GTN.

Effect due to factor in study?

See GRADE

Consistency of results with other studies?

Not applicable

Directly applicable to guideline population?

See GRADE

Internal Validity

Selection, performance, detection bias.

Sandler G;Clayton GA;

Glyceryl trinitrate in angina pectoris: tablet or aerosol?

Ref ID 262

1967 Nov 4

Study Type Randomised Controlled Trial

Funding No details are reported

Number of participant

Quasi RCT with crossover design
n=23
UK study

Inclusion/Exclusion Criteria

Inclusion criteria:
Patients with well-authenticated and typical attacks of angina
Confirmation of myocardial ischaemia with ST depression or junctional depression (QX/QT>50%)demonstrated on exercise test

Exclusion criteria:
not reported

Patient Characteristics

Patients with stable angina of duration range 3-72 months with attacks occurring 3 to 40 times weekly.
Previous MI = 4/23 participants
Age range 39-69 years
Males = 20/23

Recruitment	No details are reported
Setting	Hospital setting
Interventions/ Test/ Factor being investigated	0.26mg (2 puffs) GTN aerosol Identical aerosol placebo 0.5mg sublingual GTN tablet
Comparisons	SL GTN tablet vs GTN spray
Length of Study/ Follow-up	Patients were hospitalised for the duration of the six day trial.
Outcome measures studied	primary and secondary outcomes are not reported. Relevant outcomes : Mean change in exercise undertaken (no of circuits) Mean change in exercise time before angina (seconds)
Results	Exercise tests were made at the same time each day, in the same environment and with the same technical staff. No information about concurrent therapy is reported. Mean change in exercise undertaken (no of circuits): Effect of treatment (SL GTN tablet before exercise) = 80.9 Control (SL GTN tablet given after exercise) = 80.0 Mean change = +0.9 circuits Effect of treatment (GTN Spray before exercise) = 83.5 Control (GTN Spraygiven after exercise) = 81.5 Mean change = + 2.0 p = non significant (reported by author, no SD of means given) Mean change in exercise time before angina (seconds): On treatment: SL GTN tablet given before exercise: mean exercise time = 371.3 Control: SL GTN tablet given after exercise mean exercise time = 332.7 Mean change = + 68.2 secs On treatment: GTN Spray given before exercise mean exercise time = 339.1 Control: GTN Spray givenafter exercise mean exercise time = 350.3 Mean change = +14.5 p = non significant (reported by author, no SD of means given)
Safety and adverse effects	No meaningful data reported
Does the study answer the question?	This quasi RCT with cross over design does not provide reliable data with which to answer the question. It is likely that there is selection and performance bias because of poor randomisation technique increasing the chance of poor allocation concealment. It is unclear to what extent technical staff and patients were blinded to treatments. The trial included 23 patients with stable angina. Patients performed an exercise test each day (6 in total) with one of the three treatments being given before or after exercise according to allocated treatment schedule. No significant differences in the amount of exercise performed or in the time to onset of anginal symptom was identified between the sublingual GTN tablet group and the GTN spray group during testing.
Effect due to factor in study?	No
Consistency of results with other studies?	Not applicable

Directly applicable to guideline population?	Yes
Internal Validity	Selection bias and performance bias

Evidence Extractions

Question: What is the comparative clinical /cost effectiveness of standard antianginal drugs (beta blockers, calcium channel blockers) for the management of angina?

Grading: 1++	High-quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias

Pepine CJ;Handberg EM;Cooper DR;Marks RG;Kowey P;Messerli FH;Mancia G;Cangiano JL;Garcia BD;Keltai M;Erdine S;Bristol HA;Kolb HR;Bakris GL;Cohen JD;Parmley WW;INVEST I;

A calcium antagonist vs a non-calcium antagonist hypertension treatment strategy for patients with coronary artery disease. The International Verapamil-Trandolapril Study (INVEST): a randomized controlled trial

Ref ID 383 2003 Dec 3

Study Type Randomised Controlled Trial

Funding INVEST was supported by the University of Florida and grants from BASF Pharma and Abbot Laboratories.

Number of participant

N= 22576. N=11267 (verapamil,calcium antagonist strategy) ; N=11309 (Atenolol, non- calcium antagoinst strategy)

Inclusion/Exclusion Criteria

Inclusion criteria*
Patients were eligible if they were aged 50 years or older and had documented CAD, with essential hypertension requiring drug therapy. Documented CAD was defined as any of the following: remote (≥3 months prior to enrolment) confirmed MI, coronary angiogram with more than 50% narrowing of at least 1major coronary artery, diagnosis of classic angina pectoris, or concordant abnormalities on 2 different types of signals (electrocardiograms, echocardiograms, and/or radionuclide scans) from stress tests provided that 2 different signals showed findings consistent for ischemia. Patients with heart failure classes I through class III was included.

Exclusion criteria
Patients taking B-blockers within 2 weeks of randomisation or taking B-blockers for an MI that occurred in the previous 12 months were excluded to avoid withdrawal phenomena in patients randomised to the CAS (verapamil) group.

*Trial was designed to compare outcomes in older hypentive patients treated with Verapamil (Calcium antagonist strategy) and Atenolol (non-calcium antagonistic strategy).

Patient Characteristics

Baseline characteristics:
Characteristic- Verapamil: Atenolol
Age (yrs) mean - 66: 66.1
>70 (mean (SD)) - 3694 (32.8): 3829 (33.9)
Women (mean (SD)) – 5850 (51.9): 5920 (52.3)
Angina pectoris- 7463 (66.2): 7582 (67)
Diabetes- 3169 (28.1): 3231 (28.6)
Race/ethnicity
White- 5466 (48.5): 5459 (48.3)
Black- 1506(13.4): 1523 (13.5)
Hispanic- 4021 (35.7): 4024 (35.6)
Asian- 63 (0.6): 86 (0.8)
Other/multiracial- 211 (1.9): 217 (1.9)

Recruitment

Patients recruited from 862 sites in 14 countries.

Setting

Hospitals in 14 countries.

Interventions/ Test/ Factor being investigated

Verapamil 180 mg twice daily or 240 mg/d.

Treatment strategy*:
In Step 1 of the study: Patients received Verapamil sustained release 240 mg/d or Atenolol 50 mg/d;
Step 2: Verapamil sustained release 240 mg/d+ Trandolapril 2 mg/d(ACE inhibitor); Atenolol 50 mg/d+ Hydrochlorothiazide 25 mg/d (Diuretic)
Step 3: Doses increased in both groups
Step 4: Verapamil 180 mg twice daily+ + Trandolapril 2mg twice daily + Hydrochlorothiazide 25 mg/d ; Atenolol 50 mg/d+ Trandolapril 2mg/d+ Hydrochlorothiazide 25 mg twice daily

	Step 5: Maximum tolerated dose, and or add non study antihypertensive medication in both groups. *Trandolapril and Hydrochlorothiazide was administered to achieve blood pressure goals according to guidelines from the sixth report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High blood pressure of less than 140 mm Hg (systolic) and less than 90mm Hg (diastolic); and less than 130 mm Hg (systolic) and less than 85 mm Hg (diastolic) if diabetes or renal impairment was present.
Comparisons	Atenolol 50 mg/d.
Length of Study/ Follow-up	Mean follow-up 2.7 years (range 1 day to 5.4 years). Primary outcome: death (all cause), non fatal MI or non fatal stroke. Additional outcome: time to most serious event, cardiovascular death, angina, cardiovascular hospitalisations,blood pressure.
Outcome measures studied	Death, Non fatal MI, Cardiovascular related death, Cardiovascualr related hospitalisation.
Results	Outcomes: Verapamil (n=11267) vs. Atenolol (n=11309) Death – 873 (7.75%) vs.893 (7.90) [RR 0.98 (95% CI 0.90-1.07)] p=0.72 Non fatal MI- 151 (1.34) vs. 153 (1.35) [RR 0.99 05% CI 0.79-1.24)] P=0.95 Cardiovascular related death- 431 (3.83) vs. 431 (3.81) [RR 1.00 (95% CI 0.88-1.14)] P=0.94 Cardiovascular related hospitalisation - 726 (6.44) vs. 709(6.27) [RR1.03 (95% CI 0.93-1.14) P=0.59 Angina rate - 261 (2.32%) vs. 228 (2.02%) P=0.13 No. of angina episodes/week (mean (SD))- 0.77 (1.31) vs. 0.88 (1.62) (P=0.02) Effects of treatment strategy on primary outcomes on subgroups of patients: Baseline subgroup- Verapamil vs. Atenolol Age ≤70 – 523/7573 vs. 486/7480 [RR 1.06 (95% CI 0.94-1.20)] Age ≥70- 596/3694 vs. 664/3829 [RR 0.93 (95% CI 0.84-1.03)] Female- 524/5850 vs. 540/5920 [RR 0.98 (95% CI 0.88-1.10)] Diabetes- 463/ 3169 vs. 450/3231 [RR 1.05 (95% 0.93-1.18)] Adverse events: Verapamil (n=11267) vs. Atenolol (n=11309) Constipation - 195 (1.73) vs. 15 (0.13) (p<0.001) Dizziness- 154 (1.37) vs. 151 (1.34) (p=0.84) Light-headedness- 48 (0.43) vs. 70 (0.62) (p=0.05)
Safety and adverse effects	Both drug treatments were generally well tolerated in each treatment group.
Does the study answer the question?	Yes. There was significantly lower anginal episodes/week in the Verapamil group compared to the Atenolol group. There were no significant differences between the groups for death (all cause), Non fatal MI, cardiovascular death, cardiovascular hospitalisation.
Effect due to factor in study?	Yes
Consistency of results with other studies?	
Directly applicable to guideline population?	Not completely. However, 66% of the patients had angina pectoris.
Internal Validity	None.

Grading: 1+	Well-conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias

Dargie HJ;Ford I;Fox KM;

Total Ischaemic Burden European Trial (TIBET). Effects of ischaemia and treatment with atenolol, nifedipine SR and their combination on outcome in patients with chronic stable angina. The TIBET Study Group

Ref ID 922 1996 Jan

Study Type Randomised Controlled Trial **Funding** Not reported.

Number of participant	Total N=682. N=226 in Atenolol group; N=232 in Nifedipine group; N=224 in the combination group.
Inclusion/Exclusion Criteria	Inclusion criteria Patients of both sexes aged 40-79 years with stable angina. Patients who had developed recurrent angina following previous coronary artery bypass surgery or percutaneous transluminal coronary angioplasty were also suitable for inclusion, as were those who were asymptomatic on medical therapy. Exclusion criteria Patients with recent myocardial infarction or intervention (<3 months), contra indications to either of the study medications, conduction disturbances or medications likely to effect the interpretation of the ST segment were excluded.
Patient Characteristics	Baseline characteristics: Variable- Atenolol (n=226); Nifedipine (n=232) vs. Combination (n=224) Age yrs (mean SD) – 58.8 (7.6); 60.0 (7.7); 59.7 (7.9) Males- 196; 191; 198 Previous MI- 77; 71; 77 Diabetic- 10; 7; 18
Recruitment	Patients recruited from 69 centres in 9 European countries (Eire, Finland, France, Holland, Italy, Norway, Spain, Sweden, UK).
Setting	Hospitals in 9 countries.
Interventions/ Test/ Factor being investigated	Atenolol 50 mg bd.
Comparisons	1: Nifedipine 20 mg bd. 2: Comination (Atenolol 50 mg +Nifedipine 20 mg). Rel;evant comparisons for the review: Atenolol vs. Nifedipine; Atenolol vs. Atenolol +Nifedipine; Nifedipine vs. Atenolol+Nifedipine
Length of Study/ Follow-up	mean 2yr (1-3 yr). Primary endpoint: cardiac mortality, MI, unstable angina,CABG/angioplasty, treatment failure.Secondary endpoint: time to onset of angina, total duration of exercise, number and duration of ischaemic episodes defined as 1mm ST depression
Outcome measures studied	Cardiac death, Non fatal MI, Unstable angina.
Results	Outcomes: Atenolol vs. Nifedipine vs. Combination (no. of. Patients) Cardiac death: 3/226 vs. 6/232 vs. 13/224 Non fatal MI: 14/226 vs. 15/232 vs. 7/224 Unstable angina: 12/226 vs. 4/232 vs.8/224 Withdrawal due to side effects: Atenolol vs. Nifedipine vs. Combination (no. of patients) 60 vs. 93 vs. 64 Not reported what were the side effects. Exercise test data not reported in this paper.

Safety and adverse effects	Not reported.
Does the study answer the question?	Yes. There were no significant differences between the 3 groups for cardiac mortality, non fatal MI and unstable angina.
Effect due to factor in study?	Yes
Consistency of results with other studies?	
Directly applicable to guideline population?	correct population.
Internal Validity	

Hjemdahl P;Eriksson SV;Held C;Forslund L;Nasman P;Rehnqvist N;

Favourable long term prognosis in stable angina pectoris: an extended follow up of the angina prognosis study in Stockholm (APSIS)

Ref ID 200 2006 Feb

Study Type Randomised Controlled Trial **Funding** This extended follow-up was supported by the Stockholm County Council.

Number of participant	N=809. N=406 Metaprolol group and N=403 Verapamil group. In the extended follow-up the APSIS study cohorts were compared with the general population. The reference population consisted of people from the catchment area (about 65000) who were matched to patients in the APSIS cohort regarding sex and age during each year of follow-up.
Inclusion/Exclusion Criteria	Inclusion criteria Age<70 years and a history of chronic stable angina pectoris. Chest pain was classified as effort induced angina, vasospastic angina, or angina of mixed form. Vasospastic angina was considered when symptoms were not related to exertion. Requirements were episodes of chest pain or discomfort lasting less than 15 minutes and sublingual nitrates, when used, providing prompt relief. When in doubt, additional examinations (perfusion scintigraphy and radiological or gastrointestinal investigations) were performed to confirm the diagnosis. Exclusion criteria MI within the past 3 years (B-blockade was then considered to be indicated, based on a post-MI study); anticipated need for revascularisation within one month; significant valve disease or severe congestive heart failure; other severe diseases; contraindications to either study drug; and risk of poor compliance (for example, suspected alcohol misuse).
Patient Characteristics	Baseline characteristics- Metaprolol: Verapamil Age (yrs) - 59±7; 59±7 Women (%) – 27: 34(p<0.05) Previous history (%) Previous Acute MI-16: 16 CHF- 6:7 Hypertension- 28: 26 Previous cerebrovascular event- 5:4 Previous CABG or PTCA- 5:7 Diabetes mellitus- 8: 9 Median duration of Angina (interquartiles, years) - 2 (0;5.5) : 2 (0;5.6) Canadian Cardiovascular Society (CCS) angina classification (%) I- 27:25 I I- 68: 69 I I I- 5:6 Baseline characteristics of male and female patients in APSIS

	Variable - Men (n-561): Women (n=248) Age (years) – 59 (7): 59 (7) Previous MI- 20%: 7% (P<0.0001) Diabetes Mellitus- 10%: 6%
Recruitment	Patients with a clinical history of angina pectoris were referred to the heart research laboratory at Danderyd Hospital. Referrals came either from general practitioners in the catchment area or from the department of medicine at Danderyd Hospital.
Setting	Hospital (single centre) in Sweden (Stockholm).
Interventions/ Test/ Factor being investigated	Intervention: Metoprolol (100-200 mg once daily). After the study (3.4 years), the patients were referred for usual care with a recommendation to continue randomised treatment openly, since neither drug had a prognostic benefit compared with the other.
Comparisons	Comparison: Verapamil (120-240 mg twice daily).
Length of Study/ Follow-up	Median follow-up was 9.1 years. Primary endpoints were CV death and non fatal MI.
Outcome measures studied	Cardiovascular (CV) death and combined CV events (in comparison with reference subjects); total mortality, fatal and non fatal MI in the APSIS cohort.
Results	Total Mortality (Metaprolol vs. Verapamil) 14.1% vs. 16.3% Fatal MI (Metaprolol vs. Verapamil) 4.2% vs. 5.9% Non fatal MI (Metaprolol vs. Verapamil) 4.3% vs. 4.6% Cardiovascular death (comparison with reference population) Variable- No CV death (n=732) : CV death (n=77) Age (years)- 59 (7) : 62 (6) (p<0.001) Female - 32% : 14% (p<0.001) Diabetes Mellitus - 7% : 21% (p<0.001) Combined events (CV death or non fatal MI) (comparison with reference population) Variable - No CV event (n=670) : Combined CV event (n=139) Age (years) - 59 (8): 62 (6) (p<0.001) Female - 34% :13% (p<0.001) Diabetes Mellitus - 7% :17% (p<0.001) Death (Female vs. Male) (comparison with reference population) 19% vs. 6% (p<0.001) Fatal MI (Female vs. Male) (comparison with reference population) 6.6% vs. 1.6% (p<0.001)
Safety and adverse effects	None.
Does the study answer the question?	Yes. During the double blind phase of APSIS outcomes were similar in the two treatment groups. Results did not change after extended follow-up as total mortality (14.1% vs. 16.3%), fatal MI (4.2% vs. 5.9%) and non fatal MI (4.3% vs. 4.6%) were similar in the original verapamil and metaprolol treatment groups. Compared with the reference subjects, male APSIS patients had a higher mortality (19% vs. 6%) and fatal MI (6.6% vs. 1.6%) compared with female patients. Diabetes mellitus was a strong risk factor among both men and women. When age, sex and diabetes mellitus were included in a multivariate Cox regression model, all these risk markers were significantly (p<0.001) and independently related to prognosis.
Effect due to factor in study?	Yes.
Consistency of results with other studies?	

Directly applicable to guideline population?	Correct population.
Internal Validity	Selection bias.

Rehnqvist N;Hjemdahl P;Billing E;Bj÷rkander I;Eriksson SV;Forslund L;Held C;Nõsman P;WallÚn NH;

Effects of metoprolol vs verapamil in patients with stable angina pectoris. The Angina Prognosis Study in Stockholm (APSIS)

Ref ID 3774 1996

Study Type	Randomised Controlled Trial	**Funding**	The study was supported by grants from the Swedish Heart Lung Foundation, the Swedish Research Medical Council, Knoll AG, Germany and Astra Hassle, Sweden.

Number of participant	N=809. N=406 in the metaprolol group and N=403 in the Verapamil group.
Inclusion/Exclusion Criteria	Inclusion criteria: Inclusion was based on a clinical history of stable angina. The symptoms of angina pectoris had to be presented in a classical way i.e. localised in the central part of the chest with or without radiation and elicited by physical or psychological stimuli. The symptoms had to be relieved gradually by rest or quickly by nitroglycerin. If the description of angina was atypical, complementary tests were undertaken. These included an exercise test, perfusion scintigraphy, radiological examinations and/or gastrointestinal investigations, as indicated. Patients under the age of 70 yrs were included in the study. Exclusion criteria: Exclusion criteria were contraindications to the study drugs, myocardial infarction within the last 3 years, unstable angina or anticipated need for revascularisation within one month. Further more, the presence of other severe disorders, alcohol abuse suspected non compliance, non compensated heart failure, or significant valvular disease.
Patient Characteristics	Baseline characteristics- Metaprolol: Verapamil Age (yrs) - 59±7; 59±7 Women (%) – 27: 34 ($p<0.05$) Previous history (%) Previous Acute MI-16: 16 CHF- 6:7 Hypertension- 28: 26 Previous cerebrovascular event- 5:4 Previous CABG or PTCA- 5:7 Diabetes mellitus- 8: 9 Median duration of Angina (interquartiles, years) - 2 (0;5.5) : 2 (0;5.6) Angina class (%) I- 27:25 I I- 68: 69 I I I- 5:6
Recruitment	Patients with a clinical diagnosis of angina pectoris were referred to the heart research laboratory at Danderyd Hospital. The referred patients were then screened for angina pectoris.
Setting	Hospital in Sweden (Stockholm).
Interventions/ Test/ Factor being investigated	Intervention: Metaprolol (Seloken ZOC 200 mg) once adily.
Comparisons	Comparison: Verapamil (Isoptin Retard 240 mg) b.i.d. Comparison was made between Metaprolol and Verapamil.

Length of Study/ Follow-up	The patients were followed between 6 and 75 months (median 3.4 years). Primary endpoints for follow-up were death, cardiovascular events and 3 psychological variables reflecting quality of life.
Outcome measures studied	Outcomes: Deaths, cardiovascular death, non fatal cardiovascular events, quality of life, side effects.
Results	Outcomes: Metaprolol (n=406) vs. Verapamil (n=403) Death: 22 (5.4%) vs. 25 (6.2%) Cardiovascular death: 19 (4.7%) vs. 19 (4.7%) *Non fatal cardiovascular events: 106 (26.1%) vs. 98 (24.3%) **Quality of life: The range of scales were 39-195 (psychosomatic symptoms), 0-120 (overall life satisfaction) and 9-36 (Sleep disturbances respectively) Variable: Metaprolol (n=275) vs. Verapamil (n=282) Psychosomatic symptoms: 60± 15.6 vs. 61.8±16.6 (p=0.34) Variable: Metaprolol (n=268) vs. Verapamil (n=275) Overall 'life satisfaction': 75.2±25.6 vs.75.9±26.3 (p=0.85) Variable: Metaprolol (n=270) vs. Verapamil (n=275) Sleep disturbances: 16.2±5.2 vs. 16.6±5.5 (p=0.97) Side effects: Metaprolol (n=406) vs. Verapamil (n=403) Total no. of side effects: 54 vs. 69 Gastrointestinal: 10 vs. 22 (p=0.02) Head ache: 3 vs. 4 *The cardiovascular events constituting endpoints included acute MI, incapacitating or unstable angina, cerebrovascular events (including transitory ischemic attacks) of peripheral vascular events (threatening or overt gangrene or surgery for aortic aneurysm). ** The psychological variables included an inventory of psychosomatic symptoms defined by the Cornell Medical Index (scoring range 39-195), an evaluation of sleep disturbances (scoring range 9-36) and an estimate of life satisfaction on a visual analogue scale (range 0-120 mm).
Safety and adverse effects	Withdrawal from the drug treatment due to side effects occurred in 11.1 and 14.6% of metaprolol and verapamil treated patients, respectively (p=0.13). More verapamil treated patients were withdrawn due to gastrointestinal side effects (mainly constipation).
Does the study answer the question?	Yes.
Effect due to factor in study?	Yes. Total mortality in metaprolol and verapamil treated patients was 5.4% and 6.2% respectively. Cardiovascualr mortality was 4.7% in both groups. Non-fatal cardiovascular events occurred in 26.1% and 24.3% of metaprolol and verapamil treated patients, respectively. Psychosomatic symptoms and sleep disturbances were significantly improved in both treatment groups. The magnitudes of change were small and did not differ between treatments. Life satisfaction did not change on either drug. Withdrawals due to side effects occurred in 11.1% and 14.6% respectively.
Consistency of results with other studies?	
Directly applicable to guideline population?	Correct population
Internal Validity	Selection bias.

Grading: 1- Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias*

Kawanishi DT;Reid CL;Morrison EC;Rahimtoola SH;

Response of angina and ischemia to long-term treatment in patients with chronic stable angina: a double-blind randomized individualized dosing trial of nifedipine, propranolol and their combination

Ref ID 1335 1992 Feb

Study Type Randomised Controlled Trial

Funding This study was supported in part by a grant from Pfizer Labs, New York, NY.

Number of participant N=54 (n=36 nifedipine group; n=38 propranolol group)

Inclusion/Exclusion Criteria

Inclusion criteria:
Patients were selected on the basis of 1) a history of chronic stable angina that was mild enough for them to tolerate a 2 week (control period) with only sublingual nitroglycerin and with no prophylactic anti anginal medications. The patients had to have at least three episodes of angina/week and <50% variability in the weekly angina frequency for the 2 months before enrolment in the study. 2) Documented coronary artery disease.

Exclusion criteria
Patients were not enrolled if they had a MI or coronary revascularisation procedure within the previous 3 months or if they had insulin requiring diabetes, bronchospastic lung disease or other diseases symptoms that could be confused with angina pectoris. Patients were also excluded if they had a left bundle branch block, left ventricular hypertrophy, digoxin therapy, treatment with anti arrhythmic agents or any condition or medication that would interfere with interpretation of ST segment changes on the exercise ECG.

Patient Characteristics

Baseline characteristics:
Age (yrs) mean (SD): 57 (7)
Male/female: 49/25
NYHA Angina class
1-4%
2-73%
3-23%

There were no significant differences in the patient characteristics between the 2 groups.

Recruitment Patients were recruited from the LosAngeles County and University of Southern California Medical centre. No further details reported.

Setting Hospital in the USA.

Interventions/ Test/ Factor being investigated

Propranolol 20 mg.
I the beginning participants randomised to receive 20 mg of Propronolol or 10 mg of Nifedipine for 3 months. After 3 months each patient was then randomised to either continuation of the same single drug plus placebo or treatment with both drug for another 3 months.

Comparisons

1) Nifedipine 10 mg (not specified long or short acting)
2) Nifedipine 10 mg +Propranolol 20 mg

Relevant comparisons for the review: 1)Propranolol vs. Nifedipine
2)Propranolol vs. Propranolol +Nifedipine
3) Nifedipine vs. Propranolol +Nifedipine

Length of Study/ Follow-up 3 months and 6 months. Primary and secondary endpoints not stated.

Outcome measures studied Angina frequency, nitroglycerin use, time to onset of angina, total exercise time .

Results	6 months follow-up : Angina frequency (episodes/week): Nifedipine (n=16) vs. Propranolol (n=21) 2.7 ±5.6 vs. 2 ±2.3 Nifedpine (n=16) vs. Nifedipine +Propranolo l(n=19) 2.7 ±5.6 vs. 4.3±7.9 Propranolol (n=21) vs. Propranolol+Nifedipine (n=16) 2 ±2.3 vs. 1.3 ±1.7 Nitroglycerin tablets/week Nifedipine (n=16) vs. Propranolol (n=21) 0.7±1.6 vs. 0.7±1.2 Nifedpine (n=16) vs. Nifedipine +Propranolol (n=19) 0.7±1.6 vs. 1.1±2.2 Propranolol (n=21) vs. Propranolol+Nifedipine (n=16) 0.7±1.2 vs. 0.3±0.4 Time to onset of angina (sec): Nifedipine (n=16) vs. Propranolol (n=21) 304±108 vs. 346±76 Nifedpine (n=16) vs. Nifedipine +Propranolol (n=19) 304±108 vs. 330±155 Propranolol (n=21) vs. Propranolol+Nifedipine (n=16) 346±76 vs. 330±155 Total exercise duration (Sec) Nifedipine (n=16) vs. Propranolol (n=21) 433±132 vs. 433±159 Nifedpine (n=16) vs. Nifedipine +Propranolol (n=19) 304±108 vs. 435±144 Propranolol (n=21) vs. Propranolol+Nifedipine (n=16) 346±76 vs. 435±144
Safety and adverse effects	During the 6 month study period, untoward cardiovascular events (death, non fatal MI, revascualrisation procedure) did not occur in any patient.
Does the study answer the question?	Yes. Treatment with combination of nifedipine and propranolol for 3 months did not result in a significant further reduction of angina frequency, nitroglycerin consumption, time to onset of angina and exercise duration.
Effect due to factor in study?	Yes
Consistency of results with other studies?	
Directly applicable to guideline population?	correct population
Internal Validity	selection bias. Attrition bias.

O'Hara MJ;Khurmi NS;Bowles MJ;Raftery EB;

Diltiazem and propranolol combination for the treatment of chronic stable angina pectoris

Ref ID 1948 1987 Feb

Study Type Randomised Controlled Trial **Funding** Not reported.

Number of participant	n=34 (combination n=23)
Inclusion/Exclusion Criteria	Includion criteria Patients with stable excertional angina relieved by rest or nitroglycerin. Exclusion criteria Patients over 70 years and women of child bearing age were excluded, as were those with a MI within the previous 4 months or with symptoms so severe that it would be unsafe to give them a placebo. Other exclusion criteria were obstructive airways disease, cardiac failure, peripheral vascular disease, sustained hypertension (>160/100), and insulin dependent diabetes. Patients with vasoregulatory abnormalities or who needed to continue taking drugs which might cause false positive ST-segment changes were also excluded.
Patient Characteristics	Age 40-69 yrs. 29 men and 4 women. Other characteristics not reported.
Recruitment	Patients recruited from the Ischemic clinic.
Setting	Hospital in the UK.
Interventions/ Test/ Factor being investigated	Diltiazem (180 or 360 mg/d). First 2 weeks placebo run-in period. Then patients received daily dose of Diltiazem (180 or 360mg/day) or Propranolol (240mg/day) for 4 weeks each. Patients who continued to develop angina on treadmill exercise while on either active treatment received the same dose of diltiazem combined with Propranolol for 4 weeks. If treadmill exercise induced angina persisted, the dose of Propranolol in the combination was increased to 240 mg daily and this therapy was continued for 4 weeks.
Comparisons	1: Propranolol 240 mg/d 2: Diltiazem 180 or 360 mg +Propranolol 240 mg/d Relevant comparisons for the review: Diltiazem vs. Diltiazem +Propranolol Propranolol vs. Diltiazem +Propranolol
Length of Study/ Follow-up	18 weeks (Treadmill test performed after each 4 week active treatment period). 6 months for adverse effects. Primary and secondary endpoints not stated.
Outcome measures studied	Exercise test.
Results	Variable: Diltiazem -360 mg daily (n=34) vs. Propranolol 240 mg daily (n=34) vs. Ditiazem 360 mg + Propranolol 120mg (n=22) vs. Diltiazem 360 mg + Propranolol 240 mg (n=15) [Mean (SE)] Exercise time (mins): 6.5±0.4 vs. 6.8±0.6 vs. 8.6±0.3 vs. 9.6±0.5
Safety and adverse effects	During the 6 month follow-up period 2 death occurred. One suffered from MI anddied suddenly at home ; and the other developed unstable angina and was found to have a sinus bradycardia of <40 beats/min on ambulatory recording. Severe bradycardia refractory to temporary pacing developed in the course of a subsequent exercise test and death occurred in asystole. One patient developed a rash, probably due to diltiazem while on combiantion therapy.
Does the study answer the question?	Yes.
Effect due to factor in study?	Yes
Consistency of results with other studies?	
Directly applicable to guideline population?	correct population
Internal Validity	Selection bias. Attrition bias.

Pehrsson SK;Ringqvist I;Ekdahl S;Karlson BW;Ulvenstam G;Persson S;

Monotherapy with amlodipine or atenolol versus their combination in stable angina pectoris

Ref ID 572 2000 Oct

Study Type Randomised Controlled Trial **Funding** Not reported

Number of participant	N=351 . N=116 atenolol group, n=116 amlodipine group, n=119 atenolol +amlodipine group.
Inclusion/Exclusion Criteria	Inclusion Criteria History of clinically stable angina, defined as precordial discomfort. Tightness heaviness, pain with or without radiation, and dysonea, usually provoked by excertion or cold and relieved within 10 min by nitroglycerin, for atleast 3 months and with atleast 3 anginal attacks per week before the start of the run-in period. Also required was one positive bicycle exercise test, defined as ST depression >1mm within 7 min (max 90 w) in women and within 13 min (max 150 w) in men, with or without chest pain. Exclusion criteria Myocardial infarction, coronary bypass surgery, or percutaneuos transluminal coronary angioplasty in the preceding 3 months, unstable angina, signs and/or symptoms of congestive heart failure, significant arrhythmia, second or third degree atrioventricular block, diastolic blood pressure > 115 mmHg or blood pressure >250 mmHg, and medication influencing ECG (e.g. digoxin or antiarrhythmic drugs). Patients receiving beta-blockers or calcium antagonists that could not be safely withdrawn, those in need of supplementary anti-ischemic medication other than nitroglycerin during the run-in period, or those in need of revascularisation were also excluded.
Patient Characteristics	Baseline characteristics Variable- Amlodipine : Atenolol : Atenolol +Amlodipine Mean age (age range) - 63 (42-80): 63 (42-80): 65 (43-78) Gender (m/f) - 88/28: 92/24: 89/30 Duration of angina (years) - 5+5:5+5: 5+6 No. of attacks per week-5+5: 5+3: 6+5 Insulin dependent diabetes (%): 4:3:3 Non insulin dependent diabetes- 5: 9: 6
Recruitment	Not reported.
Setting	Hospitals. 28 centres in Sweden.
Interventions/ Test/ Factor being investigated	Atenolol 100 mg 3 phases of the study: Phase 1 (1 week): only short acting and long acting nitrates. Phase 2 (4 weeks): Amlodipine 5 mg, Atenolol 50 mg, Amlodipine 5mg +Atenolol 50 mg. Phase 3: 6 week follow-up during which the dose was increased to a forced high level in all patients, except in those who had experienced any adverse effects that could be possibly drug related, or if it could be anticipated that the higher dose would not be tolerated.
Comparisons	1: Amlodipine 10 mg. 2: Amloldipine 10 mg+ Atenolol 100 mg Relevant comparisons for the review: Atenolol vs. Amlodipine +Atenolol Amlodipine vs. Amlodipine +Atenolol
Length of Study/ Follow-up	10 weeks. Primary and secondary endpoints not stated.
Outcome measures studied	Exercise test, anginal episodes, adverse effects.

Results	Exercise test (improvement between study entry and week 10): Variable - amlodipine (n=116) vs. atenolol (116) vs. Amlodipine +Atenolol (n=119) Time to ST depression >1mm (min)- 1.0 vs. 0.8 vs. 0.9 (Intergroup pvalue, p=0.68) Time to onset of angina (min) - 0.8 vs. 1.0 vs. 0.9(Intergroup pvalue, p=0.58) Total exercise time (min) - 0.5 vs. 0.3 vs. 0.4 (Intergroup pvalue, p=0.53) No. of anginal attacks per week – 3.4 vs. 3.7 vs. 3.6 Nitroglycerin consumption (tablets/week) - 2.2 vs. 2.2 vs. 1.7 Adverse effects- (No of patients) Amlodipine (n=116) vs. atenolol (116) vs. Amlodipine +Atenolol (n=119) 69 vs. 52 vs. 59
Safety and adverse effects	Of the 171 patients who reported adverse effects of treatment, 60 (120 reactions) were taking amlodipine, 52 (76 reactions) atenolol, 59 (101) both amlodipine and atenolol. The incidence was significantly lower in the atenolol group than in other groups. There was no statistical intergroup difference for the seven most common adverse effects, except for ankle edema, which occurred more often in patients taking amlodipine alone or in combination with atenolol than in those on atenolol alone.
Does the study answer the question?	Yes. There was no significant differences between groups in terms of time to ST depression,time to onset ofangina, total exercise time,anginal attacks per week and in average weekly consumption of nitroglycerin.
Effect due to factor in study?	Yes
Consistency of results with other studies?	
Directly applicable to guideline population?	correct population
Internal Validity	selection bias, attrition bias.

Savonitto S;Ardissiono D;Egstrup K;Rasmussen K;Bae EA;Omland T;Schjelderup MP;Marraccini P;Wahlqvist I;Merlini PA;Rehnqvist N;

Combination therapy with metoprolol and nifedipine versus monotherapy in patients with stable angina pectoris. Results of the International Multicenter Angina Exercise (IMAGE) Study

Ref ID 942 1996 Feb

Study Type	Randomised Controlled Trial	**Funding**	This study was supported in part by a research grant from AB Hassle, Molndal, Sweden.

Number of participant	N=280 (data reported/analysed for n=249 patients who completed the study) [n=l 128 Metoprolol gorup;n=121 Nifedipine group]
Inclusion/Exclusion Criteria	Inclusion criteria: Patients had to report typical anginal symptoms that had been stable for ≥6 months and show a positive response to exercise testing with ≥3 min of exercise tolerance. Exclusion criteria: The exclusion criteria included >75 yrs of age, recent (<6 months) MI, heart failure and angina of such severity that even temporary withdrawal of antianginal therapy was not feasible. Patients with concomitant diseases, including obstructive lung disease and insulin dependent diabetes mellitus, or with haemoglobin levels< 11 g/dl or systolic blood pressure < 100 mm Hg, were also excluded. Only patients with sinus rhythm who had an analyzable ST segment on electrocardiography were included.
Patient Characteristics	Variable: Metoprolol+placebo : MetoprololNifedipine: Nifedipine+Placebo: Nifedipine +Metoprolol Age (yrs) : 59±8: 59±8: 60±8: 59±9 Gender (M/F): 56/9: 53/10: 51/11: 45/14 Diabetes: 3: 2: 3: 4 Anginal episodes/week: 5.7±7: 5.2±5: 5.4±6: 7.1±9

Recruitment	Not reported.
Setting	Hospitals from 25 European centres.
Interventions/ Test/ Factor being investigated	Metoprolol 200mg once daily. A baseline symptom-limited exercise test was performed and the patients were randomly assigned to Metoprolol or Nifedipine according to a parallel group design. After this period, the metoprolol treated patients were further randomised to the addition of placebo or nifedipine for a further 4 weeks, and the nifedipine treated patients were assigned to the addition of placebo or metoprolol.
Comparisons	1. Nifedipine 20 mg twice daily. 2. Nifedipine 20 mg +Metoprolol 100 mg Relevant comparisons for the review: Metprolol vs. Nifedipine; Metoprolol vs. Metoprolol +Nifedipine; Nifedipine vs. Metoprolol +Nifedipine.
Length of Study/ Follow-up	6 weeks for monotherapy and 10 weeks for combination. Primary and secondary endpoints were not stated.
Outcome measures studied	Weekly number of anginal attacks, time to 1mm ST segment depression, withdrawals due to cardiovascular events and side effects.
Results	Effect of treatment on Time to ST segment depression (sec): 6 weeks : Metoprolol (n=128) vs. Nifedipine (n=121) Mean increase (95% CI): 70 (95% 47-92) VS. 43 (95% CI 16-69) 10 weeks: Metoprolol + Placebo (n=65) vs. Nifedipine +placebo (n=62) Mean increase (95% CI): 49 (95% CI 17-80) vs. 37 (95% CI 1-72) 10 Weeks : Metoprolol +placebo (n=65) vs. Metoprolol +Nifedipine (n=63) Mean increase (95% CI): 49 (95% CI 17-80) vs. 108 (95% CI 71-145) 10 weeks: Nifedipine +placebo (n=62) vs. Nifedipine +Metoprolol (n=59) Mean increase (95% CI): 37 ((95% CI 1-72) vs. 107 (95% CI 64-151) Effect of treatment on weekly no. of anginal attacks: 6 weeks: Metoprolol (n=122) vs. Nifedipine (n=118) Mean difference (95% CI): -1.95 (95% CI -1.26 to -2.64) vs. -1.57 (95% CI -0.69 to -2.45) 10 weeks: Metoprolol+placebo (n=61) vs. Nifedipine +placebo (n=61) Mean difference (95% CI): -2.01 (95% CI -0.82 to -3.19) vs. -2.32 (95% CI-0.70 to -3.93) 10 weeks: Metoprolol +placebo (n=61) vs. Metoprolol +Nifedipine (n=61) Mean difference (95% CI): -2.01 (95% CI -0.82 to -3.19) vs. -2.06 (95% CI -1.11 to -3.02) 10 weeks: Nifedipine +placebo (n=61) vs. Nifedipine +Metoprolol (n=57) Mean difference (95% CI):-2.32 (95% CI -0.70 to -3.93) to -2.71 (-1.93 to -3.80)
Safety and adverse effects	There were 14 cardiovascular events including 1 sudden death, 3 acute MI, 8 cases of unstable angina, 1 of syncope and 1 of stroke. The incidence of these events did not differ among treatment groups. Ten patients (3.5% of the total study group) dropped out of the study because of drug related side effects that were among those expected from Metoprolol and Nifedipine. No patient withdrew because of side effects during combination therapy.
Does the study answer the question?	Yes. There was no significant difference in angina frequency between groups at 10 weeks. There was significant improvement in exercise time with combination therapy at 10 weeks.
Effect due to factor in study?	Yes.
Consistency of results with other studies?	

Directly applicable to guideline population? correct population

Internal Validity Selection bias. Attrition bias.

Singh S;

Long-term double-blind evaluation of amlodipine and nadolol in patients with stable exertional angina pectoris

Ref ID 8368 1993

Study Type Randomised Controlled Trial **Funding** Not reported

Number of participant Total N=80. N=40 in the Amlodipine group and N=40 in the Nadolol group.

Inclusion/Exclusion Criteria

Inclusion criteria:
Males and females aged 18 to 80 years with typical symptoms of angina pectoris that is chest pain usually precipitated by exertion and lasting 1-10 min. The participants also had to have a significant ST-segment deviation (of ≥1 mm) after exercise at the end of a 2 week single blind placebo run in period and at least 3 angina attacks during the period.

Exclusion criteria:
Patients with significant hepatic, renal, cardiac, bronchospastic or any other major concurrent disease were excluded. Women of childbearing potential were also excluded. Concomitant antianginal drug therapy was discontinued at least 1 week before the study, with the exception of sublingual nitroglycerin (which could be taken therapeutically but not prophylactically during the study).

Patient Characteristics Demographic details of patients:

Amlodipine group:
No. of patients - 40
Male: Female- 35:5
Mean age (years) – 64.7
Age range (years)- 46-79
White - 34
Black- 5
Hispanic-1
Mean duration of angina (months)- 79.8
Severity of attacks-
Mild- 23
Moderate- 16
Severe – 1

Nadolol group:
No. of patients – 40
Male: Female- 36:4
Mean age (years) – 62.2
Age range (years)- 41-77
White- 34
Black- 6
Hispanic-0
Mean duration of angina (months)- 78.3
Severity of attacks-
Mild- 22
Moderate-17
Severe – 1

Recruitment Method of recruitment not reported.

Setting Medical centres in the USA (multi centres)

Interventions/ Test/ Factor being investigated Intervention: Amlodipine (2.5 -10 mg) once daily. The mean final daily dosage was 7.5 mg for Amlodipine. 24 patients had the dosage adjusted to receive 10mg amlodipine once daily, 11 received 5mg amlodipine, and remaining 5mg amlodipine throughout the study.

Comparisons	Compariosn: Nadolol (40-160 mg) once daily. 16 patients received 160 mg nadolol, 17 received 80 mg, and 7 received 40 mg nadolol once daily. Study consisted of 2 week placebo run in followed by a 26 week comparison of amlodipine and nadolol.
Length of Study/ Follow-up	After 12 weeks and 24 weeks of therapy. Primary and secondary endpoints not stated.
Outcome measures studied	Outcomes: Total exercise time, time to angina onset, ST-segment depression, angina attack rate and nitroglycerin consumption (patient diary), severity of angina (patient and investigator assessment), side effects.
Results	Total exercise time: After 24 weeks of treatment, both therapies produced small changes in the total exercise time when compared with baseline values (+2% amlodpine; -3% nadolol) from 454 s to 462 s after amlodipne and 490 s to 475 s after treatment with nadolol. The difference between treatments was not statistically significant. Similar results were obtained after endpoint analysis. Time to angina onset: Treatment with amlodipine produced a greater increase in the time to onset than nadolol (+21% amlodipine; +8% nadolol). These increases were from a baseline value of 339 s to a final value of 411 s with Amlodipine, compared with 393s to 424s after treatment with nadolol. The difference between treatments did not reach statistical significance. Similar results were obtained after endpoint analysis. ST-Segment depression: Both treatments produced decrease in mean absolute ST-segment depression on exercise (-9% mean change from baseline with Amlodipine; -21% with nadolol). The difference was not statistically significant. Similar results were obtained after endpoint analysis. Angina attack rate and nitroglycerin (NTG) consumption: A greater reduction in the median number of angina attacks per week was produced by Amlodipine (from 4 to 0.3 attacks/week) compared with Nadolol (from 3 to 0.3 attacks/ week).However, the difference between treatments was not statistically significant. Similar results were obtained after endpoint analysis. Likewise, Amlodipine reduced the requirement for NTG tablets from a median value of 2 to 0.3 tablets/week compared with 1.6 to 0.1 tablets/week with Nadolol. The difference between treatments was not statistically significant. Severity of Angina: In the Amlodipine group, 18 patients rated the severity of their angina as moderate/severe at baseline compared with only 11 as moderate and 1 as severe after therapy. In the nadolol group, 21 patients were rated as moderate/severe at baseline and 16 as moderate/severe/ very severe after treatment. At the end of the treatment, 74% (29/39) were rated by the investigator as moderate/markedly improved with amlodipine compared with 54% (21/39) after treatment with nadolol. Incidence of side effects: Amlodipine vs. Nadolol No. patients evaluable - 40 vs. 40 No. patients with side effects- 17 vs. 33 No. patients withdrawn with side effects- 3 vs. 4 Most frequent reported side effects: Amlodipine vs. Nadolol Bradycardia- 1 vs. 16 Palpitations- 4 vs. 6 Peripheral oedema- 4 vs. 2 Dizziness- 5 vs. 10 Headache-9 vs. 7 Hypoesthesia- 3 vs. 0 Flushing- 3 vs. 0 Somnolence-0 vs. 3 Nausea- 2 vs.5 Fatigue- 2vs. 6 Dyspnoea- 3 vs. 6

Safety and adverse effects	A greater no. of patients receiving nadolol reported side effects (83%) compared with amlodipine (43%). Two patients on amlodipine discontinued therapy because of side effects possibly related to treatment (one with shortness of breath and one with edema, itching and rash). One patient in the amlodipine group withdrew due to treatment unrelated side effects (urticaria). Four patients on nadolol withdrew from the study; three of these suffered side effects related to nadolol treatment (one with dizziness, one with increased dyspnoea and increased angina, and one with bradycardia).
Does the study answer the question?	Yes. The effects of amlodipine and nadolol on total exercise time were minimal and not statistically significant. However, amlodipine produced a slightly but not significantly greater increase in time to onset of angina than nadolol (+21% amlodipine; +8% nadolol). No significant differences were noted between amlodipine and nadolol on ST-segment depression, angina attack rate or nitroglycerin consumption. A slightly greater improvement was attained after amlodipine on patient and investigator assessment of severity of angina. Fewer side effects were reported with amlodipine (43%) than with Nadolol (83%) ($p<0.0001$).
Effect due to factor in study?	Yes
Consistency of results with other studies?	
Directly applicable to guideline population?	Correct population
Internal Validity	Selection bias, attrition bias

Tweddel AC;Beattie JM;Murray RG;Hutton I;

The combination of nifedipine and propranolol in the management of patients with angina pectoris

Ref ID 2530 1981 Aug

Study Type Randomised Controlled Trial **Funding** Not reported

Number of participant	n=25
Inclusion/Exclusion Criteria	Not reported. Of the 25 patients selected, each had stable angina of more than 3 months duration and reproducible exertional chest pain.
Patient Characteristics	Not reported.
Recruitment	Not reported.
Setting	Hospital in the UK.
Interventions/ Test/ Factor being investigated	Propranolol (exact dose not reported). After an initial placebo phase patients were commenced on Propranolol, with increasing doses at weekly intervals until a resting heart rate of less than 60 beats/min was obtained, and there was a 30% reduction in exercise tachycardia. Patients were then randomly allocated to the addition of placebo or nifedipine in a dose of 10mg, three times daily to their B-blocker therapy in a double blind cross over fashion over two consecutive 3 week periods. Finally the B-blocker dose of Propranolol was gradually halved over a 2 week period. Patients continued on the 50% B-blocker dose and Nifedipine for a further 2 weeks.
Comparisons	Nifedipine 10 mg , 3 times daily + Propranolol (dose not reported) Relevant comparison for the review: Propranolol vs. Nifedipine+ Propranolol
Length of Study/ Follow-up	10 weeks. Primary and secondary endpoints not stated.
Outcome measures studied	Exercise test, anginal frequency

Results	Exercise time:[Mean (SE) N=18] Propranalol vs. Nifedipine +Propranolol vs. Nifedipine +1/2 Propranolol 4.8±0.4 vs. 4.82±0.5 vs. 5.06±0.4 Anginal frequency (anginal attacks per day) :n=18 Propranalol vs. Nifedipine +Propranolol vs. Nifedipine +1/2 Propranolol 7±2 vs.5±2 vs.4±2
Safety and adverse effects	Two patients died, one during escalation of the dosage of propranolol and the second having just started on Nifedipine therapy. One patient suffered a MI, one patients anginal pattern became unstable. Authors reported- None of the patients reported adverse side effects related to Nifedipine therapy in combination with propranolol and no abnormality was found on routine haematological and biochemical screening.
Does the study answer the question?	Yes.The combination of Nifedipine and Propranolol was shown to be effective with an increase in exercise time to angina. There was an associated reduction in anginal attack rate.
Effect due to factor in study?	Yes
Consistency of results with other studies?	
Directly applicable to guideline population?	correct population
Internal Validity	Selection bias. Attrition bias.

van Dijk RB;Lie KI;Crijns HJ;

Diltiazem in comparison with metoprolol in stable angina pectoris

Ref ID 1719 1988 Nov

Study Type Randomised Controlled Trial **Funding** Not reported

Number of participant	N=33 in both metaprolol and groups (cross over trial)
Inclusion/Exclusion Criteria	Inclusion criteria: Patients with a history of typical stable angina induced by moderate exercise, cold or emotions and significant ST-segment changes (horizontal or downsloping ST-segment depression of 1 mm or more) on the pre-entry bicycle exercise tolerance test (ETT) as well as on the ETT that was performed after the two week running in period. Exclusion criteria: Unstable angina; occurrence of a myocardial infarction within the preceding 3 months; severe aortic stenosis; congestive heart failure; severe hypertension; bradycardia (less than 50 beats min); sick sinus syndrome; uncontrolled cardiac arrhythmias for which antiarhythmic medication was indicated; any degree of AV block; bundle branch block at rest or during exercise; and any other serious medical disease.
Patient Characteristics	Not reported.
Recruitment	Not reported.
Setting	Hospital in the Netherlands.
Interventions/ Test/ Factor being investigated	Metaprolol 200 mg (100 mg two times daily) for 6 weeks.

Comparisons	Diltiazem 240 mg (60 mg 4 times daily) for 6 weeks. Dose adjustment to either360 mg (120 t.i.d) or 400 mg metoprolol (200 b.i.d) was allowed two weeks after the start of treatment.
Length of Study/ Follow-up	End of 6 weeks of treatment for each drug. Primary and secondary endpoints not stated.
Outcome measures studied	Exercise test, weekly angina frequency.
Results	Outcome (mean (SD)): Diltiazem (n=33) vs. Metoprolol (n=33) Exercise duration in mins- 10.0 (3.4) vs. 9.8 (3.1) Time to angina in mins- 7.0 (3.5) vs. 7.4 (4.4) Max. ST segment depression- 1.3 (1.1) vs. 1.2 (1.0) Weekly angina frequency- 2.5 (5.2) vs. 2.5 (3.0)
Safety and adverse effects	Not reported
Does the study answer the question?	Yes. Compared to baseline both drugs reduced the number of anginal attacks and showed improvement of the measured exercise variables.
Effect due to factor in study?	Yes
Consistency of results with other studies?	
Directly applicable to guideline population?	correct population.
Internal Validity	Selection bias, attrition bias.

Vliegen HW;van der Wall EE;Niemeyer MG;Holwerda NJ;Bernink PJ;de WP;Bosma AH;van der Wieken LR;Timmermans AJ;Molhoek GP;

Long-term efficacy of diltiazem controlled release versus metoprolol in patients with stable angina pectoris

Ref ID 1350 1991

Study Type	Randomised Controlled Trial	**Funding**	Not reported. But the authors have acknowledged Lorex Pharmaceutica B.V for supply of Diltiazem CR.

Number of participant	n=56 (n=26 metoprolol, n=30)
Inclusion/Exclusion Criteria	Inclusion criteria: Patients with stable effort induced angina pectoris for at least 3 months, relieved by sublingual nitrates, and had had more than three anginal attacks /week. All patients had to have a positive baseline exercise test as defined by 1mm ST segment depression 0.08s after the J point of the ECG, and they had to achieve a workload of at least 60 W during the exercise tolerance test. Patients were between 21 and 79 yrs of age. Women had to have proof of coronary insufficiency, such as an angiographic demonstration of >70% obstruction in one or more major coronary arteries, a documented MI, or a diagnostic positive thallium perfusion test during exercise. Exclusion criteria: Patients were not eligible for entry in to study if one or more of the following conditions was present: unstable angina pectoris; recent MI (<3 months previously); by-pass surgery <3 months previously; severe valvular disease; congestive heart failure; moderate or severe hypertension; a functioning cardiac pacemaker; atrial fibrillation or sever symptomatic arrhythmias; resting ECG abnormalities that render the interpretation of ST-segment changes difficult; bundle branch block at rest or during exercise; any degree of atrioventricular block; contraindication to the use of diltiazem or metoprolol; inability to perform an exercise test or adhere to the protocol

	for whatever reason; the presence of any condition disregulating the pharmacokinetics of the medication during the study that might interfere with the efficacy or adverse effects of diltiazem or metoprolol; pregnancy or lactation in women; or any other serious medical disease.
Patient Characteristics	At baseline, the patient groups differed slightly in age and height: the mean age in the diltiazem group was 58±9 yrs and in the metoprolol group was 64±9 yrs ($p<0.05$); mean height was 174±8 cm in the diltiazem group as compared to 169±9 cm in the metoprolol group ($p<0.05$). No differences between the 2 groups were seen in weight, gender, and smoking habits. Drop-out >20% (30.3%)33% in the diltiazem group and 26% in the Metoprolol group).
Recruitment	Not reported.
Setting	Hospitals in the Netherlands (Multicentre study)
Interventions/ Test/ Factor being investigated	Metoprolol 100 mg b.i.d. The treatment was preceded by a 2 week run-in period. If the patients were already taking antianginal medication (other than short acting nitrates) this was gradually discontinued.In the second week of the run-in period, only short acting nitrates were used by all patients. If the patients were not taking antianginal medication , the single blind run-inperiod was 1 week.
Comparisons	Diltiazem 120 mg b.i.d.
Length of Study/ Follow-up	Follow-up 8 weeks, 20 weeks and 32 weeks. Primary and secondary endpoints not stated.
Outcome measures studied	Duration of exercise (min), time to onset of angina (min),time to 1 mm ST depression, Maximum ST depression, frequency of anginal attacks per week, side effects.
Results	Note: Values of results reported graphically. Below results reported as in the text of the paper. Exercise test (32 weeks): During treatment, mean changes in duration of exercise, time to angina pectoris, time to 1 mm ST segment depression, maximal ST segment depression were not significantly different between the patients on diltiazem and those on Metoprolol. However at 20 weeks, exercise duration was longer in patients on Diltiazem than in patients on Metoprolol. Frequency of angina (8 weeks): The mean frequency of anginal attacks/ week decreased in Diltiazemgroup from 5.9 at baseline to 3.5 during treatment ($p<0.05$) and in the metoprolol group from 7.4 at baseline to 4.7 during treatment ($p<0.01$). No difefrences were observed between the two treatment groups. Side effects: No significant differences were found in incidence and severity of side effects in 2 groups.
Safety and adverse effects	Almost all of side effects reported were mild. Fatigue and sleep disturbances were slightly more often seen in the metoprolol group.
Does the study answer the question?	Yes. No significant differences between Diltiazem and Metoprolol in exercise duration, time to onset of angina, maximum ST depression, frequency of anginal attacks/ week and side effects.
Effect due to factor in study?	Yes
Consistency of results with other studies?	
Directly applicable to guideline population?	Correct population.
Internal Validity	Attrition bias.

Morse JR;Nesto RW;

Double-blind crossover comparison of the antianginal effects of nifedipine and isosorbide dinitrate in patients with exertional angina receiving propranolol

Ref ID 2091 **RID:** 212 1985 Dec

QUALITY

A. Selection bias (systematic differences between the comparison groups)

A4 Based on your answers t, in your opinion was selection bias present? If so, what is the likely direction of its effect?:

High risk of bias **Direction =**

B. Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)

B4 Based on your answers to the above, in your opinion was performance bias present? If so, what is the likely direction of its effect?:

Unclear/unknown risk **Direction =**

C. Attrition bias (systematic differences between the comparison groups with respect to loss of participants)

C4 Based on your answers to the above, in your opinion was attrition bias present? If so, what is the likely direction of its effect?:

High risk of bias **Direction =**

D. Detection bias (bias in how outcomes are ascertained, diagnosed or verified)

D6 Based on your answers to the above, in your opinion was detection bias present? If so, what is the likely direction of its effect?:

low risk of bias **Direction =**

Overall Study Quality -Strengths and Weaknesses:

Strengths- randomised cross over, double blind, drop out 10%

Weakness- small sample size (n=30), allocation concealment not reported, intention to treat analysis not reported, data cannot be analysed as results reported graphically.

DETAILS

# of patients: n=30 (n=27 analysed)

Prevalence (Diagnostic):

Patient Characteristics	Male: n=23 Female: n=4 Mean age: 61.2 years (range 45 to 74) History of previous MI: n=12 Positive coronary angiogram: n=25 All patients except one had an exercise tolerance test diagnostic of myocardial ischemia before study entry. Inclusion criteria: All patients were between 35 and 75 years of age and were required to have had atleast 4 episodes of angina per week during the month before study enrollment despite propranolol therapy. Exclusion criteria: If patients had evidence of symptomatic congestive heart failure, arrhythmias refractory to conventional therapy, uncontrolled hypertension or insulin dependent diabetes mellitus. Patients who had had a MI within the month before enrollment or who had undergone aorto coronary bypass surgery within the 6 month period before enrolment were excluded from the study.
Interventions/ Test/ Factor being investigated	Propranolol + Isosorbide dinitrate (adjunctive isosorbide) . The median dose of Propranolol was 120 mg/day (range 60-240). The average daily dose of isosorbide dinitrate was 90.4mg/day.
Comparisons	Propranolol + Nifedipine. The average daily dose of Nifedipine was 77.0 mg/day for.
Length of Study/ Follow-up	Patients followed up for 15 weeks.
Outcome measures studied	Primary and secondary endpoints not stated. Primary outcomes: Anginal attacks, nitroglycerin consumption, total exercise time.
Results	
Effect Size	Cannot be analysed as data reported graphically.
Source of funding:	The study was supported from a grant from Pfizer Laboratories Division, Pfizer Pharmaceuticals, New York.
Does the study answer the question?/Further Comments	No. The authors report that the combination of nifedipine and propranolol was superior to the combination of isosorbide and propranolol in reducing the number of anginal attacks ($p=0.03$) and increasing total exercise time ($p<0.02$). Although nitroglycerin consumption was reduced from baseline levels during combination nifedipine therapy ($p<0.001$), there was no statistical difference between nifedipine combination therapy and isosorbide combination therapy.

de Vries RJ;Dunselman PH;van Veldhuisen DJ;van den Heuvel AF;Wielenga RP;Lie KI;

Comparison between felodipine and isosorbide mononitrate as adjunct to beta blockade in patients > 65 years of age with angina pectoris

Ref ID 9109 RID: 462 1994

QUALITY

A. Selection bias (systematic differences between the comparison groups)

A4 Based on your answers t, in your opinion was selection bias present? If so, what is the likely direction of its effect?:

Unclear/unknown risk

Direction =

B. Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)

B4 Based on your answers to the above, in your opinion was performance bias present? If so, what is the likely direction of its effect?:

Unclear/unknown risk

Direction =

C. Attrition bias (systematic differences between the comparison groups with respect to loss of participants)

C4 Based on your answers to the above, in your opinion was attrition bias present? If so, what is the likely direction of its effect?:

Unclear/unknown risk

Direction =

D. Detection bias (bias in how outcomes are ascertained, diagnosed or verified)

D6 Based on your answers to the above, in your opinion was detection bias present? If so, what is the likely direction of its effect?:

Low risk of bias

Direction =

Overall Study Quality -Strengths and Weaknesses:

Strengths- Randomised, double blind, cross over, single centre, sample size calculation reported, 4/46 (8.6%) lost to follow-up*
Weakness- Allocation concealment not reported, Intention to treat analysis not reported.

*Of the 46 patients, 4 did not complete the study: 1 receiving placebo was withdrawn from the study due to development of unstable angina; 2 receiving ISMN stopped because of persistent headaches; and 1 patient experienced a transient ischemic attack during felodipine treatment. Of the 42 patients who completed the study, 6 had ≥ 1 technically inadequate exercise test, leaving 36 patients who were used for primary analysis.

DETAILS

# of patients: n=46 (cross over)

Prevalence (Diagnostic):

Patient Characteristics

Baseline characteristics: (n=46)
Age (yrs): 72±5
65-70 yrs: 20
71-75 yrs: 15
76-80 yrs: 11
M/F: 32/14
Duration of angina (years): 2.7±3.4
<1 year: 22

	1-5 years: 17 >5 years: 7 NYHA class II /III: 44/2 B-blocker medication- Metoprolol: 37 Atenolol: 5 Other: 4 Other concomitant cardiac medication Aspirin: 20 Diuretics: 10 Previous MI: 16 During the study, only sublingual nitroglycerin was allowed for treatment of anginal attacks, in addition to fixed dose B-blockade and the study medication. Except for diuretics, cardiovascular drugs (and cimetidine) were not allowed. Inclusion criteria: 1)Age between 65 and 80 years 2) regular sinus rhythm with a PR interval <0.20 second 3) documented stable angina pectoris (New York Heart Association class II to III) diagnosed ≥2 months before the start of the study and despite optimal B-blocker mono therapy 4) reproducible exercise test, which was limited by angina pectoris, as rated by the Borg scale, and signs of myocardial ischemia occurring within 12 minutes. Exclusion criteria were: unstable angina pectoris, hypotension (systolic blood pressure <100 mm Hg), myocardial infarction, coronary angioplasty or cardiac surgery all within the previous months, second or third degree atrio ventricular block, significant ST segment abnormalities at rest, symptoms of chronic heart failure, chronic obstructive pulmonary disease, relevant hepatic, hematologic, or renal disease, insulin-dependent diabetes mellitus, psychiatric illness, and known intolerance of the study drugs or physical inability to perform the exercise test, or any reason to discontinue exercise testing other than chest pain at entry to the study.
Interventions/ Test/ Factor being investigated	ISMN*(10 mg twice daily for the first 2 days, and 20 mg twice daily there after) or matching placebo.*Fixed dose B-blocker given for both groups.
Comparisons	Felodipine extended release 5 mg daily or matching placebo.
Length of Study/ Follow-up	Follow-up 12 weeks
Outcome measures studied	Primary and secondary endpoints not reported. Outcomes: Exercise time (sec), time to onset of angina (sec),time to 1 mm ST segment depression (sec), anginal attacks/per week, nitroglycerin consumption per week, adverse effects
Results	
Effect Size	Results: mean (95% CI) Outcome: Felopdipine +BB (n=36) vs. ISMN +BB (n=36) Exercise time (sec): 22 (44 to -1) vs. 12 (35 to -11) Time to angina pectoris (sec): 52 (86 to 18) vs. 21 (55 to -14) time to 1 mm ST segment depression (sec): 50 (90 to 10) vs. 3 (43 to -38) (p=0.02) Headache: 4 vs. 10 Adverse events (overall): 15 vs. 22 stopping due to adverse events : 14 vs. 22 Anginal attacks and nitroglycerin consumption (data not reported): There were no significant group differences with respect to the incidence of anginal attacks per week, and the number of nitroglycerin tablets required was also similar. In general, nitroglycerin consumption was low, and only a few anginal attacks were reported by the patients during the whole study. Adverse effects: Felodipine +BB (N=43) vs. ISMN +BB (N=46)

	Headache: 4 vs. 10 Cerebro vascular disorder: 1 vs. 1 Any adverse event: 14 vs. 22 Serious adverse events*: 2 vs. 1 Stopping due to adverse events: 2 vs. 8 *ISMN (1 transient ischemic attack and 1 unstable angina); Felodipine (transient ischemic attack)
Source of funding:	This study was supported by a grant from Astra/Hassle, Molndal, Sweden.
Does the study answer the question?/Further Comments	Yes. There was no significant difference between the groups for exercise duration, time to onset of angina. Time to 1mm ST segment depression and adverse events. Authors conclusion: Felodipine, but not ISMN , leads to an additional significant reduction in ischemic parameters during exercise. Also Felodipine was significantly better tolerated than ISMN.

Poole-Wilson PA;Lubsen J;Kirwan B;van Dalen FJ;Wagener G;Danchin N;Just H;Fox KAA;Pocock SJ;Clayton TC;Motro M;Parker JD;Bourassa MG;Dart AM;Hildebrandt P;Hjalmarson +;Kragten JA;Molhoek GP;Otterstad J;Seabra-Gomes R;Soler-Soler J;Weber S;

Effect of long-acting nifedipine on mortality and cardiovascular morbidity in patients with stable angina requiring treatment (ACTION trial): randomised controlled trial

Ref ID 3319 RID: 468 2004 Sep 4

QUALITY

A. Selection bias (systematic differences between the comparison groups)

A4 Based on your answers t, in your opinion was selection bias present? If so, what is the likely direction of its effect?:

Low risk of bias **Direction =**

B. Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)

B4 Based on your answers to the above, in your opinion was performance bias present? If so, what is the likely direction of its effect?:

Unclear/unknown risk **Direction =**

C. Attrition bias (systematic differences between the comparison groups with respect to loss of participants)

C4 Based on your answers to the above, in your opinion was attrition bias present? If so, what is the likely direction of its effect?:

Low risk of bias **Direction =**

D. Detection bias (bias in how outcomes are ascertained, diagnosed or verified)

D6 Based on your answers to the above, in your opinion was detection bias present? If so, what is the likely direction of its effect?:

Low risk of bias **Direction =**

Overall Study Quality -Strengths and Weaknesses:

Strengths- Sample size calculation reported. Baseline comparison made. Allocation concealment reported. Blocked randomistion. Drop-out <20% (12.8% in the Nifedipine group and 12.2% in the placebo group). Intention to treat analysis reported.
Weakness- Blinding not reported

DETAILS

# of patients:

n=7665 (n=3825 in nifedipine group and 3840 in placebo group)

Prevalence (Diagnostic):

Patient Characteristics

Baseline characteristics
Variable: Nifedipine +Basic regimen (n=3825): Placebo +basic regimen (n=3840)
Age (years)mean (SD): 63.5 (9.3) ; 63.4 (9.3)
Men: 3041 (80%) - 3043 (79%)
no history of coronary artery disease:13 (0.3%) ; 21 (0.5%)
Past use of calcium antagonists:854 (22%); 823 (21%)
Current NYHA class 1-3- 1756 (46%): 1776 (46%)
Anginal attacks- 3544 (93%):3256 (92%)
Diabetes mellitus- 565 (15%):545 (14%)

Concomitant treatments at baseline:
Antianginal drug: Nifedipine +Basic regimen (n=3825): Placebo +basic regimen (n=3840)
B-blocker- 3032 (79%): 3066 (80%)
Organic nitrate, as needed- 2157 (56%): 2175 (57%)
Organic nitrate, daily maintenance- 1455 (38%): 1417 (37%)
Other vasodilator- 158 (4%): 148 (4%)
Any of the above- 3775 (99%):3784 (99%)
Any two of the above- 1888 (49%): 1960 (51%)
Any three or four of the above- 563 (15%): 520 (14%)
Lipid lowering:
Statin- 2409 (63%): 2389 (62%)
Fibrate 242 (6%): 246 (6%)
Other- 45 (1%): 68 (2%)
Any of the above- 2607 (68%): 2591 (67%)
Blood pressure lowering:
ACE inhibitor – 771 (20%): 792 (21%)
Angitensin II antagonist- 90 (2%):93 (2%)
Diuretic – 432 (1%): 447 (12%)
Other- 113 (3%): 81 (2%)
Any of the above- 1165 (30%): 1166 (30%)

Inclusion criteria:
Three categories of ambulatory patients who were age 35 years or older, had angina pectoris that had been stable for at least 1 month, and needed oral or transdermal treatment either to treat or prevent anginal attacks were eligible for the study: 1) those with a history of MI 2) those with angiographic coronary artery disease but no history of MI 3) those with a positive exercise test or perfusion defect who had never had coronary angiography and had no history of MI.

Exclusion criteria:
Reasons for exclusion were: overt heart failure; any major cardiovascular event or intervention within the past 3 months; planned coronary angiography or intervention; known intolerance to dihydropyridines; clinically significant valvular or pulmonary disease; unstable insulin-dependent diabetes mellitus ; any gastro intestinal disorder that could compromise absorption of nifedipine GITS or passage of the tablet; any condition other than coronary artery disease that limited life expectancy; symptomatic orthostatic hypotension or supine systolic blood pressure 90mm Hg or less; systolic blood pressure at least 200 mm Hg, diastolic blood pressure at least 105 mm Hg or both; creatinine more than twice the local; upper limit of normal; and alanine or aspartate transaminase greater than three times the local upper limit of normal. Women could only participate if pregnancy

	was not a risk.
Interventions/ Test/ Factor being investigated	Nifedipine GITS + basic regimen Symptomatic angina was treated with conventional drugs. Lipid lowering therapy was either continued or started according to local guidelines.
Comparisons	Placebo
Length of Study/ Follow-up	Mean follow-up 4.9 years
Outcome measures studied	Primary endpoint was major cardiovascular event free survival, defined as time to occurrence of the first of the following events: death from any cause, acute MI, refractory angina, new overt heart failure, debilitating stroke, and peripheral revascularisation. Secondary endpoint: any cardiovascular event: any death, cardiovascular event or procedure; and any vascular event or procedure.
Results	
Effect Size	Results: Outcome (no. of events): Nifedipine +basic regimen (n=3825) vs. Placebo +basic regimen (n=3840) [hazard ratio (95% CI)] All cause mortality: 310/3825 vs. 291/3840 [1.07 (0.91 to 1.25)] p=0.41 Non cardiovascular mortality: 132/3825 vs. 114/3840 [1.16 (0.90 to 1.49)] p=0.24 Cardiovascular or unknown: 178/3825 vs. 177/3840 [1.01 (0.82 to 1.24)] p=0.93 Myocardial infarction: 320/3825 vs. 296/3840 [1.04 (0.88 to 1.24)] p=0.62 Effect of Nifedipine on primary endpoint (combined) for efficacy in predefined subgroups Sub group: Nifedine +basic regimen (n=3825) vs. Placebo +basic regimen (n=3840) Age >65 yrs: 467/3825 vs. 466/3840 Women: 166 /3825 vs. 147/3840 Diabetes: 164/3825 vs. 170/3840 Withdrawal due to adverse events*: Nifedipine (n=3825) vs. Placebo (n=3840) 389/3825 vs. 172/3840 *The most frequent events were peripheral edema (139 nifedipine, 20 placebo) and headache (43 Nifedipine, 20 placebo).
Source of funding:	The study was supported by Bayer Health care AG, Wuppertal, Germany.
Does the study answer the question?/Further Comments	Yes. Addition of Nifedipine GITS to conventional treatment of angina had no effect on all cause mortality, cardio vascular mortality and myocardial infarction. Also there was no significant difference between groups for combined primary endpoint for sub groups of people (age >65 yrs, females, diabetes).

Evidence Extractions

Question: What is the clinical /cost effectiveness of newer drugs for the management of angina?

Grading: 1++	High-quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias

Borer JS;Fox K;Jaillon P;Lerebours G;

Antianginal and antiischemic effects of ivabradine, an I_f inhibitor, in stable angina: A randomized, double-blind, multicentered, placebo-controlled trial

Ref ID 146 2003

Study Type Randomised Controlled Trial **Funding** Institut de Recherches International Servier

Number of participant	N=360 randomised: n=90 ivabradine 2.5mg bd, n=91 ivabradine 5mg bd, n=88 10mg bd, n=91 placebo
Inclusion/Exclusion Criteria	Inclusion: 18 yrs or over with a three month history of chronic, stable, effort-induced angina, coronary artery disease or previous MI 3 mths or more prior to randomisation, positive ETT. Exclusion: women of childbearing potential, unstable angina, Prinzmetal angina, microvascular angina, significant valvular disease, atrial fibrillation/flutter, indwelling pacemaker, 2ry or 3ry atrioventricular block, inability to perform ETT.
Patient Characteristics	Mean age 58.5 yrs, 89.7% male, mean frequency of angina 5.3 (7.9) attacks per week, 60.6% prior MI, 16.4% prior CABG, 18.3% prior PTCA.
Recruitment	Not reported
Setting	Not reported
Interventions/ Test/ Factor being investigated	Ivabradine 2.5mg bd, 5mg bd, 10mg bd
Comparisons	vs placebo
Length of Study/ Follow-up	14 days double-blind randomised phase; then 2 or 3 month open label extension (all 10mg ivabradine bd), then double-blind randomised to continue ivabrainde 10mg or placebo (withdrawal phase)
Outcome measures studied	1ry: Change in time to 1-mm horizontal/down-sloping ST segment depression 0.08s or more after the J point and time to limiting angina during ETT at trough of drug activity (12 hours after last dose) 2ry: time to angina onset (peak 4 hr after), attack freq

Results

Trough of drug activity	Placebo	2.5mg bd	5mg bd	10mg bd	p value
Time to 1mm ST depression (s):					
Baseline	369.1 (119.0)	343.7 (120.7)	364.1 (119.3)	370.2 (120.8)	
Day 14	378.0 (124.2)	375.7 (121.2)	408.2 (122.8)	416.4 (155.7)	
Difference	9.0 (63.6)	32.0 (74.3)	44.1 (80.1)*	46.2 (78.2)*	0.016
Time to limiting angina (s):					
Baseline	417.8 (115.6)	402.5 (121.0)	432.8 (124.0)	430.5 (125.4)	
Day 14	430.5 (119.0)	425.0 (116.4)	460.0 (115.1)	471.3 (148.4)	
Difference	12.7 (51.3)	22.5 (55.4)	27.2 (56.8)	40.8 (69.3)*	0.049
Time to angina onset (s):					
Baseline	352.8 (98.2)	330.5 (105.4)	355.6 (110.9)	351.5 (123.1)	
Day 14	377.5 (116.3)	368.1 (112.5)	394.4 (132.3)	420.8 (148.8)	
Difference	24.7 (64.2)	37.6 (57.7)	38.8 (81.7)	69.4 (74.8)*	0.003

Rate-pressure product (heart rate x systolic BP) at peak of exercise (bpm/mmHg):					
Baseline	23057 (5498)	23924 (4885)	24772 (5757)	24183 (4623)	
Day 14	23323 (5488)	23187 (5052)	23630 (5253)	22640 (4540)	
Difference	266 (3074)	-737 (2950)	-1142 (3354)*	-1543 (3526)*	0.011
Total work performed (W/min):					
Baseline	501.7 (246.2)	473.9 (240.6)	538.0 (269.6)	534.0 (278.8)	
Day 14	529.1 (256.8)	515.6 (241.8)	588.3 (260.2)	633.1 (373.5)	
Difference	27.4 (104.7)	41.7 (112.7)	50.3 (122.4)	99.1 (192.0)*	0.019

Peak of drug activity	Placebo	2.5mg bd	5mg bd	10mg bd	p value
Time to 1mm ST depression (s):					
Difference	9.9 (68.5)	32.6 (76.4)	62.8 (79.7)*	69.6 (78.5)*	<0.001
Time to limiting angina (s):					
Difference	7.4 (50.5)	23.1 (60.3)	41.0 (71.1)*	54.9 (74.4)*	<0.001
Time to angina onset (s):					
Difference	28.9 (66.5)	44.9 (69.0)	72.1 (83.1)*	94.9 (88.5)*	<0.001
Rate-pressure product (heart rate x systolic BP) at rest (bpm/mmHg):					
Difference	167 (1952)	-740 (1696)*	-1740 (2059)*	-2621 (1652)*	<0.001
Rate-pressure product (heart rate x systolic BP) at peak of exercise (bpm/mmHg):					
Difference	765 (3389)	-931 (3730)*	-1490 (3774)*	-2148 (3057)*	<0.001

* Significantly different from placebo in pairwise comparisons

Safety and adverse effects

Adverse events - incidence 'low and generally similar to placebo' except for visual symptoms: photopsia (n=10), stroboscopic effect (n=4), non-typical blurred vision (n=1) reported by no patients in placebo group, 1 patient in each of the ivabradine 2.5mg and 5mg bd groups and by 13 paitents (14.8%) on ivabradine 10mg bd. No serious cardiac symptoms after withdrawal (i.e. absence of rebound phenomena).

Does the study answer the question?

Ivabradine produces dose dependent improvements in exercise tolerance, time to development of ischaemia and reduced angina attacks.

Effect due to factor in study?

yes

Consistency of results with other studies?

Directly applicable to guideline population?

direct population

Internal Validity

none

Chaitman BR;Pepine CJ;Parker JO;Skopal J;Chumakova G;Kuch J;Wang W;Skettino SL;Wolff AA;

Effects of Ranolazine with Atenolol, Amlodipine, or Diltiazem on Exercise Tolerance and Angina Frequency in Patients with Severe Chronic Angina: A Randomized Controlled Trial

Ref ID 9026 2004

Study Type Randomised Controlled Trial **Funding** CV Therapeutics inc

Number of participant

N=823 - n=269 placebo; n=279 750 mg Ranolazine; n=275 1000 mg Ranolazine

Inclusion/Exclusion Criteria

Patients with coronary artery disease (confirmed by angiography, documented prior MI or diagnostic stress MI study) and a minimum of a three month history of exertional angina. Antianginal drugs were withdrawn at least 5 days before first qualifying exercise test and for the remainder of the trial. Inclusion criteria: reproducible angina, ischemic ST-segment depression of at least 1 mm and limited exercise capacity on treadmill testing. Exclusion criteria: Factors precluding satifactory interpretation of the ECG, class III or IV heart failure, or acute coronary syndrome or coronary revascularisation procedure within the prior 2 mths

Patient Characteristics

	Placebo	Ranolazine 750 mg	Ranolazine 1000 mg
Background medication (once daily):			
Atenolol 50mg n (%)	118 (43.9%)	119 (42.7%)	117 (42.6%)
Amiodipine 5mg n (%)	81 (30.1%)	86 (30.8%)	89 (32.4%)
Diltiazem 180mg n (%)	70 (26.0%)	74 (26.5%)	69 (25.1%)
Mean age (years)	63.7 (8.9)	64.3 (9.3)	63.9 (9.3)
Male n (%)	202 (75.1%)	217 (77.8%)	219 (79.6%)
Hypertension n (%)	173 (64.3%)	177 (63.4%)	177 (64.4%)
Unstable angina n (%)	54 (20.1%)	58 (20.8%)	65 (23.6%)
MI n (%)	150 (55.8%)	166 (59.5%)	158 (57.5%)
Congestive heart failure n (%)	77 (28.6%)	87 (31.2%)	78 (28.4%)
Coronary Artery Bypass Graft n (%)	36 (13.4%)	53 (19.0%)	56 (20.4%)
Percutaneous coronary intervention n (%)	53 (19.7%)	46 (16.5%)	53 (19.3%)
Diabetes mellitus	57 (21.2%)	68 (24.4%)	64 (23.3%)
Angina frequency mean (SD) attacks/wk	4.6 (5.7)	4.3 (5.3)	4.5 (5.4)
Nitroglycerin use mean (SD) tablets/wk	4.0 (6.7)	4.0 (7.7)	3.7 (6.9)

Recruitment

Not stated

Setting

Through outpatient settings in several countries

Interventions/ Test/ Factor being investigated

Ranloazine 750 twice daily and 1000 mg twice daily

Comparisons

vs placebo comparisons

Length of Study/ Follow-up

12 wks - exercise duration at trough of drug activity (12 hours after dose)

Outcome measures studied

1ry: Change from baseline in exercise treadmill time at trough
2ry: Exercise duration at peak (4hr), times to angina and to 1 mm ST-segment depression at peak/trough, angina attacks, nitroglycerin use

Results

Primary
TROUGH RANOLAZINE LEVELS

	Placebo	Ranolazine 750 mg	Ranolazine 1000 mg
Exercise duration mean (SE) s:			
Baseline	418.3 (6.3)	416.4 (6.2)	414.7 (6.3)
Change from baseline	91.7 (8.3)	115.4 (8.0)	115.8 (8.2)
Difference from placebo	-	23.7 (10.9)	24.0 (11.0)
p value vs. placebo	-	p=0.03	

p=0.03			
Secondary			
TROUGH RANOLAZINE LEVELS			
Time to onset of angina mean (SE) s:			
Baseline	326.7 (6.4)	324.7 (6.5)	326.7 (6.7)
Change from baseline	114.3 (9.2)	144.0 (8.9)	140.3 (9.1)
Difference from placebo	-	29.7 (12.1)	26.0 (12.2)
p value vs. placebo	-	p=0.01	p=0.03
Time to ECG ischaemia mean (SE) s:			
Baseline	298.9 (8.9)	310.0 (9.1)	301.6 (9.2)
Change from baseline	125.1 (9.2)	145.1 (9.0)	146.2 (9.3)
Difference from placebo	-	19.9 (12.2)	21.1 (12.4)
p value vs. placebo	-	p=0.10	p=0.09
PEAK RANOLAZINE LEVELS			
Exercise duration mean (SE) s:			
Baseline	466.5 (8.2)	464.8 (8.1)	470.4 (7.9)
Change from baseline	65.4 (8.1)	99.4 (7.8)	91.5 (8.1)
Difference from placebo	-	34 (10.7)	26.1 (10.8)
p value vs. placebo	-	p=0.001	p=0.02
Time to onset of angina mean (SE) s:			
Baseline	389.2 (8.3)	387.8 (8.5)	383.6 (8.2)
Change from baseline	88.9 (9.4)	126.9 (9.1)	126.8 (9.4)
Difference from placebo	-	38.0 (12.4)	37.9 (12.6)
p value vs. placebo	-	p=0.002	p=0.003
Time to ECG ischaemia mean (SE) s:			
Baseline	404.3 (9.5)	410.5 (9.4)	400.4 (10.3)
Change from baseline	59.2 (9.0)	100.0 (8.7)	93.8 (8.9)
Difference from placebo	-	40.8 (11.8)	34.5 (11.9)
p value vs. placebo	-	p<0.001	p=0.004
Angina frequency:			
Mean (SD) attacks/wk at baseline	4.6 (5.7)	4.3 (5.3)	4.5 (5.4)
Mean (SE) attacks/wk at 12 weeks	3.3 (0.3)	2.5 (0.2)	2.1 (0.2)
p value vs. placebo	-	p=0.006	p=<0.001
Calculated mean (SD) at 12 weeks:	3.3 (4.8)	2.5 (3.3)	2.1 (3.2)
Adverse events	26.4%	31.2%	32.7% (n=5 syncope)
Mortality at 12 weeks	3/269 (1.1%)	2/279 (0.7%)	1/275

(0.4%)

Open-label follow-up
Survival at year 1 on rinolazine 98.4% (95%CI 97.4% to 99.5%) and yr 2 95.9% (95% CI 94.0% to 97.7%). Doses and numbers in each group unclear; also unclear whether this was only patients still on drug or those who had taken it but discontinued.

Safety and adverse effects

Adverse events	26.4%	31.2%	32.7% (n=5 syncope)
Mortality at 12 weeks	3/269 (1.1%)	2/279 (0.7%)	1/275 (0.4%)

The most common adverse events were constipation, dizziness, nausea and asthenia (less than or equal to 7.3% in both ranolazine groups vs. more than or equal to 0.7% on placebo)

Does the study answer the question?

Twice-daily doses of ranolazine increased exercise capacity and provided additional angina relief to symptomatic patients with severe chronic angina taking standard doses of atenolol, amlodipine or diltiazem.

Effect due to factor in study?

Consistency of results with other studies?

Directly applicable to guideline population?

Internal Validity

Ruzyllo W;Tendera M;Ford I;Fox KM;

Antianginal efficacy and safety of ivabradine compared with amlodipine in patients with stable effort angina pectoris: A 3-month randomised, double-blind, multicentre, noninferiority trial

Ref ID 8971 2007

Study Type Randomised Controlled Trial **Funding** Servier, France

Number of participant

N=1195 randomised: Ivabradine 7.5mg bd: n=400; ivabradine 10mg bd n=391; amlodipine 10mg daily n=404

Inclusion/Exclusion Criteria

Inclusion criteria: 18 to 90 yr inclusive with a) a 3 mth history of chronic stable effort-indcued angina relieved by rest/nitrates b) coronary artery disease c) positive bicycle exercise tolerance test
Exclusion criteria: inability to perform ETT, ECG abnormalities confounding ETT interpretation, NYHA III or IV,atrial fibrillation/flutter, pacemaker, heart disease other than CAD, symptomatic hypotension, uncontrolled hypertension, drugs that could interact with study drugs, treatment with bepridil < 7 days prior to selection, treatment with amlodopine < 3 mths prior to selection, resting bradycardia, contraindications to drugs, women of child-bearing potential

Patient Characteristics

	Ivabradine 7.5mg bd	Ivabradine 10mg bd	Amlodipine 10mg daily
Mean (SD) age (years)	59.7 (9.0)	59.6 (8.9)	60.0 (8.9)
Male n (%)	341 (85.3%)	346 (88.5%)	347 (85.9%)
Previous MI (%)	43.8%	42.7%	45.5%
Previous CABG (%)	13.3%	15.1%	13.9%
Previous PTCA (%)	10.8%	12.0%	11.6%

Recruitment

Not reported

Setting

Not reported

Interventions/ Test/ Factor being investigated	Ivabradine 7.5mg bd or 10mg bd
Comparisons	vs amlodipine 10 mg daily
Length of Study/ Follow-up	12 weeks
Outcome measures studied	1RY: Change from baseline in total exercise duration at trough of drug activity (am, 12 hours after last dose) 2RY: Change in time to angina onset and time to 1mm ST depression and rate-pressure product (trough), nitrate use and freq angina attacks
Results	PRIMARY Amlod. Ivabrad. 7.5mg Diff (vs. amlod, 95%CI) Ivabrad. 10mg Diff (95%CI) Mean (SD) total exercise duration (s): Baseline 400.1 (131.9) 414.4 (133.0) 423.6 (142.6) 3 months 431.2 (140.9) 442.0 (154.4) 445.3 (155.5) Change at 3 mo 31.2 (92.0) 27.6 (91.7) -1.8 (-14.6 to +11.1) 21.7 (94.5) -6.6 (-19.5 to +6.3) SECONDARY Mean (SD) time to angina onset (s): Baseline 313.0 (121.8) 325.2 (119.9) 331.4 (125.7) 3 months 379.5 (143.2) 389.9 (156.4) 391.1 (157.2) Change at 3 mo 66.6 (99.1) 64.7 (104.9) -0.6 (-15.2 to +14.0) 59.7 (110.8) -4.6 (-19.3 to +10.1) Mean (SD) time to 1mm ST depression (s): Baseline 347.4 (123.9) 355.0 (122.4) 366.9 (130.9) 3 months 387.1 (138.4) 400.0 (152.2) 401.5 (149.6) Change at 3 mo 39.7 (103.20) 44.9 (98.6) 6.5 (-7.6 to +20.6) 34.7 (104.5) -1.8 (-16.0 to +12.3) Mean (SD) heart rate at rest (bpm) Baseline 78.8 (13.4) 78.6 (13.0) 78.1 (14.1) 3 months 78.6 (13.2) 67.4 (11.8) 65.1 (12.8) Change at 3 mo -0.2 (12.2) -11.2 (12.5) -11.1 (-12.6 to -9.6) -13.1 (13.5) -13.6 (-14.7 to -11.6) p vs. baseline p=0.720 p<0.001 p<0.001 p vs. amlodipine p<0.001 p<0.001 Mean (SD) heart rate at peak exercise (bpm) Baseline 131.0 (18.4) 132.1 (18.9) 132.1 (18.8) 3 months 130.8 (17.5) 119.7 (7.1) 117.0 (17.6) Change at 3 mo -0.2 (12.8) -12.4 (15.3) -11.1 (-13.6 to -10.1) -15.1 (14.4) -14.5 (-16.3 to -12.7) p vs. baseline p=0.829 p<0.001 p<0.001 p vs. amlodipine p<0.001 p<0.001 Rate-pressure product at rest Baseline 10377 (2284) 10437 (2282) 10428 (2418) 3 months 9827 (2112) 8990 (2019) 8764 (2064)

Change at 3 mo -550 (1978) -1447 (2071) -865 (-1105 to -625) -1664 (2238) -1078 (-1319 to -838)
p vs. baseline p<0.001 p<0.001 p<0.001
p vs. amlodipine p<0.001 p<0.001

Rate-pressure product at peak of exercise
Baseline 23483 (5084) 23850 (5203) 24158 (5240)
3 months 23012 (4955) 21925 (5002) 21854 (5012)
Change at 3 mo -471 (4042) -1926 (3848) -1325 (-1831 to -819) -2304 (4077) -1588 (-2095 to -1080)
p vs. baseline p=0.019 p<0.001 p<0.001
p vs. amlodipine p<0.001 p<0.001

Frequency of angina (attacks/week)
Baseline 5.1 (7.8) 5.1 (7.7) 5.1 (7.6)
3 months 2.0 (5.7) 2.1 (5.0) 1.9 (3.6)
Change at 3 mo -3.0 (6.0) -3.0 (12.5) 0.1 (-0.7 to +0.9) -3.2 (6.3) -0.2 (-1.0 to +0.6)
p vs. baseline p<0.001 p<0.001 p<0.001
p vs. amlodipine p=0.564 p=0.318

Short attacking nitrate use (units/week)
Baseline 4.3 (8.2) 3.7 (7.1) 4.5 (8.3)
3 months 1.6 (3.8) 1.7 (4.5) 1.9 (4.5)
Change at 3 mo -2.7 (6.3) -1.9 (12.5) 0.8 (-0.0 to +1.6) -2.7 (6.3) 0.0 (-0.8 to +0.9)
p vs. baseline p<0.001 p<0.001 p<0.001
p vs. amlodipine p=0.972 p=0.541

	Ivabradine 7.5mg bd	Ivabradine 10mg bd	Amlodipine 10mg daily
Adverse events:			
Total:	47.8%	54.7%	37.6%
Visual symptoms:	13.0%	25.1%	4.5%
of which luminous phenomena (mainly phosphenes):	96.2%	95.0%	77.8%
Number of patients who withdrew as a result of visual symptoms:	4	2	0
Peripheral oedema:	0.8%	1.3%	7.9%
Number of patients who withdrew as a result of peripheral oedema:	0	0	6
Sinus bradycardia:	6.5%	10.5%	1.7%
Number of patients who withdrew as a result of sinus bradycardia:	2	1	0
Ventricular extrasystoles:	4.5%	4.1%	2.7%
Cardiovascular deaths n (%)	4 (1%)	3 (0.7%)	2 (0.5%)

Safety and adverse effects

Adverse events SDs not report. Higher frequency in ivabradine groups. Higher incidence of visual symptoms and sinus brachycardia in ivabradine groups.

	Ivabradine 7.5mg bd	Ivabradine 10mg bd	Amlodipine 10mg daily
Adverse events:			
Total:	47.8%	54.7%	37.6%
Visual symptoms:	13.0%	25.1%	4.5%
of which luminous phenomena (mainly phosphenes):	96.2%	95.0%	77.8%
Number of patients who withdrew as a result of visual symptoms:	4	2	0
Peripheral oedema:	0.8%	1.3%	7.9%
Number of patients who withdrew as a result of peripheral oedema:	0	0	6
Sinus bradycardia:	6.5%	10.5%	1.7%
Number of patients who withdrew as a result of sinus bradycardia:	2	1	0
Ventricular extrasystoles:	4.5%	4.1%	2.7%
Cardiovascular deaths n (%)	4 (1%)	3 (0.7%)	2 (0.5%)

Does the study answer the question?

Ivabradine is of similar efficacy to amlodopine (p value for non-inferiority p<0.001 in total exercise duration, time to angina onset and time to 1mm ST depression). There were no sigfnificant differences between groups in angina attack frequency or short-acting nitrate use. The most frequent adverse events were visual symptoms and sinus bradycardia with ivabradine and peripheral oedema with amlodipine.

Effect due to factor in study?

Consistency of results with other studies?

Directly applicable to guideline population?

Internal Validity

Stone PH;Gratsiansky NA;Blokhin A;Huang IZ;Meng L;

Antianginal Efficacy of Ranolazine When Added to Treatment With Amlodipine. The ERICA (Efficacy of Ranolazine in Chronic Angina) Trial

Ref ID 8977 2006

Study Type Randomised Controlled Trial **Funding** CV Therapeutics

Number of participant N=565 (1 patient withdrew before receiving study drug)
n=281 ranolazine n=284 placebo

Inclusion/Exclusion Criteria

Inclusion critiera: 18 yrs or over with a documented history of CAD, chronic stable angina for 3 mths or more, and 3 or more episodes of angina per week during 2 wk qualifying period despite amolodipine 10 mg/day for at least 2 wks prior to 2 wk qualification period. All other antiaginal medications were proscribed excepts long acting nitrates (LANs) and sublingual NG as required. LANs were permitted if they had been taken at a constant dosage for 2 wks or more prior to study entry
EXCLUSION CRITERIA: New York Heart Association functional class IV congestive heart failure, a history of myocardial infarction or unstable angina within the 2 mths previous, active acute myocarditis, pericarditis, hypertrophic cardiomyopathy, uncotrolled hypertension, torsades de pointes, drugs prolonging QT interval, cytochrome P450 inhibitors, significant hepatic disease, creatinine clearance <30mL/min, chronic illness, digiitalis preparations, perhexiline, trimetazidine, beta blockers or calcium channel blockers except for amolodipine, in another trial within last 30 days.

Patient Characteristics

	Ranolazine	Placebo	p value
Mean (SD) age (years)	61.3 (9.0)	62.0 (8.7)	0.36
Male: female (%)	73:27	72:28	0.66
Use of long acting nitrates (%)	43	46	0.72
History of unstable angina n (%)	98 (35%)	100 (36%)	0.87
History of congestive heart failure n (%)	145 (51%)	146 (52%)	0.58
NYHA Class I n (%)	38 (13%)	32 (11%)	
NYHA Class II n (%)	86 (30%)	99 (35%)	0.69
NYHA Class III n (%)	21 (7%)	15 (5%)	
NYHA Class IV n (%)	0	0	
Diabetes mellitus n (%)	54 (19%)	52 (19%)	0.82
Previous MI n (%)	233 (82%)	218 (78%)	0.16
Previous CABG n (%)	34 (12%)	28 (10%)	0.52
Previous PCI n (%)	25 (9%)	34 (12%)	0.095
Intermittent claudication n (%)	32 (11%)	39 (14%)	0.48
Hypertension n (%)	257 (91%)	246 (88%)	0.33

Recruitment

Not reported

Setting

Hospital

Interventions/ Test/ Factor being investigated

Rinolazine 500 mg twice daily during run in period (1 week) and then 1000 mg twice daily

Comparisons

vs placebo. Both groups received amlodipine 10mg daily. Compared using "trimmed means" i.e. averaging all observations except top 2% and bottom 2% to reduce influence of outliers.

Length of Study/ Follow-up

6 wks treatment phase

Outcome measures studied

1RY: Weekly average frequency of angina attacks
2RY: Nitroglycerin use, change from baseline on 5 dimensions of Seattle Angina Questionnaire (SAQ): anginal frequency, physical limitation, anginal stability, disease perception, treatment satisfacion

Results

PRIMARY

	Ranolazine	Placebo	p value
Trimmed mean (SE) angina attacks per week:	3.31 (0.22)	2.88	

(0.19) p=0.028

SECONDARY
Trimmed mean (SE) nitroglycerin use per week: 2.68 (0.22) 2.03 (0.20) p=0.014
Angina frequency dimension of SAQ: 18.5 (18.8) 22.5 (19.0) p=0.008
No other dimension of SAQ reported; all non-significant

Subgroup analysis by baseline angina frequency separated at the median (4.5 episodes per week); trimmed mean and SEM only shown graphically:
Angina frequency reduced by ranolazine for baseline frequency 4.5 episodes or less (p=0.036) or 4.5 episodes or more (p=0.029).
Nitroglycerin use not significant for baseline frequency 4.5 episodes or less (p=0.28) but significant for 4.5 episodes or more (p<0.001).
SAQ angina frequency domain not significant for baseline frequency 4.5 episodes or less (p=0.57) but significant for 4.5 episodes or more (p<0.001).

Weekly angina attacks (trimmed mean, SE) by subgroups (gender, age, long-acting nitrate [LAN] use)

	Placebo		Ranolazine	
	Women	Men	Women	Men
	3.48 (0.45)	3.19 (0.24)	2.86 (0.41)	2.91 (0.23)
p value vs. placebo			p=0.33	p=0.026
	Age <65yr	Age 65 yr or more	Age <65yr	Age 65 yr or more
	3.30 (0.27)	3.25 (0.38)	2.83 (0.25)	2.91 (0.34)
p value vs. placebo			p=0.074	p=0.15
	LAN users	LAN non-users	LAN users	LAN non-users
	3.70 (0.41)	2.99 (0.26)	3.26 (0.39)	2.64 (0.21)
p value vs. placebo			p=0.15	p=0.16

NB The study was not powered for testing treatment effects among subgroups.

	Placebo	Ranolazine
Adverse events (total)	35.3%	39.9%
Constipation	1.8%	8.9%
Peripheral oedema	2.8%	5.7%
Dizziness	2.5%	3.9%
Nausea	0.7%	2.8%
Headache	2.5%	2.8%
Cardiac adverse events	7.8%	5.7%
Discontinued due to adverse events:	4	3
Deaths	1	1

Safety and adverse effects

	Placebo	Ranolazine
Adverse events (total)	35.3%	39.9%
Constipation	1.8%	8.9%
Peripheral oedema	2.8%	5.7%
Dizziness	2.5%	3.9%
Nausea	0.7%	2.8%
Headache	2.5%	2.8%
Cardiac adverse events	7.8%	5.7%
Discontinued due to adverse events:	4	3

	Deaths	1	1

Does the study answer the question? Ranolazine significantly reduced frequency of angina attack and nitroglycerin consumption compared with placebo

Effect due to factor in study?

Consistency of results with other studies?

Directly applicable to guideline population?

Internal Validity

Tardif JC;Ponikowski P;Kahan T;ASSOCIATE S;

Efficacy of the I(f) current inhibitor ivabradine in patients with chronic stable angina receiving beta-blocker therapy: a 4-month, randomized, placebo-controlled trial

Ref ID 8981 2009 Mar

Study Type Randomised Controlled Trial **Funding** Servier France

Number of participant
Ivabradine N=449
Placebo N=440

Inclusion/Exclusion Criteria
Patients aged between 18 and 75 yrs with a 3 month or more history of chronic stable angina and evidence of coronary artery disease
EXCLUSION criteria included
Heart rate < 60 bpm on ECG at rest and significant heart disease other than CAD

Patient Characteristics
Ivabradine mean age 60 yrs, male 85%, diabetes 97&
Placebo mean age 60 yrs, male 84%, diabetes 96%

Recruitment Not reported

Setting Outpatients

Interventions/ Test/ Factor being investigated Ivabradine 5 mg bid plus Atenolol 10 mg/daily

Comparisons Ivabradine 5 mg bid plus Atenolol 10 mg/daily vs Atenolol 10 mg/daily

Length of Study/ Follow-up 5 mg bid two months

Outcome measures studied
PRIMARY
Total exercise duration
SECONDARY
Time to angina onset

Results
PRIMARY
Ivabradine plus Atenolol vs Atenolol
Total exercise duration seconds
15.5 (60.0) vs 6.8 (56.5)
SECONDARY
Ivabradine plus Atenolol vs Atenolol
Time to angina onset seconds
30.2 (72.2) vs 17.2 (72.3)

Safety and adverse effects
Ivabradine vs placebo:
Withdrawal from treatment to to AEs
2.9% vs 0.9%
Serious Aes
1.1 vs 0.7%

	Bradycardia 1.1 vs 0%
Does the study answer the question?	Yes.
Effect due to factor in study?	
Consistency of results with other studies?	
Directly applicable to guideline population?	
Internal Validity	

Grading: 1+ Well-conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias

Fox K;Ford I;Steg PG;Tendera M;Robertson M;Ferrari R;

Relationship between ivabradine treatment and cardiovascular outcomes in patients with stable coronary artery disease and left ventricular systolic dysfunction with limiting angina: a subgroup analysis of the randomized, controlled BEAUTIFUL trial

Ref ID 9037 2009 Aug 31

Study Type Randomised Controlled Trial **Funding** Servier France

Number of participant

Post hoc subgroup analysis of 1507/10917 (13.8%) of the BEAUTIFUL population (patients with stable coronary artery disease and left ventricular systolic dysfunction) whose limiting symptoms at baseline was angina n=1507 (Ivabradine 734; placebo 773); patients without limiting angina n=9410 (Ivabradine 4745; placebo 4665). Further subgroups: limiting angina and heart rate 70 bpm or more (ivabradine 349, placebo 363); and without limiting angina but with heart rate 70 bpm or more (ivabradine 2350, placebo 2330).

Inclusion/Exclusion Criteria

Patients with limiting angina aged 55 yrs or older (18 yrs or older if diabetic) with coronary artery disease, left-ventricular ejection fraction < 40% and end diastolic short axis internal dimension of greater than 56 mm by echocardiography. Sinus rhythm and resting heart rate 60 bpm or more. Angina stable for 3 mths and appropriate doses of cardiovascualar drugs for at least one month.
EXCLUSION
Patients with MI or coronary revascularisation within the past 6 mths, stroke or TIA within past 3 mths, symptoms of severe heart failure (NYHA IV)

Patient Characteristics

	Patients with limiting angina		Patients without limiting angina
	Ivabradine	Placebo	Ivabradine Placebo
Mean (SD) age (yrs)	64.8 (8.1)	64.1 (8.4)	65.4 (8.5) 65.1 (8.4)
Male n (%)	594 (81%)	639 (83%)	3946 (83%) 3868 (83%)
Smoking n (%)	111 (15%)	123 (16%)	702 (15%) 711 (15%)
BMI (kg/m2)	28.4 (4.4)	28.4 (4.0)	28.5 (4.4) 28.5 (4.5)
History of hypertension n (%)	581 (79%)	622 (80%)	3301 (70%) 3216 (69%)
History of diabetes n (%)	234 (32%)	266 (34%)	1783 (38%) 1753 (38%)
History of dyslipidaemia n (%)	566 (77%)	577 (75%)	3733 (79%) 3701 (79%)
Previous MI n (%)	659 (90%)	716 (93%)	4169 (88%) 4101 (88%)
Previous PCI/CABG n (%)	275 (37%)	258 (33%)	2544 (54%) 2566 (55%)
Previous stroke n (%)	138 (19%)	138 (18%)	882 (19%) 834 (18%)
Peripheral artery disease n (%)	78 (11%)	93 (12%)	614 (13%) 655 (14%)
Left ventricular ejection fraction (%)	33.1 (5.2)	33.6 (4.9)	32.3 (5.5) 32.1 (5.6)
NYHA Class II n (%)	549 (75%)	574 (74%)	2797 (59%) 2785 (60%)
NYHA Class III n (%)	185 (25%)	199 (26%)	1108 (23%) 1040 (22%)

	Patients with limiting angina and heart rate 70 bpm or more		Patients without limiting angina and heart rate 70 bpm or more
	Ivabradine	Placebo	Ivabradine Placebo

	Ivabradine	Placebo	Ivabradine Placebo
Mean (SD) age (yrs)	64.4 (7.8)	63.1 (8.4)	64.9 (8.7) 64.6 (8.6)
Male n (%)	278 (80%)	298 (82%)	1928 (82%) 1911 (82%)
Smoking n (%)	69 (20%)	66 (18%)	363 (15%) 415 (18%)
BMI (kg/m2)	28.9 (4.2)	28.7 (4.3)	28.8 (4.6) 28.7 (4.7)
History of hypertension n (%)	278 (80%)	297 (82%)	1669 (71%) 1630 (70%)
History of diabetes n (%)	122 (35%)	138 (38%)	1010 (43%) 1017 (44%)
History of dyslipidaemia n (%)	266 (76%)	261 (72%)	1853 (79%) 1862 (80%)
Previous MI n (%)	312 (89%)	330 (91%)	2043 (87%) 2019 (87%)
Previous PCI/CABG n (%)	122 (35%)	117 (32%)	1211 (52%) 1243 (53%)
Previous stroke n (%)	60 (17%)	66 (18%)	441 (19%) 437 (19%)
Peripheral artery disease n (%)	40 (11%)	43 (12%)	333 (14%) 359 (15%)
Left ventricular ejection fraction (%)	33.0 (5.1)	33.4 (4.9)	31.8 (5.7) 31.7 (5.8)
NYHA Class II n (%)	251 (72%)	265 (73%)	1324 (56%) 1350 (58%)
NYHA Class III n (%)	98 (28%)	98 (26%)	637 (27%) 607 (26%)

Recruitment

Not reported

Setting

Hospital

Interventions/ Test/ Factor being investigated

Ivabradine 5 mg bid increasing to 7.5 mg if resting heart rate 60 bpm or more

Comparisons

Placebo

Length of Study/ Follow-up

median 18 mths. End point was composite of cardiovascular death, hospitalisation for fatal and non-fatal MI, hospitalisation for new or worsening heart failure; time to event curves

Outcome measures studied

PRIMARY
CV death or hospitalisation for MI or HF
SECONDARY
All cause/CV/cardiac mortality
Hospitalisation for HF
Hospitalisation for MI
Hospitalisation for MI/unstable angina/revascularisation

Results

	Patients with limiting angina Ivabradine	Placebo	Hazard ratio (95% CI) p value
CV death or hospitalisation for MI or HF:	88/734 (12%)	120/773 (15.5%)	0.76 (0.58 to 1.00) p=0.05
All cause mortality:	64/734 (8.7%)	77/773 (10.0%)	0.87 (0.62 to 1.21) 0.41
Cardiovascular death:	54/734 (7.4%)	64/773 (8.3%)	0.88 (0.62 to 1.27) 0.51
Cardiac death:	11/734 (1.5%)	16/773 (2.1%)	0.72 (0.33 to 1.55) 0.40
Hospitalisation for HF:	33/734 (4.5%)	41/773 (5.3%)	0.84 (0.53 to 1.33) 0.45
CV death or hospitalisation for HF:	73/734 (9.9%)	95/773 (12.3%)	0.80 (0.59 to 1.09) 0.15

Hospitalisation for MI: 28/734 (3.8%) 50/773 (6.5%) 0.58 (0.37 to 0.92) p=0.021
Hospitalisation for MI or unstable angina: 56/734 (7.6%) 65/773 (8.4%) 0.90 (0.63 to 1.29) 0.58
Coronary revascularisation: 23/734 (3.1%) 34/773 (4.4%) 0.70 (0.41 to 1.19) 0.19

Patients without limiting angina

	Ivabradine	Placebo	Hazard ratio (95% CI)	p value
CV death or hospitalisation for MI or HF:	756/4745 (15.9%)	712/4665 (15.3%)	1.04 (0.94 to 1.16)	0.41
All cause mortality:	508/4745 (10.7%)	470/4665 (10.1%)	1.06 (0.94 to 1.21)	0.33
Cardiovascular death:	415/4745 (8.7%)	371/4665 (8.0%)	1.10 (0.96 to 1.27)	0.18
Cardiac death:	125/4745 (2.6%)	135/4665 (2.9%)	0.91 (0.71 to 1.16)	0.45
Hospitalisation for HF:	393/4745 (8.3%)	386/4665 (8.3%)	1.00 (0.87 to 1.15)	0.99
CV death or hospitalisation for HF:	684/4745 (14.4%)	628/4665 (13.5%)	1.07 (0.96 to 1.19)	0.21
Hospitalisation for MI:	171/4745 (3.6%)	176/4665 (3.8%)	0.96 (0.78 to 1.18)	0.67
Hospitalisation for MI or unstable angina:	247/4745 (5.2%)	252/4665 (5.4%)	0.96 (0.81 to 1.15)	0.68
Coronary revascularisation:	132/4745 (2.8%)	152/4665 (3.3%)	0.70 (0.41 to 1.19)	0.19

Patients with limiting angina and heart rate 70 bpm or more

	Ivabradine	Placebo	Hazard ratio (95% CI)	p value
CV death or hospitalisation for MI or HF:	43/349 (12.3%)	65/363 (17.9%)	0.69 (0.47 to 1.01)	p=0.06
All cause mortality:	37/349 (10.6%)	47/363 (12.9%)	0.83 (0.54 to 1.28)	0.40
Cardiovascular death:	32/349 (9.2%)	38/363 (10.5%)	0.90 (0.56 to 1.44)	0.66
Cardiac death:	5/349 (1.4%)	6/363 (2.5%)	0.59 (0.20 to 1.77)	0.34
Hospitalisation for HF:	18/349 (5.2%)	20/363 (5.5%)	0.96 (0.51 to 1.82)	0.91
CV death or hospitalisation for HF:	41/349 (11.7%)	52/363 (14.3%)	0.84 (0.56 to 1.26)	0.41
Hospitalisation for MI:	6/349 (1.7%)	23/363 (6.3%)	0.27 (0.11 to 0.66)	p=0.002
Hospitalisation for MI or unstable angina:	20/349 (5.7%)	31/363 (8.5%)	0.68 (0.39 to 1.19)	0.18
Coronary revascularisation:	7/349 (2.0%)	18/363 (5.0%)	0.41 (0.17 to 0.99)	p=0.04

Patients without limiting angina and heart rate 70 bpm or more

	Ivabradine	Placebo	Hazard ratio (95% CI)	p value
CV death or hospitalisation for MI or HF:	420/2350 (17.9%)	433/2330 (18.6%)	0.95 (0.83 to 1.09)	0.45
All cause mortality:	294/2350 (12.5%)	277/2330 (11.9%)	1.05	

(0.89 to 1.24) 0.55
Cardiovascular death: 237/2350 (10.1%) 255/2330 (9.7%) 1.04 (0.87 to 1.25) 0.65
Cardiac death: 77/2350 (3.3%) 88/2330 (3.8%) 0.86 (0.64 to 1.17) 0.34
Hospitalisation for HF: 250/2350 (10.6%) 251/2330 (10.8%) 0.97 (0.82 to 1.16) 0.77
CV death or hospitalisation for HF: 395/2350 (16.8%) 390/2330 (16.7%) 0.99 (0.86 to 1.14) 0.94
Hospitalisation for MI: 79/2350 (3.4%) 108/2330 (4.6%) 0.72 (0.54 to 0.96) p=0.025
Hospitalisation for MI or unstable angina: 123/2350 (5.2%) 151/2330 (6.5%) 0.80 (0.63 to 1.02) 0.07
Coronary revascularisation: 67/2350 (2.9%) 90/2330 (3.9%) 0.76 (0.55 to 1.03) 0.08

Safety and adverse effects

Ivabradine vs placebo
Rate of discontinuation
23% vs 15% (82 [11%] of patients on ivabradine withdrew due to bradycardia vs. 11 [1.4%] on placebo; 3 [0.4%] on ivabradine withdrew due to phosphenes vs. 1 [0.1%] on placebo)
Serious adverse events
18% vs 19% (not significant).

Does the study answer the question?

Ivabradine may reduce cardiovascualr events in patients with stable CAD and LVSD who present with limiting angina; based on post hoc analysis so should be considered hypothesis-generating.

Effect due to factor in study?

Consistency of results with other studies?

Directly applicable to guideline population?

Internal Validity

post hoc subgroup analysis

Rich MW;Crager M;McKay CR;

Safety and efficacy of extended-release ranolazine in patients aged 70 years or older with chronic stable angina pectoris

Ref ID 500 2007 Jul

Study Type Randomised Controlled Trial **Funding** CV Therapeutics

Number of participant

N=1387
Younger than 70 yrs: n=420 placeb, n=604 ranolazine 1000 mg
80 yrs or older: n=132 placebo, n=231 ranolazine 1000 mg

Inclusion/Exclusion Criteria

CARISA - inclusion criteria included reproducible angina, ischemic ST-segment depression of at least 1 mm and limited exercise capacity on the treadmill
ERICA - inclusion criteria included patients with chronic angina and remained symptomatic, having at least 3 angina attacks per week, while receiving amlodipine 10 mg qd alone or in combination with a stable dose of long acting nitrate preparation.

Patient Characteristics

	< 70yrs		70 yrs or older	
	Placebo	Ranolazine	Placebo	Ranolazine
Mean (SD) age (years) range	58.9 (7.2) 36-69	59.2 (6.9) 36-69	73.7 (3.1) 70-84	74.3 (3.6) 70-92
Men (%)	76%	77%	68%	74%
Mean (SD) BMI (kg/m2)	28.2 (3.9)	28.4 (4.1)	26.4 (3.5)	27.1 (3.5)

	Hypertension (%) 79% 72% 75% 72% Diabetes mellitus (%) 19% 21% 23% 26% Unstable angina (%) 29% 28% 24% 24% Prior MI (%) 72% 68% 60% 58% Prior PCI (%) 14% 15% 14% 17% Prior CABG (%) 14% 17% 9% 16% History of heart failure (%) 40% 38% 40% 36%
Recruitment	Not stated
Setting	Not stated
Interventions/ Test/ Factor being investigated	CARISA: ranolazine extended-release (ER) 750 mg bid or 1000 mg bid ERICA: ranolazine ER 1000 mg bid
Comparisons	CARISA and ERICA: ranolazine vs placebo
Length of Study/ Follow-up	CARISA: end of 12 wks treatment ERICA: end of 6 wks treatment
Outcome measures studied	PRIMARY CARISA: treadmill exercise time ERICA: average weekly freq angina attacks SECONDARY CARISA: time to angina or 1mm ST depression, average weekly freq of angina attacks, nitroglycerin consumption ERICA: nitroglycerin consumption
Results	Exercise duration, time to onset of angina, time to 1mm ST depression in CARISA by age group (shown graphically only) PRIMARY OUTCOME (CARISA)

	< 70yrs			70 yrs or older	
	Placebo	Ranolazine 750mg bd	Ranolazine 1g bd	Placebo	Ranolazine 750mg bd	Ranolazine 1g bd
Mean exercise duration (s):	107.6	130.0	127.4	56.5	86.3	88.9
Time to onset of angina (s):	129.5	158.3	155.2	80.6	115.5	106.1
Time to 1mm ST depression	140.8	156.5	158.3	90.8	121.9	117.0

Average weekly rate of angina and nitroglycerin consumption - 6 weeks
PRIMARY OUTCOME (ERICA) SECONDARY OUTCOME (CARISA)

	< 70yrs			70 yrs or older		
	Placebo	Ranolazine	p value*	Placebo	Ranolazine	p value*
Mean weekly rate of angina mean (SE) (excluding outliers):	3.61 (0.20)	3.11 (0.23)	p<0.001	3.21 (0.41)	2.08 (0.23)	p=0.065
Mean weekly rate of nitroglycerin consumption	3.15 (0.26)	2.18 (0.22)	p<0.001	2.45 (0.35)	1.51 (0.21)	p=0.077

* values not normally distributed; p value from non-parametric tests

	< 70yrs			70 yrs or older		
	Placebo	Ranolazine	p value	Placebo	Ranolazine	p value
Adverse events n (%):	131 (31.2%)	194 (32.1%)	0.79	43 (32.6%)	102 (44.2%)	p=0.034

Safety and adverse effects

Adverse events - no Ses or SDs reported. No significant differecnes reported overall.

Does the study answer the question?

Outcomes are similar for older and younger patients exxcept adverse events more common among older patients; includes patients in CARISA trial (Chaitman 2004 ID 9026) and ERICA trial (Stone 2006 ID 8977) so beware doubling counting; results not normally distributed, so while means (and some SE) given, these should not be relied on.

Effect due to factor in study?

Consistency of results with other studies?

Directly applicable to guideline population?

Internal Validity

Tardif JC;Ponikowski P;Kahan T;ASSOCIATE S;

Efficacy of the I(f) current inhibitor ivabradine in patients with chronic stable angina receiving beta-blocker therapy: a 4-month, randomized, placebo-controlled trial

Ref ID 8981 2009 Mar

Study Type Randomised Controlled Trial **Funding** Servier, France

Number of participant

Ivabradine N=449
Placebo N=440

Inclusion/Exclusion Criteria

INCLUSION CRITERIA: Patients aged between 18 and 75 yrs with a 3 month or more history of chronic angina on effort.
Evidence of coronary artery disease, sinus rhythm, beta-blocker at least 3 months (atenolol50mg daily or equivalent), 3 positive ETTs
EXCLUSION CRITERIA: heart rate < 60 bpm on ECG at rest,significant heart disease other than CAD, angina at rest, unstable angina,Prinzmetal or microvascular angina, , NHYA class III or IV, symptomatic hypotension or uncontrolled hypertension, chronic or paroxysmal atrial fibrillation, atrial flutter, pacemaker or implanted defibrillator, any condition interfering with performance or interpretation of ETT, contraindication/intolerance to beta-blocker, amiodarone in last 3 months, bepridil last 7 days, severe renal failure, LFT abnormal, electrolyte disorder, Hb <110g/L, thyroid disorder unless controlled by thyroxine >3months

Patient Characteristics

	Ivabradine	Placebo	p value
Mean (SD) age (years)	59.6 (7.6)	60.1 (8.0)	0.30
Male n (%)	380 (84.6%)	370 (84.1%)	0.82
Previous MI n (%)	225 (50.1%)	226 (51.4%)	0.71
Previous PCI n (%)	95 (21.2%)	89 (20.2%)	0.49
Previous CABG n (%)	135 (30.1%)	123 (28.0%)	0.73
Diabetes mellitus n (%)	97 (21.6%)	96 (21.8%)	0.94

	Heart rate at rest (bpm)	66.9 (6.9)	67.2 (6.9%)	0.57
	Heart rate at peak exercise (bpm)	128.6 (16.9%)	129.9 (18.0%)	0.29
	Rate-pressure product at rest (bpm.mmHg)	9389 (1661)	9427 (1830)	0.75
	RPP at peak exercise (bpm.mmHg)	21110 (4300)	21249 (4566)	0.64

Recruitment

Not reported

Setting

Outpatients

Interventions/ Test/ Factor being investigated

Ivabradine7.5 mg plus Atenolol 50 mg/day
Placebo plus Atenolol 50 mg/day

Comparisons

Ivabradine plus Atenolol vs Placebo plus Atenolol

Length of Study/ Follow-up

4 mths (2 mths 5 mg bid Ivabradine plus 2 mths 7.5 mg)

Outcome measures studied

PRIMARY: Change in total exercise duration at end of treatment (month 4) during ETT at trough of drug activity. SECONDARY: Changes from baseline to end of treatment in other ETT variables, angina attack frequency and short-acting nitrate consumption

Results

PRIMARY

	Ivabradine	Placebo	Difference* (95% CI)	p value
Total exercise duration (s):				
Baseline	445.6 (105.6)	450.7 (107.5)		
End of treatment	469.9 (119.2)	458.4 (111.1)		
Change	24.3 (65.3)	7.7 (63.8)	16.3 (7.9 to 24.7)	p<0.001

SECONDARY

Time to limiting angina (s):				
Baseline	441.9 (105.7)	446.6 (107.4)		
End of treatment	467.9 (119.8)	456.0 (111.1)		
Change	26.0 (65.7)	9.4 (63.8)	16.3 (7.9 to 24.7)	p<0.001
Time to angina onset (s):				
Baseline	352.5 (104.6)	357.2 (104.8)		
End of treatment	401.6 (125.5)	379.9 (115.8)		
Change	49.1 (83.3)	22.7 (79.1)	25.5 (15.0 to 36.0)	p<0.001
Time to 1mm ST depression (s):				
Baseline	337.8 (97.2)	347.2 (104.0)		
End of treatment	383.5 (123.2)	362.6 (122.5)		
Change	45.7 (93.0)	15.4 (86.6)	28.5 (16.8 to 40.3)	p<0.001
Heart rate at rest (bpm)				
Baseline	67.0 (6.8)	67.2 (6.9)		
Change to end treatment	-8.7 (9.8)	-1.4 (9.8)	-7.4 (-8.7 to -6.2)	
Heart rate at peak exercise (bpm)				
Baseline	128.6 (16.9)	130.1 (1795)		
Change to end treatment	-11.3 (13.2)	-0.9 (12.3)	-10.8 (-12.4 to -9.1)	
Rate-pressure product at rest (bpm.mmHg)				
Baseline	9403 (1662)	9429 (1830)		
Change to end treatment	-1269 (1655)	-360 (1622)	-920 (-1115 to -725)	

RPP at peak exercise (bpm.mmHg)			
Baseline	21125 (4287)	21288 (4552)	
Change to end treatment	-1630 (3474)	-66 (3447)	-1612 (-2041 to -1183)

*Difference ivabradine minus placebo, estimate from parametric approach adjusted on baseline and country factors.

Frequency of angina attacks per week:			
Baseline	1.8 (3.3)	1.6 (2.4)	
End of treatment	0.9 (2.4)	0.9 (2.1)	Not significantly different

Adverse events:

Bradycardia	19 (4.2%)	2 (0.5%)	
Phosphenes/blurred vision	9 (2%)	4 (0.9%)	
Withdrawn due to adverse events n (%)	13 (2.9%)	4 (0.9%)	Not significantly different
Bradycardia	5 (1.1%)	0	
Unstable or aggravated angina	3 (0.7%)	1 (0.2%)	
Serious adverse events n (%)	5 (1.1%)	3 (0.7%)	
Deaths (n)	1	2	

Safety and adverse effects

Adverse events
Ivabradine vs placebo
Serious adverse events
1.1 vs 0.7%
Bradycardia leading to withdrawal
1.1 vs 0%
Unstable or aggrevated angina leading to withdrawal
0.7 vs 0.2%
Phosphenes
2 vs 0.9%

Does the study answer the question?

The combination of Ivabradine and Atenolol produced additional effiacacy with no untoward effect on safety or tolerability

Effect due to factor in study?

Consistency of results with other studies?

Directly applicable to guideline population?

Internal Validity

Timmis AD;Chaitman BR;Crager M;

Effects of ranolazine on exercise tolerance and HbA_{1c} in patients with chronic angina and diabetes

Ref ID 8978 2006

Study Type Randomised Controlled Trial **Funding** CV Therapeutics

Number of participant

823 randomised: 269 placebo (of whom 57 with diabetes); 279 ranolazine 750mg bd (of whom 68 with diabetes); 275 ranolazine 1000mg bd (of whom 64 with diabetes)

Inclusion/Exclusion Criteria

Patients with coronary artery disease (confirmed by angiography, documented prior MI or diagnostic stress MI study) and a minimum of a three month history of exertional angina. Antianginal drugs were withdrawn at least 5 days before first qualifying exercise test and for the remainder of the trial. Inclusion criteria: reproducible angina, ischemic ST-segment depression of at least 1 mm and limited exercise capacity on treadmill testing. Exclusion criteria: Factors precluding satifactory interpretation of the ECG, class III or IV heart failure, or acute coronary syndrome or coronary revascularisation procedure within the prior 2 mths

Patient Characteristics

	Diabetic	Non-diabetic
Mean (SE) age (years)	65 (0.6)	64 (0.4)
Men n (%)	136 (72%)	501 (79%)
Prior MI n (%)	113 (60%)	361 (57%)
Prior CABG n (%)	51 (27%)	101 (16%)
History of hypertension n (%)	140 (74%)	387 (61%)

Recruitment

Not reported

Setting

Not reported

Interventions/ Test/ Factor being investigated

Ranolazine 750 mg or 1000 mg twice daily

Comparisons

vs placebo

Length of Study/ Follow-up

12 weeks

Outcome measures studied

1ry: Change from baseline in exercise treadmill time at trough
2ry: Exercise duration at peak (4hr), times to angina and to 1 mm ST-segment depression at peak/trough, angina attacks, nitroglycerin use

Results

PRIMARY

	Diabetic	Non-diabetic	p for treatment by subgroup interaction
Change from baseline in exercise duration at trough mean (SE) (s)			
Placebo	85.4 (17.2)	93.4 (9.2)	
Ranolazine 750 mg	114.1 (15.5)	115.9 (9.1)	p=0.89
Ranolazine 1000 mg	119.6 (16.6)	114.6 (9.2)	
Change from baseline in time to onset of angina at trough mean (SE) (s)			
Placebo	94.9 (19.1)	119.5 (10.2)	
Ranolazine 750 mg	145.7 (17.2)	143.4 (10.1)	p=0.54
Ranolazine 1000 mg	143.9 (18.4)	139.1 (10.2)	
Change from baseline in time to 1mm ST depression at trough mean (SE) (s)			
Placebo	103.0 (20.0)	130.6 (10.2)	
Ranolazine 750 mg	148.0 (17.4)	144.1 (10.3)	p=0.44
Ranolazine 1000 mg	152.7 (18.8)	144.3 (10.5)	

SECONDARY

	Diabetic	Non-diabetic	p for treatment by subgroup interaction
Angina episodes per week mean (SE):			
Placebo	2.99 (0.56)	3.39 (0.35)	
Ranolazine 750 mg	2.08 (0.37)	2.59 (0.28)	p=0.81
Ranolazine 1000 mg	1.03 (0.19)	2.46 (0.31)	
Nitroglycerin consumption per week mean (SE):			
Placebo	4.35 (1.27)	2.80 (0.34)	
Ranolazine 750 mg	2.03 (0.54)	2.14 (0.31)	p=0.063
Ranolazine 1000 mg	0.56 (0.09)	2.11 (0.35)	

Effects of ranolazine in patients with diabetes comparable to those without diabetes.

HbA1c (%) assessed post hoc in 131 (69%) of diabetic patients who had baseline andon-treatment values (least squares mean +/-SEM):

	Placebo (n=37)	Ranolazine 750mg (n=47)	Ranolazine 1g (n=47)
Baseline	7.46 (0.21)	7.65 (0.20)	7.92 (0.21)
Week 12 or early termination	7.62 (0.14)	7.14 (0.13)	6.93 (0.13)
Change from baseline	-0.02 (0.14)	-0.50 (0.13)	-0.72 (0.13)
Difference vs. placebo		-0.48 (0.18)	-0.70 (0.18)
p value vs. placebo		p=0.008	p=0.0002

Adverse events (%)

	Diabetic			Non-diabetic		
	Plac	Ran 750mg	Ran1g	Plac	Ran 750mg	Ran 1g
Adverse events (%)	24.6	25.0	34.4	26.9	33.2	32.2
Discontinuations due to adverse events (%):	5.3	2.9	10.9	6.1	9.5	8.5

No notable differences between patients with and without diabetes.

Safety and adverse effects

Adverse events - no Ses or SDs reported. No significant differences reported

Does the study answer the question?

The safety and efficacy of ranolazine were similar between diabetic and non-diabetic patients

Effect due to factor in study?

Consistency of results with other studies?

Directly applicable to guideline population?

Internal Validity

Grading: 1- Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias*

Tardif JC;Ford I;Tendera M;Bourassa MG;Fox K;

Efficacy of ivabradine, a new selective I_f inhibitor, compared with atenolol in patients with chronic stable angina

Ref ID 101 2005

Study Type Randomised Controlled Trial **Funding** Servier France

Number of participant N=939
Ivabradine 7.5mg bd n=315; ivabradine 10mg bd n=317; Atenolol 100mg daily n=307

Inclusion/Exclusion Criteria Inclusion: 18 yrs or over with a 3 mth or greater history of stable effort angina plus 1) evidence of coronorary artery diease; 2) two positive exercise tolerance tests
Exclusion: significant heart disease other than CAD, high-grade left main CAD, NYHA Stage III/IV, symptomatic hypotension or uncontrolled hypertension, atrial fibrillation/flutter, pacemaker/implanted defibrillator, 2nd/3rd degree AV block, resting heart rate <50bpm, sick sinus syndrome, inability to perform ETT or condition making interpretation difficult, contraindications to drugs, recent amiodarone (<3 months) or bepridil (<7 days), ALT > 3 times normal, serum creatinine >180micomol/L, electrolyte disorders, thyroid disorders (unless controlled by thyroxine >3 months), Hb <100g/L, severe psychiatric disorders.

Patient Characteristics

	Ivabradine 7.5mg	Ivabradine 10mg	Atenolol
Mean (SD) age (years)	60.8 (8.5)	61.1 (8.4)	61.6 (6.6)
Male n (%)	266 (84.4%)	275 (86.8%)	257 (83.7%)
Angina class:			
I n (%)	64 (20.3%)	68 (21.5%)	62 (20.2%)
II n (%)	225 (71.4%)	222 (70.0%)	215 (70.0%)
III n (%)	26 (8.3%)	27 (8.5%)	30 (9.8%)
Previous MI n (%)	168 (53.3%)	171 (53.9%)	167 (54.4%)
Previous PCI n (%)	65 (20.6%)	73 (23.0%)	48 (15.6%)
Previous CABG n (%)	60 (19.0%)	63 (19.9%)	52 (16.9%)
Total exercise duration mean (SD) (s)	592.1 (145.4)	590.7 (144.9)	575.7 (148.4)
Time to limiting angina mean (SD) (s)	584.0 (141.2)	583.5 (140.7)	565.0 (144.6)
Time to angina onset mean (SD) (s)	466.0 (149.4)	476.6 (147.3)	455.1 (147.3)
Time to 1mm ST depression mean (SD) (s)	504.4 (163.9)	505.3 (157.0)	494.2 (156.8)
Heart rate at rest mean (SD) (bpm)	0.2 (13.4)	78.3 (13.7)	79.1 (13.6)
Heart rate at peak exercise mean (SD) (bpm)	125.1 (17.0)	124.3 (17.3)	124.7 (17.8)
Rate pressure product at rest (bpm.mmHg)	10943 (2482)	10683 (2522)	10801 (2418)
RPP at peak exercise (bpm.mmHg)	21419 (4621)	21127 (4629)	21643 (5195)

Recruitment Not reported

Setting Hospital

Interventions/ Test/ Factor being investigated	Ivabradine 5mg bd for four weeks increasing to 7.5mg bd or 10mg bd for twelve weeks
Comparisons	Atenolol 50 mg daily for four weeks increaing to 100 mg for twelve weeks
Length of Study/ Follow-up	End of treatment four months
Outcome measures studied	1RY: Change in total exercise duration at drug trough. 2RY: Time to onset/limiting angina, 1mm ST depression, heart rate, rate-pressure product, total exercise duration at drug peak, frequency of angina attacks, short-acting nitrate use
Results	PRIMARY

	Ivabradine 7.5mg	Ivabradine 10mg	Atenolol
Total exercise duration (trough) mean (SD) (s):			
Baseline	594.9 (141.6)	590.8 (142.9)	578.2 (144.2)
Change baseline to month 4 (end therapy)	86.8 (129.0)	91.7 (118.8)	78.8 (133.4)
Difference from atenolol (95% CI)	10.3 (-8.3 to +28.8)	15.7 (-2.9 to +34.3)	-

SECONDARY

Time to limiting (trough) mean (SD) angina (s)			
Baseline	587.0 (138.0)	583.5 (139.6)	568.1 (139.8)
Change baseline to month 4 (end therapy)	91.8 (131.1)	96.9 (121.2)	85.4 (133.7)
Difference from atenolol (95% CI)	9.3 (-9.6 to +28.3)	15.1 (-3.9 to +34.0)	-
Time to angina onset (trough) mean (SD) (s)			
Baseline	468.0 (147.1)	477.0 (147.8)	457.4 (145.0)
Change baseline to month 4 (end therapy)	145.2 (153.4)	139.6 (140.6)	135.2 (154.7)
Difference from atenolol (95% CI)	12.1 (-10.5 to +34.7)	10.1 (-12.5 to +32.8)	-
Time to 1mm ST depression (trough) mean (SD) (s)			
Baseline	521.7 (164.3)	528.6 (161.8)	510.7 (156.0)
Change baseline to month 4 (end therapy)	98.0 (153.7)	86.9 (128.2)	95.6 (147.5)
Difference from atenolol (95% CI)	4.3 (-16.8 to +25.3)	-3.3 (-24.4 to +17.8)	-
Heart rate at rest (trough) mean (SD) (bpm)			
Baseline	80.1 (13.4)	78.4 (13.6)	78.9 (13.6)
Change baseline to month 4 (end therapy)	-14.3 (11.9)	-14.3 (13.3)	-15.6 (12.0)
Difference from atenolol (95% CI)	2.1 (0.6 to 3.7)	1.1 (-0.4 to +2.7)	-
Heart rate at peak exercise (trough) mean (SD) (bpm)			
Baseline	125.2 (17.1)	124.3 (17.1)	124.4 (17.2)
Change baseline to month 4 (end therapy)	-8.6 (13.7)	-10.3 (14.1)	-14.0 (14.4)
Difference from atenolol (95% CI)	5.6 (3.5 to 7.6)	3.6 (1.6 to 5.6)	-
Rate-pressure product at rest (trough) mean (SD) (bpm.mmHg)			
Baseline	10919 (2494)	10721 (2499)	10759 (2400)
Change baseline to month 4 (end therapy)	-1845 (2145)	-1852 (2400)	-2417 (1969)

Difference from atenolol (95% CI) 682 (417 to 948) 555 (288 to 821) -

Rate-pressure product at peak exercise (trough) mean (SD) (bpm.mmHg)
Baseline 21435 (4658) 21063 (4653) 21599 (5214)
Change baseline to month 4 (end therapy) -1068 (4085) -1449 (3595) -3152 (3924)
Difference from atenolol (95% CI) 1980 (1387 to 2573) 1466 (878 to 2054) -

Weekly no. of angina attacks
Baseline 3.1 (5.3) 3.3 (5.4) 3.7 (14.5)
Change baseline to month 4 (end therapy) -2.2 (11.9) -2.3 (4.2) -2.7 (12.3)

Short-acting nitrate consumption (units per week)
Baseline 2.2 (4.9) 2.1 (5.1) 1.8 (4.5)
Change baseline to month 4 (end therapy) -1.6 (4.1) -1.4 (4.7) -1.2 (2.4)

Adverse events:
Number of patients who withdrew due to visual symptoms (mainly phosphenes): 2 3 0

Sinus bradycardia (%) 2.2% 5.4% 4.3%
Headache (%) 2.6% 4.8% 1.6%
Cardiac deaths (n) 2 3 1

No rebound phenomena after ivabradine discontinuation.

Safety and adverse effects

Ivabradine was 'well tolerated' with symptoms rated as transient and non-serious. 6 deaths occurred: n=2 ivabradine 7.5 mg; n=3 ivabradine 10 mg and n=1 atenolol
Headache
2.6% Ivabradine vs 1.6% Atenolol

Does the study answer the question?

Ivabradine 7.5 mg was non-inferior to atenolol for the exercise parameters, weekly angina attacks and short-acting nitrate use.

Effect due to factor in study?

Consistency of results with other studies?

Directly applicable to guideline population?

Internal Validity

Evidence Extractions

Question: What is the clinical /cost effectiveness of standard antianginal drugs (nicorandil) for the management of angina?

Grading: 1++	High-quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias

Ulvenstam G;Diderholm E;Frithz G;Gudbrandsson T;Hedback B;Hoglund C;Moelstad P;Perk J;Sverrisson JT;

Antianginal and anti-ischemic efficacy of nicorandil compared with nifedipine in patients with angina pectoris and coronary heart disease: a double-blind, randomized, multicenter study

Ref ID 15934 1992

Study Type Randomised Controlled Trial **Funding** Not reported.

Number of participant	N=58 (n=29 Nicorandil, n=29 Nifedipine)
Inclusion/Exclusion Criteria	Patients <76 years old with a history of typical effort induced angina pectoris relieved by nitroglycerin or rest were eligible for inclusion in the study. Patients with a recent MI<3 months), unstable angina, angina at rest, or vasospastic angina were excluded from the study, as were patients with uncontrolled hypertension. Also excluded were patients with ECG tracings disturbing the evaluation of the ST segment and patients with congestive heart failure, a history of exercise-induced arrhythmia, concomitant medication with digitalis, antiarrhythmics, and anti anginal dugs (e.g. B-Blockers, Calcium channel blockers, vasodilators, nitrates).
Patient Characteristics	54 of the randomised patients were men (mean age, 62. Years; range 42-64 years), and four were women (mean age, 60.3 years, range49-70 years). History of cardiovascular disease CVD: Nicorandil (n=29) vs. Nifedipine (n=29) Myocardial infarction: 13vs. 6 Cardiac failure: 1 vs. 1 Bypass surgery: 3 vs. 1 Cerebrovascular disease: 1 vs.0 Peripheral vascular disease: 3 vs. 2 Hypertension: 6 vs. 4 The pre-treatment of coronary heart disease, which occurred before entry in to pre-phase of the trial, ranged from no treatment except for nitroglycerin to triple therapy with a combination of B-Blockers, calcium antagonists, and long acting nitrates.
Recruitment	Not reported.
Setting	
Interventions/ Test/ Factor being investigated	Nicorandil 10mg b.i.d for first 4 weeks. During the last 4 week period, the dose of Nicorandil was increased to 20 mg b.i.d. Total 8 weeks treatment.
Comparisons	Nifedipine 20 mg b.i.d for first 8 weeks.
Length of Study/ Follow-up	At 4 weeks and at the end of 8 weeks of treatment (i.e. immediately after the treatment)
Outcome measures studied	Exercise duration (min), time to onset of angina pectoris (min), time to 1 mm ST depression, ST depression on maximal work load (mm), weekly anginal attack rate, adverse events.
Results	At 4 weeks : Weekly anginal attack rate: Nicorandil (n=26 vs. nifedipine (n=24) [Mean±SD] 2.6± 3.6 vs. 7.0±12.2 Exercise duration (min): nicorandil (n=25) vs. nifedipine (n=23) [mean±SE] 10. ±0.56vs. 10.6±0.55 Time to onset of angina pectoris (min): nicorandil (n=23) vs. nifedipine (n=22) [mean±SE] 7.4±0.64 vs. 7.8 ±0.60 Time to 1mm ST depression (min) : nicorandil (n=23) vs. nifedipine (n=20) [mean±SE] 7.8 ±0.54 vs.7.0 ±0.60 ST depression on maximal identical work load (mm) : nicorandil (n=24) vs. nifedipine

	(n=20) [mean±SE] 1.9±0.17 vs. 1.8±0.17 At 8 weeks: Weekly anginal attack rate: Nicorandil (n=27) vs. nifedipine (n=23) [Mean±SD] 2.1±2.1 vs. 7.4±15.0 Exercise duration (min): nicorandil (n=25) vs. nifedipine (n=23) [mean±SE] 11.4±0.64 vs. 10.4±0.51 Time to onset of angina pectoris (min): nicorandil (n=23) vs. nifedipine (n=22) [mean±SE] 8.7±0.74 vs. 7.6 ±0.57 Time to 1mm ST depression (min) : nicorandil (n=23) vs. nifedipine (n=20) [mean±SE] 8.0 ±0.66 vs.6.4±0.50 ST depression on maximal identical work load (mm) : nicorandil (n=24) vs. nifedipine (n=20) [mean±SE] 1.9±0.18 vs. 1.7±0.17
Safety and adverse effects	Adverse events: 4 patients in the nicorandil group dropped out due to adverse events (one because of acute MI and 3 because of headaches in combination with other symptoms of vasodilatation). Two patients in the nifedipine group dropped due to adverse events (one because of atrial fibrillation with high ventricular response and one because of vertigo, palpitations and nausea), and one patient dropped out because of poor compliance. Adverse events: Nicorandil (n=29) vs. nifedipine (n=29) Cardiovascular symptoms due to vasodilatation (symptoms such as dizziness, flush, ankle oedema, reported most frequently): 4 vs. 9 Headache: 13 vs. 9 Miscellaneous events (infections, gastrointestinal events, muscular or skeletal pain) : 6 vs. 5 No adverse events: 11 vs. 11
Does the study answer the question?	Yes. In the nicorandil group, an improvement was noted with the 20 mg dose compared with the 10mg dose, but no significant differences were noted between the nicorandil and nifedipine groups after either treatment. Symptoms caused by peripheral vasodilatation were commonly reported in the nifedipine group.
Effect due to factor in study?	
Consistency of results with other studies?	
Directly applicable to guideline population?	
Internal Validity	Allocation concealment and ITT not reported.

Grading: 1+ Well-conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias

Chatterjee T;Fleisch M;Meier B;Eber A;

Comparison of the antiischaemic and antianginal effects of nicorandil and amlodipine in patients with symptomatic stable angina pectoris: The SWAN study

Ref ID 3629 1999

Study Type Randomised Controlled Trial **Funding** Not reported

Number of participant N=121 (N=57 in nicorandil group and N=64 in Amlodipine group).

Inclusion/Exclusion Criteria Patients aged 18-80 years with symptomatic stable angina were screened for enrolment in the study. Eligible patients had a history of stable angina for ≥ 3 months and CHD confirmed by a history of myocardial infarction or a positive angiogram (>50% stenosis of a main coronary artery).
Exclusion criteria included: myocardial infarction, invasive coronary intervention, unstable angina, angina at rest or vasospastic angina within the last 3 months; hypertension with supine diastolic blood pressure (DBP) >105 mmHg; electrocardiogram (ECG) recordings not allowing a evaluation of the ST segment; manifest congestive heart failure (New York Heart Association class 3-4); peripheral arterial obstructive disease or any other exercise test limiting disease; cardiac valvular disease with haemodynamic or clinical consequences; supine systolic blood pressure (SBP) <100 mmHg or DBP <70 mmHg; postural hypotension (>20% decrease in SBP after 1 min standing); and severe concomitant disease. Female patients were to be postmenopausal or surgically sterile.

Patient Characteristics

Characteristic:	Nicorandil (N=57);	Amlodipine (N=64)
Gender (male: female):	44: 13;	53:11
Age (years):	62±9;	62±9
Bodyweight (Kg):	76±12;	76±10
No. of anginal attacks/week:	4.3±4.1;	4.4±5.5
Duration of history of angina pectoris (months):	51±69;	57±64
No. of patients with previous history of MI:	14;	26
No. of units of nitroglycerin required for immediate relief:	1.9±2.9;	1.6±2.4
Exercise tolerance test parameters		
Time to onset of 0.1 Mv ST-depression (min):	4.7±0.3;	5.1±0.3
Time to onset of anginal pain (min):	5.2±0.3;	5.6±0.3
Total exercise duration (min):	6.7±0.3;	7.3±0.4
ST-segment depression (Mv):	-0.17±0.01;	-0.17±0.01

Recruitment Participants recruited from 25 centres in Austria (n=11) and Switzerland (n=14).

Setting Hospital centre

Interventions/ Test/ Factor being investigated Intervention is Nicorandil 10 mg bd orally.Depending on the patient's clinical condition, study medication was either maintained at the same dosage for the remainder of the study or increase after 2-4 weeks to nicorandil 20 mg bd.
Dose titration: The percentage of patients following the high dosage regimen was similar in the nicorandil and amlodipine groups (50% and 43.5%, respectively at the end of the study).

Comparisons Comparison is is Amlodipine 5 mg od orally. Depending on the patient's clinical condition, study medication was either maintained at the same dosage for the remainder of the study or increased after 2-4 weeks to amlodipine 10 mg od.

Length of Study/ Follow-up The patients were followed up for 8 weeks.

Outcome measures studied Primary and Sec. endpoints not specified.
Outcome measures: Exercise tolerance test using an upright bicycle, patients recorded no. of anginal attacks/day and the no. of nitroglycerin tablets, quality of life (4 variable questionairre), adverse events.

Results

Exercise tolerance tests (ETT):
Nicorandil (n=56)
Parameter: Baseline; 2 weeks; 8 weeks (mean±SEM)
Time to onset of 0.1 mv ST-segment depression (min): 4.7±0.3; 5.0±0.3; 5.1 ±0.3
Time to onset of anginal pain (min): 5.2±0.3; 6.1±0.3*; 6.1±0.4*
Total exercise duration (min): 6.7±0.3; 7.2±0.3*; 7.2±0.4*
ST-segment depression at maximal identical workload (mv):-0.17±0.01; -0.14±0.01*; -0.13±0.01*

Amlodipine (n=62)
Parameter: Baseline; 2 weeks; 8 weeks (mean±SEM)
Time to onset of 0.1 mv ST-segment depression (min): 5.1±0.3; 6.0±0.4*; 5.7±0.3*
Time to onset of anginal pain (min): 5.6±0.3; 6.6±0.3*; 7.0±0.4*
Total exercise duration (min):7.3±0.4; 7.9±0.4*; 7.9±0.3*
ST-segment depression at maximal identical workload (mv):-0.17±0.01; -0.12±0.01*;-0.12±0.01*

*indicates that the difference to baseline was statistically significant.

Weekly anginal attacks:
Nicorandil (n=56)
Parameter: Baseline; 2 weeks; 8 weeks (mean±SEM)
Sum of weekly anginal attacks: 3.4±0.5; 2.9±0.6; 2.1±0.4
No. of nitroglycerin units for immediate relief: 2.3±0.6; 1.9±0.6; 1.5±0.5

Amlodipine (n=62)
Parameter: Baseline; 2 weeks; 8 weeks (mean±SEM)
Sum of weekly anginal attacks: 3.3±0.5; 2.5±0.5; 0.9±0.2*
No. of nitroglycerin units for immediate relief: 1.0±0.2; 0.8±0.2; 0.6±0.3

*indicates that the difference to baseline was statistically significant.

Adverse events (8 weeks): 29 adverse events reported by 20/57 patients in Nicorandil group; 34 adverse events reported by 20/64 patients in amlodipine group.
Adverse event: Nicorandil (n=57) vs. Amlodipine (n=64)
Peripheral oedema: 0 vs. 7
Headache: 3 vs. 1
Vertigo: 2 vs. 0
Flushing/burning face: 0 vs. 2
Nausea: 0 vs. 1
Abdominal pain: 0 vs. 1
Tachycardia: 0 vs. 1
Itching: 0 vs. 1
Trembling: 0 vs. 1

Quality of life: Overall, the ratings for all 4 quality of life variables improved during the study in both treatment groups (data not reported).

Safety and adverse effects

A total of 29 adverse events were reported by 20/57 (35.1%) patients in the nicorandil group, while 20/64 (31.3%) patients in the amlodipine group reported 34 adverse events. The most common adverse events that were considered at least probably related to treatment included mild or moderate headache and vertigo in the nicorandil group, and peripheral oedema in the amlodipine group. No death occurred during treatment with either nicorandil or amlodipine.
Among 5 patients withdrawn because of adverse events, one nicoradil treated patient experienced severe, long-lasting vertigo judged to be causally related to the study medication. Two other patients in each treatment group experienced adverse events necessitating treatment withdrawal (nicorandil: severe angina pectoris and tachycardia, one patient each; amlodipine: severe angina pectoris and MI, one patient each). In each case, however, causal relationship with the study medication was considered remote.

Does the study answer the question?

Yes.
Time to onset of ST-segment depression increased in both treatment groups during the study. However, the difference compared to baseline was only statistically significant in the amlodipine group. Time to onset of angina pain and total exercise duration was significantly higher in all patients at 2 weeks and 8 weeks compared to baseline, while the magnitude of ST-segment depression at maximal identical work load was significantly decreased. There were no significant differences between the two treatment groups and no significant medication and country interactions for any

of the ETT target variables.

The sum of weekly anginal attacks decreased progressively in both the treatment groups during the 8 week treatment period, becoming statistically significant compared to baseline after 4 weeks. There was no significant difference between the two treatment groups in terms of antianginal efficacy.

The number of nitroglycerine units required for immediate relief similarly decreased in both groups. The decrease was significant at 4, 6 and 8 weeks in patients receiving nicorandil, and at 4 and 6 in the amlodipine group. No significant between group differences were apparent.

Conclusion reported in the study: The antianginal effects of nicorandil were comparable to amlodipine in patients with symptomatic stable angina pectoris. In addition, both drugs were generally well tolerated and had a positive effect on quality of life in this patient population.

Effect due to factor in study? Yes

Consistency of results with other studies? Yes

Directly applicable to guideline population? No. Study conducted in Austria and Switzerland.

Internal Validity selection bias

Dargie HJ;

Effect of nicorandil on coronary events in patients with stable angina: The Impact Of Nicorandil in Angina (IONA) randomised trial

Ref ID 6190 2002

Study Type Randomised Controlled Trial

Funding Sponsored by Merck Pharmaceuticals Ltd, Aventis Pharma Ltd, and Chugai Pharmaceutical Co Ltd.

Number of participant N=2561 Placebo
N=2565 Nicorandil

Inclusion/Exclusion Criteria The study recruited men (aged≥ 45 years) and women (aged≥ 55 years), with evidence of stable angina of effort, who also required regular treatment with one or more symptom relieving oral anti anginal drugs (long acting nitrates, B-blocker, or calcium channel blocker) and had experienced at least one of the following: Previous myocardial infarction; previous coronary artery bypass graft; coronary heart disease proven by angiography or a documented positive exercise test (≤ 1 mm ST depression) in the previous 2 years. The last of the 3 inclusion criteria was required to be accompanied by at least one of the following: left ventricular hypertrophy; evidence of left ventricular dysfunction (ejection fraction ≤45% or end diastolic dimension > 5.5 cm) ; age ≥ 65 years; diabetes (types 1 or 2);hypertension (treated, and/or systolic blood pressure>160 mm Hg or diastolic blood pressure >95 mm Hg); documented evidence of other vascular disease (stroke, transient ischaemic attack requiring hospital admission, peripheral arterial disease).
Patients with any of the following were excluded:
Uncontrolled cardiac failure or arrhythmias; unstable angina; coronary artery bypass graft or myocardial infarction in the previous 3 months; percutaneous transluminal coronary angioplasty in the previous 6 months; uncontrolled hypertension (systolic blood pressure >180 mm Hg or diastolic blood pressure >110 mm Hg); the presence of other diseases that in the investigators opinion would reduce life expectancy or influence significantly the patients cardiovascular condition; current treatment with Nicorandil; current treatment with sulfonylureas; pregnancy or lactation; legal incapacity or limited legal capacity; participation in another clinical study within the previous 30 days; presence of contraindications to the study medication; known drug

	or alcohol abuse.
Patient Characteristics	Nicorandil (N=2565) Male 1962 (76%) Diabetic 197 (8%) Hypertensive 1197 (47%) Current smoker 417 (16%) Previous MI 1696 (66%) Previous CABG 572 (22%) Previous PTCA 360 (14%) Previous angiogram 1508 (59%) Previous stroke 134 (5%) Hospital admission for TIA 47 (2%) History of PVD 289 (11%) History of LVD 230 (9%) CCSF classification for angina I 671 (26%) II 1605 (63%) III 272 (11%) IV 15 (1%) Mean age 67 (SD8) BMI (kg/m²) 28 (SD5) Placebo (N=2561) Male 1948 (76%) Diabetic 232 (9%) Hypertensive 1178 (46%) Current smoker 425 (17%) Previous MI 1682 (66%) Previous CABG 590 (23%) Previous PTCA 392 (15%) Previous angiogram 1525 (60%) Previous stroke 116 (5%) Hospital admission for TIA 335 (13%) History of PVD 335 (13%) History of LVD 206 (8%) CCSF classification for angina I 692 (27%) II 1583 (62%) III 275 (11%) IV 9 (<1%) Mean age 67 (SD9) BMI (kg/m²) 28 (SD4)
Recruitment	Subjects were recruited in more than 200 trial centres in hospitals and general practices throughout the UK.
Setting	General practices and hospital centres.
Interventions/ Test/ Factor being investigated	Nicorandil 10 mg b.d for two weeks 20 mg b.d thereafter
Comparisons	Compared with placebo
Length of Study/ Follow-up	Between 1 and 3 yrs. Primary endpoint combined outcome of coronary artery disease, non-fatal myocardial infarction, or unplanned hospital admission for cardiac chest pain
Outcome measures studied	Primary end point-Combined outcome of CHD death, non-fatal myocardial infarction, or unplanned hospital admission for cardiac chest pain.Sec. end point- CHD death or non-fatal MI. Other outcomes-Acute coronary syndromes, CV events,mortality
Results	Primary outcomes Mean follow-up 1.6 years Composite events Nicorandil (n=2565) vs Placebo (N=2561) CHD death, non-fatal MI, or hospital admission for cardiac chest pain 337 (13.1%) vs 398 (15.5%); HR 0.83 (0.72 to 0.97); p=0.014 Secondary outcomes

Nicorandil (n=2565) vs Placebo (N=2561)
CHD death 60 (2.3%) vs 73 (2.9%)
Non-fatal MI 56 (2.1%) vs 72 (2.8%)
Unstable angina 115 (4.5%) vs 127 (5.0%)
Presumed angina 128 (5.0%) vs 153 (6.0%)
Stroke or hospital admission 37 (1.4%) vs 40 (1.6%)
CHD or non-fatal MI 107 (4.2%) vs 134 (5.2%); HR 0.79 (0.61 to 1.02); p=0.068
CHD death, non-fatal MI or unstable angina 156 (6.1%) vs 195 (7.6%); HR 0.79 (0.64 to 0.98); p=0.028
All cardiovascular events 378 (14.7%) vs 436 (17.0%); HR 0.86 (0.75 to 0.98); p=0.027
All-cause mortality 111 (4.3%) vs 129 (5.0%); HR 0.85 (0.66 to 1.10); p=0.222
Worsening of angina status 569 (22%) vs 602 (24%); OR 0.93 (0.81 to 1.06); p=0.26

Canadian Cardiovascular Society Functional classification of angina at the end of the study (follow-up mean 1.6 years):
Class I - Nicorandil 985 (43%); Placebo 989 (43%)
Class II- Nicorandil (1159 (50%); Placebo 1124 (49%)
Class III- Nicorandil 162 (7%); Placebo 163 (7%)
Class IV- Nicorandil 9(<1%) ; Placebo 15 (1%)

Safety and adverse effects

Adverse events
No. of GI events 194 vs 132
No. of withdrawals from study medication 413 (16.1%) vs 163 (6.4%) at two weeks, 566 (22.1%) vs 308 (12.0%) at 8 weeks, 758 (29.6%) and 499 (19.5%) at 6 months, and 1003 (39.1%) and 809 (31.6%) at the end of the study

Does the study answer the question?

The study reported a significant improvement in outcome from antianginal treatment in patients with stable angina. Outcome was defined as a combination of morbidity and mortality by a composite primary endpoint of coronary heart disease, non-fatal MI, or unplanned hospital admission for chest pain. Event rates in all components of the primary endpoint were lower in the patients on nicorandil than on placebo.

Effect due to factor in study?

Yes

Consistency of results with other studies?

Yes

Directly applicable to guideline population?

Yes. Study conducted in the UK.

Internal Validity

selection bias

Meeter K;Kelder JC;Tijssen JG;Bucx JJ;Henneman JA;Kerker JP;Hugenholtz PG;

Efficacy of nicorandil versus propranolol in mild stable angina pectoris of effort: a long-term, double-blind, randomized study

Ref ID 1251 1992

Study Type Randomised Controlled Trial **Funding** Rhone-Poulenc Sante Inc

Number of participant

Nicorandil N=32 and N=37 propanolol

Inclusion/Exclusion Criteria

Male patients with a history of typical and stable angina pectoris for at least 2 months duration. The anginal episodes had occurred a minimum of four times within the previous four weeks. The patients had to be limited by chest pain in their daily activities. Candidates must have expected angina during the exercise test and have had reversible ischemic repolariation disturbances during the ECG of at least 0.1 mV. Exclusion criteria: recent myocardial infarction, obvious atrioventricular or intraventricular conduction defects, systemic hypertension or hypotension, valvular abnormalities with hemodynamic consequences, and any metabolic disorder or known nocardiac disease. Patients who required antianginal drugs other than sublingual nitroglycerin and patients to whom propranolol had been prescribed during the past 6 monmths also were excluded.

Patient Characteristics	Nicorandil (N=38): mean age 61 (SD7), mean body weight index 26 (2) kg/m2, median duration of angina pectoris 12 mths, median frequency of attacks per month 9, median average duration of attacks 5 min, actual achieved work load vs. expected maximum work load: first exercise test on placebo 103% Propanolol (N=39): mean age 62 (SD9), mean body weight index 26 (2) kg/m2, median duration of angina pectoris 20 mths, median frequency of attacks per month 7, median average duration of attacks 7 min, actual achieved work load vs. expected maximum work load: first exercise test on placebo 95%
Recruitment	Not reported
Setting	Nine hospitals, The Netherlands
Interventions/ Test/ Factor being investigated	Medication was withdrawn over a 1 to 2 week period. Nicorandil 10mg b.i.d for three weeks then doasge increased to 20mg b.i.d for three weeks or 10 mg b.i.d otherwise. Propanolol 40 mg t.i.d for three weeks and then 80mg t.i.d if tolerated otherwise 40mg t.i.d. The dose was not increased if systolic blood pressure at rest was less than 100 mm Hg, diastolic pressure was less than 60 beats/min, or intraventricular conduction defects were present on the ECG.
Comparisons	Nicorandil baseline vs 3 weeks treatment vs 6 weeks treatment Propanolol baseline vs 3 weeks treatment vs 6 weeks treatment Nicorandil vs propanolol 3 and 6 weeks treatment
Length of Study/ Follow-up	6 weeks.Primary and sec. end points not specified.
Outcome measures studied	Median no. of angina attacks per week; proportion of patients were angina free in daily life; Maximal work load and time to angina pectoris both baseline, 3 and 6 weeks treatment. All 12 hrs after medication and 2 hr after medication.
Results	12 hrs after medication Nicorandil (n=32) and Propanolol (n=37) Maximal work load (W) Baseline on placebo 154 (36) vs 140 (32) Change from baseline to first treatment (3 wks) -1 (SD19) vs +5 (18); ns Change from baseline to second treatment (6 wks) +1 (24) vs +6 (21); ns Time to angina pectoris (deciminal min) Baseline on placebo 6.2 (2) vs 5.8 (2) Baseline to first treatment +0.4 (2) vs +0.5 (2); ns Baseline to second treatment +0.4 (2) vs +0.8 (2)* * p<0.05, difference within treatment group vs. baseline 2 hrs after medication Nicorandil (n=32) and Propanolol (n=37) Maximal work load (W) Baseline on placebo 158 (31) vs 140 (28) Change from baseline to first treatment (3 wks) +3 (SD14) vs +8 (20); ns Change from baseline to second treatment (6 wks) +4 (17) vs +9 (23); ns Time to angina pectoris (deciminal min) Baseline on placebo 5.9 (2) vs 5.9 (2) Baseline to first treatment +1.0 (1)* vs +0.8 (2)*; ns Baseline to second treatment +1.5 (2) vs +0.9 (2)* * p<0.05, difference within treatment group vs. baseline NB Exercise capacity of patients whilst taking placebo was near normal and a further increase was not expected
Safety and adverse effects	Withdrawal due to worsening angina
Does the study answer the question?	Patients had near normal exercise tolerance on placebo. Patient group may not be representative i.e male only population

Effect due to factor in study?	Analysis did not take into account baseline differences. No ITT.
Consistency of results with other studies?	No other identified
Directly applicable to guideline population?	Applicable to a sub-set of patients
Internal Validity	

Grading: 1- Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias*

Doring G;

Antianginal and anti-ischemic efficacy of nicorandil in comparison with isosorbide-5-mononitrate and isosorbide dinitrate: results from two multicenter, double-blind, randomized studies with stable coronary heart disease patients

Ref ID 1249 1992

Study Type Randomised Controlled Trial **Funding** Not reported

Number of participant N=129 (N=95 received nicorandil, N=34 received ISDN, N=63 received ISMN)

Inclusion/Exclusion Criteria For both the studies, men and women 25-75 years with a typical history of stable coronary heart disease and stress-induced reproducible anginal pain and ST-segment depression of at least 0.2mv at 0.08 after the J-point in two successive exercise tolerance tests (ETT). Exclusion criteria: Not reported

Patient Characteristics

Characteristics: Study 1 (Nicorandil vs. ISMN)
Number: 63
Male: 38
Female:25
Age (mean ±SD years): 62±8.54
Height (mean±SD cm): 169.9±8.02
Weight (mean±SD kg):75.7±10.93
History of MI (n):13
Coronary angiography (n):19

Study 2 (Nicorandil vs. ISDN)
Characteristics: Nicorandil ; ISDN
Number: 32; 34
Male: 22; 28
Female: 10; 6
Age (mean ±SD years): 60.5±6.93; 58.0±7.14
Height (mean±SD cm): 168.9±7.34; 171.1±7.82
Weight (mean±SD kg):73.9±11.66; 75.4±10.72
History of MI (n): 13; 17
Coronary angiography (n): 21; 19

Recruitment Not reported.

Setting Multicentres in Germany

Interventions/ Test/ Factor being investigated

20 mg Nicorandil b.i.d (for study-1) and 20 mg Nicorandil t.i.d (for study-2)
Patients underwent a 2 week placebo run-in before the randomisation.

Study-2: After a single blind 2 week pre-phase of 10 mg t.i.d ISDN, patients received either 10 mg t.i.d nicorandil or 10 mg t.i.d ISDN with a dose increase after 2 weeks to 20 mg t.i.d nicorandil or 20 mg t.i.d ISDN, respectively for an additional 4 weeks.

Comparisons Study 1- 20 mg b.i.d ISMN (Isosorbide mononitrate)
Study 2- 20 mg t.i.d ISDN (Isosorbide dinitrate)

Length of Study/ Follow-up 4 weeks

Outcome measures studied Primary and Secondary end points not specified.EET, anginal attack rate, adverse effects. (Headache questionnaire)

Results

A. ETT
1.Total exercise duration- Data not extractable, results reported in graphically.
2.Time to onset of anginal pain- Data not extractable, results reported graphically.
3.ST-segment depression:
Study 1- 0.273 mv for baseline, 0.143 mv for 10 mg nicorandil, and 0.128 mv for 20 mg nicorandil.
Study 2- Nicorandil group: 0.220 mv for baseline, 0.143 for 10 mg nicorandil, and

0.128 mv for 20 mg nicorandil.
Study 2- ISDN group: 0.208 mv for baseline, 0.127 mv for 10 mg ISDN, and 0.121 mv for 20 mg ISDN.
All changes were significant compared with the respective baseline values ($p<0.05$). Significant differences between groups could not be found ($p>0.05$).

B. Anginal attack rates- Data not extractable, results reported graphically.

C. Adverse effect-
Head ache (no. of patients)-
Study -1(4 weeks): Nicorandil (20 mg)– 25 patients; ISMN (20 mg)- 21 patients (not clear out of how many patients).
Study 2- baseline (ISDN 10mg); 4 weeks (10 mg); 4 weeks (20 mg)
Nicorandil group: 18 of 32; 14 of 30; 12 of 30
ISDN group: 7 of 34; 9 of 34; 9 of 30

Safety and adverse effects

The most frequently reported adverse event was headache. The incidence of other adverse events was very low in both studies.Gastrointestinal disturbances occurred in 3 patients during treatment with nicorandil (vomiting, severe abdominal pain, mild abdominal pain) and in 3 patients during treatment with ISDN (epigastric discomfort, diarrhea, gastroenteritis).

Does the study answer the question?

No, the study does not help to answer the question.
Conclusion reported by the authors: Nicorandil, ISMN and ISDN are equieffective antianginal drugs with regard to improvement of angina attack rates as well as to increased exercise capacity. With regard to adverse events, nicorandil compares well with ISMN and ISDN.

Effect due to factor in study?

Yes

Consistency of results with other studies?

Yes

Directly applicable to guideline population?

No. Study conducted in Germany.

Internal Validity

Attrition bias

Guermonprez JL;Blin P;Peterlongo F;

A double-blind comparison of the long-term efficacy of a potassium channel opener and a calcium antagonist in stable angina pectoris

Ref ID 1187

1993 Jul

Study Type Randomised Controlled Trial

Funding Not reported

Number of participant

N=123; N=63 (Diltiazem group) and N=60 (Nicorandil group)

Inclusion/Exclusion Criteria

Inclusion criteria: Patients with stable angina. Positive exercise tolerance test showing a 1 mm ST segment depression between 3 and 12 min associated with typical anginal pain, a history of myocardial infarction, or significant stenosis (>50%) as revealed by coronary angiography (which was obligatory for women if they had not had myocardial infarction). Exclusion criteria : Not reported.

Patient Characteristics

N : Diltiazem (N=63) ; Nicorandil (N=60)
Sex : 54 M/9 F ; 54 M/6F
Age (yrs): 60.7 ±0.8; 60.1±0.9
Duration of angina (yrs): 3.7±0.5; 3.6±0.9
Previous myocardial infarction: 22 (34.9); 21 (35.0)
Patients with coronary angiography (%): 28 (44.4); 27 (45.0)
One-vessel disease (%): 9(32.1); 10 (37.0)
Two-vessel disease (%): 8(28.6); 9 (33.3)
Three-vessel disease (%): 10 (35.7); 8 (29.6)

Recruitment

Between May 1987 and Feb 1989, 123 patients with stable angina were enrolled in the study which involved 19 centres (No further details of recruitment reported).

Setting	Medical centres
Interventions/ Test/ Factor being investigated	After a 7-day period during which all patients received placebo, patients were assigned to receive either the intervention or comparison drug.The intervention is Nicorandil (20 mg.day) in two divided doses (at 0800h and 2000h) for the first 2 weeks and then 40mg.day for the rest of the study. Patients were allowed to take Nitroglycerin tablets, if necessary, but their consumptiom of this drug was to be noted by the patient and it was not to be taken within 2 h before performing the exercise tolerance test.
Comparisons	Comparison is Diltiazem(180 mg.day) in three divided doses (0800h, 1300h and 2000h).
Length of Study/ Follow-up	The patients were followed up to 90 days (3 months). Outcomes were assessed at day 0 and day 90. Primary and Secondary endpoints not specified.
Outcome measures studied	Outcome measures: Exercise tolerance test, patients asked to note in diary number of anginal attacks, questions to evaluate compliance and identify adverse events. Primary outcomes: Exercise capacity, Frequency of anginal attacks, adverse events.
Results	Exercise capacity: Time; Nicorandil (N=50) vs. Diltiazem (N=56); comparison of evaluation in the 2 groups (mean±SE) Work to angina onset (kj): Day 0; 38.1±17.9 vs. 33.3± 18.1; p=ns Day 90; 48.1±24.7; 44.7±20 Work to ischaemic threshold (kj): Day 0; 29.3±15.7 vs. 23.1±11.7; p=ns Day 90; 38.7±24.2 vs. 37.8±19.4 Work to peak exercise(kj): Day 0; 42.3±19.0 vs. 37.3±18.6; p=ns Day 90; 49.2±24.4 vs. 46.8±20.6 Frequency of attacks: Data not reported seperately for the two treatment groups. In both groups there was a marked reduction in the frequency of angina attacks from a mean value of 2.9/week in the first week on placebo to 0.7/week at the end of the 3 months. Repeated measure analysis of variance showed that this clinical improvement was significant (p=0.0001) and the difference between the two groups was not significant (p=0.56). This was also reflected in the decrease in consumption of trinitrin. For the group receiving Nicorandil, consumption of rapid acting nitrates was reduced from 2.51±3.28/week on day 0 to 0.74±1.78/week on day 90, while for the diltiazem group the reduction was from 2.83±3.56/week to 0.78±1.54/week.The differences between the two treatment groups in terms of trinitrin consumption were not significant. Adverse events: 31.7% of patients in Nicorandil group vs. 30.2%of patients Diltiazem group. Nicorandil (N=60) vs. Diltiazem (N=63) Patients with side effects: 17 (28.3%) vs.15 (23.8%) Head ache (no. of patients): 13 (21.7%) vs. 5 (7.9%) Gastro intestinal disturbances (no. of patients): 2 (3.3%) vs. 6 (9.5%) Flush (no. of patients): - vs. 3 (4.8%) Palpitation, tachycardia (no. of patients): - vs. 3 (4.8%) Dizziness (no. of patients): 2 (3.3%) vs. - Asthenia (no. of patients): 2(3.3%) vs. - Other (no. of patients): 2(3.3%) vs. 4 (6.3%)
Safety and adverse effects	Adverse events reported in about a third of the patients in both the groups. By far the most common complaint for the patients receiving nicorandil was headcahe (22%), whereas adverse events noted with diltiazem were more diverse, with gastrointestinal disorders coming first (9.5%).
Does the study answer the question?	Yes, the study helps answer the clinical question. Nicorandil and diltiazem were both found to decrease the frequency of anginal attacks and the consumption of nitroglycerin tablets (p=0.0001) but the difference between the groups was not significant (p=ns). Maximum exercise capacity, the amount of work required to reach onset of angina were significantly increased for both groups of patients on day 90 compared with day 0. Differences between the 2 groups were not significant. Approximately the same number of patients in each group experienced at least one adverse event (nicorandil-31.7%; diltiazem-30.2%) and an equal number of patients in each group (5 patients in the diltiazem group and 7 in the nicorandil group) withdrew from the study because of insufficient efficacy .

	These results indicate that the efficacy and safety profile of Nicorandil 20.mg b.d, is comparable with that of Diltiazem, 60 mg.t.d for the treatment of stable angina.
Effect due to factor in study?	Yes
Consistency of results with other studies?	Yes
Directly applicable to guideline population?	No. Study conducted in France.
Internal Validity	Selection bias, no ITT

IONA Study Group;

Impact of nicorandil in angina: subgroup analyses

Ref ID 311 2004 Dec

Study Type	Randomised Controlled Trial	**Funding**	Sponsored by Merck Pharmaceuticals Ltd, Aventis Pharma Ltd, and Chugai Pharmaceutical Co Ltd.

Number of participant	N=2561 Placebo N=2565 Nicorandil
Inclusion/Exclusion Criteria	The study recruited men (aged≥ 45 years) and women (aged≥ 55 years), with evidence of stable angina of effort, who also required regular treatment with one or more symptom relieving oral anti anginal drugs (long acting nitrates, B-blocker, or calcium channel blocker) and had experienced at least one of the following: Previous myocardial infarction; previous coronary artery bypass graft; coronary heart disease proven by angiography or a documented positive exercise test (≤ 1 mm ST depression) in the previous 2 years. The last of the 3 inclusion criteria was required to be accompanied by at least one of the following: left ventricular hypertrophy; evidence of left ventricular dysfunction (ejection fraction ≤45% or end diastolic dimension > 5.5 cm) ; age ≥ 65 years; diabetes (types 1 or 2);hypertension (treated, and/or systolic blood pressure>160 mm Hg or diastolic blood pressure >95 mm Hg); documented evidence of other vascular disease (stroke, transient ischaemic attack requiring hospital admission, peripheral arterial disease). Patients with any of the following were excluded: Uncontrolled cardiac failure or arrhythmias; unstable angina; coronary artery bypass graft or myocardial infarction in the previous 3 months; percutaneous transluminal coronary angioplasty in the previous 6 months; uncontrolled hypertension (systolic blood pressure >180 mm Hg or diastolic blood pressure >110 mm Hg); the presence of other diseases that in the investigators opinion would reduce life expectancy or influence significantly the patients cardiovascular condition; current treatment with Nicorandil; current treatment with sulfonylureas; pregnancy or lactation; legal incapacity or limited legal capacity; participation in another clinical study within the previous 30 days; presence of contraindications to the study medication; known drug or alcohol abuse.
Patient Characteristics	See main trial ref ID 4190
Recruitment	Primary care and hospital UK
Setting	Primary care and hospital UK
Interventions/ Test/ Factor being investigated	Nicorandil 10 mg b.d for two weeks and then 20 mg b.d thereafter
Comparisons	Compared with placebo

Length of Study/ Follow-up	Follow-up 1 to 3 yrs. Mean 1.6 yrs
Outcome measures studied	Primary endpoint combined outcome of coronary artery disease, non-fatal myocardial infarction, or unplanned hospital admission for cardiac chest pain.
Results	Combined outcome of coronary artery disease, non-fatal myocardial infarction, or unplanned hospital admission for cardiac chest pain. Diabetes YES Placebo 40/232 Nicorandil 27/197 NO Placebo 358/2329 Nicorandil 310/2368 p=0.95 Age > 70 yrs Placebo 167/948 Nicorandil 131/927 65-70 yrs Placebo 81/567 Nicorandil 82/599 < 65 yrs Placebo 150/1948 vs Nicorandil 124/1039 p=0.67 Sex Female Placebo 87/613 Nicorandil 86/603 Male Placebo 311/1948 vs Nicorandil 251/1962 p=0.19
Safety and adverse effects	Not reported in this sub-group analysis
Does the study answer the question?	The subgroup analyses provide no significant evidence of any quantitative or qualitative interactions between nicorandil treatment benefit and subgroup status.
Effect due to factor in study?	Yes
Consistency of results with other studies?	Yes
Directly applicable to guideline population?	Yes. Study conducted in the UK.
Internal Validity	post-hoc sub-group analysis

Zhu WL;Shan YD;Guo JX;Wei JP;Yang XC;Li TD;Jia SQ;He Q;Chen JZ;Wu ZG;Li ZQ;You K;

Double-blind, multicenter, active-controlled, randomized clinical trial to assess the safety and efficacy of orally administered nicorandil in patients with stable angina pectoris in China

Ref ID 108 2007 Jun

Study Type Randomised Controlled Trial

Funding This trial was supported by Chugai Pharmaceutical Co Ltd, Japan.

Number of participant	N=249 (N=125 in nicorandil group and N=124 in the ISMN group).
Inclusion/Exclusion Criteria	Male or female patients had to meet the following inclusion criteria: at least 18 years old; history of typical stable angina for at least 1 month (As defined in the guideline for diagnosis of anginal pectoris in China); achieved relief from anginal attacks with short acting nitroglycerin (NTG); had a positive result for an exercise tolerance test (ETT) at the end of the washout period; able to give written informed consent. Exclusion criteria: History of MI, unstable angina, or coronary revascularisation procedure within the past 6 months; symptomatic congestive heart failure (New York Heart Association class 3-4); peripheral arterial obstructive disease or other diseases limiting ETT; arrhythmias requiring active treatment; use of concomitant drugs such as calcium channel blockers and nitrates (excluding NTG for reliving anginal pain), trimetazidine, and Chinese herbal medicine; type 1 or type 2 diabetes mellitus with a fasting serum glucose level >160mg/dl.

Patient Characteristics	Characteristics: Nicorandil (n=115); ISMN (n=117) Male: 73.9%; 75.2% Female: 26.1%; 24.8% Age: 55.1±9.4; 56.6±8.4 Duration of history of angina pectoris ≤1 month:0% ; 0% >1 month ≤1 year: 58.3%; 50.4% >1 year ≤5 years: 28.7%; 37.6% >5 years: 15%; 12% History of cardiovascular disease All: 46.1%; 44.4% Old MI: 4.3%; 1.7% Hypertension: 35.7%; 32.5% Hyperlipidemia: 7%; 5.1% Type 2 diabetes: 7.8%; 7.7% Pre-treatment with antianginal drug Yes: 53.9%; 54.7% B-blockers: 32.2%; 32.5% Ca antagonists: 1.7%; 3.4% Nitrates: 7% vs. 9.4% Concomitant medication Yes: 65.2%; 59.8% B-blockers: 31.3%; 30.8% Statins: 23.5%; 22.2% ACEI: 12.2%; 18.8% ARB: 7%; 2.6% Antiplatelet agents: 45.2%; 47%
Recruitment	Recruited from 10 institutions in china. No further details reported.
Setting	Medical institutions
Interventions/ Test/ Factor being investigated	Nicorandil 5 mg t.i.d for 2 weeks
Comparisons	ISMN 20 mg b.i.d for 2 weeks
Length of Study/ Follow-up	After 2 weeks of treatment
Outcome measures studied	Primary end point: Time to ST-depression. Secondary end points: Total exercise time, number of anginal attacks, NTG consumption, adverse effects.
Results	1. ETT (mean±SD) Time to 1 mm ST-depression : Nicorandil (n=114); ISMN (n=116) Baseline: 333.1±168.9; 322.7±142.7 After 2 weeks of treatment: 392.8±169.1; 390±141.9(p<0.001) Total exercise time: : Nicorandil (n=115); ISMN (n=117) Baseline: 400.4 ±145.4;409.6±139.2 After 2 weeks of treatment: 439.7 ± 135.2 ; 442.9±129.4(p<0.001) Time to onset of chest pain: Nicorandil (n=37); ISMN (n=37) Baseline: 324.2 ± 122.6;357.8±123.6 After 2 weeks of treatment: 408 ±137.1; 418.6±119.2 (p<0.001) Maximum ST-depression (mv): Nicorandil (n=114); ISMN (n=117) Baseline: 0.183± 0.069 After 2 weeks of treatment: 0.139±0.080 (p<0.001) 2.Number of anginal attacks(mean±SD): Nicorandil (n=52) Baseline: 4.3±4.4 times/week After 2 weeks:1.9±3.8 times/week (p<0.001) Number of anginal attacks(mean±SD): ISMN (n=54) Baseline: 4.0±4.9 times/week

	After 2 weeks:2.3 ±3.6 times/week (p<0.001) No significant difference between groups 3. Reduction in NTG consumption per week (patient number): Nicorandil vs. ISMN (p=ns) >80%: 20 vs. 15 ≤50% ≤80%: 4 vs. 2 <50%: 5 vs. 2 Increase: 6 vs. 13 No consumption of NTG: 78% vs. 81 Over 50%: 68.6% vs. 53.1% 95% CI: 53.2-84.0 vs. 35.8-70.4 No significant difference between groups. 4. Adverse events: Headache: 15/123 patients in nicorandil group vs.18/123 patients in the ISMN group.
Safety and adverse effects	Headache was the most common adverse reaction. No deaths were reported in this trial. Four serious adverse events were reported in 4 patients, authors report that there was no causal relationshipwith the study drugs.
Does the study answer the question?	Yes. Both Nicorandil and ISMN improved total exercise time and the time to onset of chest pain. There was no significant difference between the 2 groups. Niocrandil and ISMN significantly decreased the number of anginal attacks, but there was no significant difference between the two groups. Nicorandil was well tolerated and there was no safety profile difference compared with ISMN. Authors conclusion: Nicorandil may have equivalent or better anginal effect than ISMN.
Effect due to factor in study?	Yes
Consistency of results with other studies?	Yes
Directly applicable to guideline population?	No. Study conducted on Chinese population.
Internal Validity	selection bias

Evidence Table

Question: In adults with stable angina, what is the clinical/cost effectiveness of revascularisation techniques versus optimal medical treatment to alleviate angina symptoms and to improve long term outcomes?

Study Type	Randomised Controlled Trial

Myocardial infarction and mortality in the coronary artery surgery study (CASS) randomized trial

Ref ID 2047 **RID:** 515 1984 Mar 22

QUALITY

A. Selection bias (systematic differences between the comparison groups)

A4 Based on your answers t, in your opinion was selection bias present? If so, what is the likely direction of its effect?:

Unclear/unknown risk **Direction =**

B. Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)

B4 Based on your answers to the above, in your opinion was performance bias present? If so, what is the likely direction of its effect?:

Low risk of bias **Direction =**

C. Attrition bias (systematic differences between the comparison groups with respect to loss of participants)

C4 Based on your answers to the above, in your opinion was attrition bias present? If so, what is the likely direction of its effect?:

Low risk of bias **Direction =**

D. Detection bias (bias in how outcomes are ascertained, diagnosed or verified)

D6 Based on your answers to the above, in your opinion was detection bias present? If so, what is the likely direction of its effect?:

Unclear risk of bias **Direction =**

Overall Study Quality -Strengths and Weaknesses:

Strengths: randomised (stratified randomisation). Baseline comparisons made. One patient lost to follow-up after 4.5 years. Intention to treat analysis reported.
Limitations: Allocation concealment not reported.
This is a 6 year follow-up of the CASS trial

DETAILS

# of patients: N=780 (n=390 medical and n=390 surgical)

Prevalence (Diagnostic):

Patient Characteristics	Baseline characteristics: Characteristic: medical (n=390) vs. surgical (n=390) Mean age (yr): 51; 52 Male %: 90; 91 Diabetes %: 8; 9 BB usage %: 43; 44 Prior history of MI %: 63; 57 Q-wave MI or baseline ECG%: 29; 29 Angiographic variables One vessel disease %: 27; 27 Two vessel disease %: 38; 41 Three vessel disease %: 35; 32 Ejection fraction ≥0.50 %: 73; 75 Patients were eligible for the CASS only if they fell in to one of the three groups: (1)Mild angina (CCS class I or II) and Normal ventricular function (2) Mild angina and moderately impaired left ventricular function (3) Free of angina after MI. These three clinical subsets were used as strata for block randomisation.
Interventions/ Test/ Factor being investigated	Surgery. All patients received medical therapy including those assigned to the surgical group.
Comparisons	Medical therapy. (no further details)
Length of Study/ Follow-up	Mean 6 years (range 4-8 years)
Outcome measures studied	Primary and secondary outcomes not stated. Outcomes assessed: Death, nonfatal MI, recurrent hospitalisation.
Results	
Effect Size	Results: Outcome: Surgery (n=390)* vs. Medical (n=390) ** Death: 26 vs. 34 Non fatal MI***: 53 vs. 43 *Forty one (41) of the 390 refused surgery initially, but 10 of these 41 subsequently had CABG. Of the 41, 4 died- 2 of whom had CABG-and 5 had a new non fatal MI, none at the time of CABG. ** 95 of the 390 had CABG. The peri-operative infarction rate among the 95 medically treated patients who crossed to surgery was 8%. Among these 95, 6 died and 15 had a new, nonfatal infarction; 8 of the non fatal infarctions occurred in the peri-operative period. *** Patients with one non fatal MI. In surgery group, 9 patients had two nonfatal infarcts. In medical group 5 patients had two or more nonfatal infarcts. Sub-groups: Death: Med vs. Surgery No. of diseased vessels: 1 vessel: Death: 93±3 vs. 96±2 (p=0.56) Without non fatal MI: 89 ±3 vs. 89±3 (p=0.94) 2 vessels: Death: 94±2 vs. 96±2 (p=0.83) Without non fatal MI: 90±3 vs. 87±3 (p=0.38) 3 vessels: Death: 89±3 vs. 92±3 (p=0.16) Without non fatal MI: 87±3 vs. 83±4 (p=0.32) Ejection fraction ≥0.50 Death: 95±1 vs. 95±1 (p=0.80) Without non fatal MI: 89±2 vs. 88±2 (p=0.54)
Source of funding:	Supported by research contracts of the National Heart, Lung, and Blood Institute, Bethesda, Maryland

Does the study answer the question?/Further Comments

Yes. As compared to medical therapy, CABG appeared neither to prolong life nor to prevent MI in patients who have mild angina or who are asymptomatic after infarction in the five year period after coronary angiography.
There were no statistically significant differences in survival rate or in MI rate between subgroups of patients randomly assigned to medical and surgical therapy when they were analysed according to number of diseased vessels or ejection fraction.

Coronary-artery bypass surgery in stable angina pectoris: Survival at two years. European Coronary Surgery Study Group

Ref ID 9157 **RID:** 681 1979 Apr 28

QUALITY

A. Selection bias (systematic differences between the comparison groups)

A4 Based on your answers t, in your opinion was selection bias present? If so, what is the likely direction of its effect?:

Unclear/unknown risk **Direction =**

B. Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)

B4 Based on your answers to the above, in your opinion was performance bias present? If so, what is the likely direction of its effect?:

Unclear/unknown risk **Direction =**

C. Attrition bias (systematic differences between the comparison groups with respect to loss of participants)

C4 Based on your answers to the above, in your opinion was attrition bias present? If so, what is the likely direction of its effect?:

Low risk of bias **Direction =**

D. Detection bias (bias in how outcomes are ascertained, diagnosed or verified)

D6 Based on your answers to the above, in your opinion was detection bias present? If so, what is the likely direction of its effect?:

Unclear **Direction =**

Overall Study Quality -Strengths and Weaknesses:

Strengths: randomised. Low attrition bias. Intention to treat analysis used
Weaknesses: reporting of outcome is not always very clear; crossover 26/394 (6.5%) of patients assigned to surgery did not complete treatment ; medical gp 50/373 (13%) had surgery; unclear allocation concealment

DETAILS

# of patients:

N=768 (n=373 Medical ; n=394 Surgery)

Prevalence (Diagnostic):

Patient Characteristics

Recruitment between September 1973 and March 1976
Inclusion criteria: men <65 years with angina pectoris for >3months and good left ventricular function. Consent for angiographic investigation and treatment. Angiographic criteria for inclusion were 50% or more obstruction in at least 2 major coronary vessels (at least one of which was suitable for grafting) and a left ventricular ejection fraction of 50% or more. Inclusion or exclusion of patients with 50% or more obstruction in the left main coronary artery was discretionary.

Baseline characteristics:
Variable Medical gp(n=373) ; Surgical gp (n=394)
smoking 43% ; 43%
hypertension 15% ; 18%
diabetes 6% ; 6%
previous MI 46% ; 45%
elevated serum cholesterol 35% ; 34%
heart enlargement, x ray 5% ; 3%
left main disease 8% ; 7%
2-vessel disease 41% ; 37%
3-vessel disease 50% ; 56%
Left ventricular end-diastolic pressure before ventriculography(SD) 12.1 (5.4mmHg) ; 11.6 (5.4mmgHg)
left ventricular ejection fraction 64.6(10%) ; 64.6 (10.3%)
age(SD) 49.9(7.1) ; 49.9 (6.6)

Interventions/ Test/ Factor being investigated

CABG with either saphenous-vein graft or internal mammary artery vs medical treatment (no details on drugs used)

Comparisons

CABG vs medical treatment

Length of Study/ Follow-up

2 years

Outcome measures studied

deaths;survival ; revascularisation

Results

Effect Size

Deaths
Surgical gp ; Medical gp
Before operation ; In hospital ; late ; operated on ; medically treated
Cardiac 5; 5; 0; 2; 25
Non-cardiac 0 ; 2; 1; 0 ; 0
Related to surgical procedure 0 ; 5 ; 0 ; 0 ; 0
Insufficient data 1 ; 1 ; 1 ; 0 ; 2

Revascularisation
Narrative results. Graft angiography performed within 9 months of operation in 84 patients showed patency-rate of 90%. In 223 patients (55%) it was done between 9 and 18 months after surgery and showed a 77% patency rate

Survival rate at 24 months follow up
Medical gp ; Surgical gp
Total 92.2%(SE 1.4) ; 94.7(SE 1.1) non significant difference
Patients with left main disease (n=31) 87.1%(SE6) ; (n=28) 93.1(SE4.7) non significant difference

Patients with 2-vessel disease (n=154) 96.1%(SE1.6) ; (n=147) 93.2(SE2.1) non significant difference
Patients with 3-vessel disease (n=188) 89.9(SE2.2) ; (n=219) 95.9(SE1.3) significant difference p<0.05

Compliance:
Surgery gp : 1/394 did not respond to call for surgery ; 26/394 didn't follow protocol (6 died before operation, 1 developed liver disease, 19 refused surgery).Operations should have been performed within 3 months of randomisation: mean delay was 3.9 (SD 3.5) months.
Medical treatment group: 50/373 later underwent surgery because of unacceptable symptoms.

Source of funding: not reported

Does the study answer the question?/Further Comments Yes. This is a progress report on survival at 2 years follow up. It reported no significant difference between the two groups in mortality. A significant difference was however found in the subset of patients with 3-vessel disease, survival being significantly better for surgical patients. Operative (in hospital) mortality was 3.6% in all operated patients and 1.5% in the last third. Symptomatic improvement was significantly better and deteriorated less in the surgical group

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Coronary artery surgery study (CASS): a randomized trial of coronary artery bypass surgery. Quality of life in patients randomly assigned to treatment groups

Ref ID 2055 **RID:** 619 1983 Nov

QUALITY

A. Selection bias (systematic differences between the comparison groups)

A4 Based on your answers t, in your opinion was selection bias present? If so, what is the likely direction of its effect?:

Unclear/unknown risk **Direction =**

B. Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)

B4 Based on your answers to the above, in your opinion was performance bias present? If so, what is the likely direction of its effect?:

Low risk of bias **Direction =**

C. Attrition bias (systematic differences between the comparison groups with respect to loss of participants)

C4 Based on your answers to the above, in your opinion was attrition bias present? If so, what is the likely direction of its effect?:

Low risk of bias **Direction =**

D. Detection bias (bias in how outcomes are ascertained, diagnosed or verified)

D6 Based on your answers to the above, in your opinion was detection bias present? If so, what is the likely direction of its effect?:

Low risk of bias

Direction =

Overall Study Quality -Strengths and Weaknesses:

See Ref ID 2047.

Follow-up was 99.9% complete (779/780) for vital status.
This is a 1 year follow-up of the CASS trial

DETAILS

# of patients: n=780

Prevalence (Diagnostic):

Patient Characteristics See Ref ID 2047.

Interventions/ Test/ Factor being investigated surgery

Comparisons medical therapy

Length of Study/ Follow-up mean duration of follow-up was 5.5 years (range 3.8 to 7.7 years)

Outcome measures studied Primary outcome: Functional status- as measured by : chest pain, heart failure, activity limitation employment status, recreational status ; Treatment- , drug therapy, hospitalisation, smoking, supervised exercise program, miscellaneous.

Results

Effect Size

Results:
Chest pain status: Before randomisation, chest pain classification was similar between the two groups. In both groups the percent of surgical group patients without chest pain declined over the 5 year follow-up period, where as the percent of medical group patients without chest pain showed an apparent increase. However, when data from patients who did not follow-up the assigned treatment (medical or surgical) were censored from the analysis, the percentage of patients in the medical group without chest pain remained more constant during follow-up.
Heart failure: Symptoms of heart failure were reported in 2.6% of the patients in the medical group and 4.6% in the surgical group. No significant differences in heart failure prevalence in the two groups were observed.
Activity limitation: At baseline there were no significant differences between the activity levels of the patients in the medical and surgical groups. At follow-up there were highly significant differences between the degree of activity limitation in the two groups, with more patients in the surgical group reporting no limitation of activity.
Graded exercise tests: At baseline there was no sig. difference in exercise test performance. The percentage of patients in the medical group with exercise induced ST segment depression of ≥1 mm remained essentially constant during the follow-up period. However, the percentage of patients in the surgical group with abnormal ST depression fell sharply at 6 months after entry and gradually rose over the next 4.5 years, although at 60 months after entry the percentage was still significantly less than that in the medical group.
Recreational status: There were no differences between the two groups with respect to classification of recreational status as strenuous, mild/moderate, or sedentary at baseline or during follow-up.

Hospitalisation: The total number of periods of hospitalisation was significantly higher among patients in the surgical group than among those in the medical group The difference is primarily explained by a higher frequency of hospitalisation in the surgical group during the first year of the study, when these patients were being admitted for surgery.

Definition of terms:
Chest pain status: the average or typical levels of chest discomfort were classified as follows- 1) class I, chest pain only with strenuous or prolonged physical activity 2) class II, chest pain with rapid or moderate to extensive walking or stair climbing (more than 2 blocks or more than 1 flight) or in cold or wind or when under emotional stress 3) class III , chest pain with minimal walking or stair climbing, such as walking 2 level blocks or less or climbing 1 flight of stairs or less at normal pace under normal conditions 4) class IV , chest pain with any level of physical activity or even at rest.
Heart failure: HF was coded as present if the patient reported ankle edema, dyspnea, and/or orthopnea.
Activity limitation: The patients classified limitations in performing their daily activities (hobbies, recreation, job, yard work, housework, routine) : 1) none 2) intermittent limitation 3) mild limitation 4) moderate limitation 5) severe limitation 6) un certain due to medical restrictions or recovering from surgery.
Recreational status: the patients daily recreational or physical activity was classified as: 1) strenuous 2) moderate 3) mild 4) sedentary.
Drug therapy: Medication use was similar in the two treatment groups at entry, there was subsequently a marked reduction in use of both BB and nitrates in the surgically assigned patients.
Hospitalisation: no. of days hospitalisased and reasons for hospitalisation.

Note: Compliance with randomised treatment: of 390 patients randomly assigned to medical treatment, 100 (26%) subsequently had coronary revascularisation surgery. Of the 390 patients randomly assigned to surgery, 41 (11%) initially refused, but of these 41, 1o patients subsequently underwent surgery at a mean of 2.5 years after randomisation

Source of funding: This trial was supported by the National Heart, Lung and Blood Institute.

Does the study answer the question?/Further Comments Yes. This study shows that CABG improved the quality of life as manifested by relief of chest pain, improvement in both subjective and objective measurements of functional status, and a diminished requirement for drug therapy. However, no significant effect on employment or recreational status was observed.

Eleven-year survival in the Veterans Administration randomized trial of coronary bypass surgery for stable angina. The Veterans Administration Coronary Artery Bypass Surgery Cooperative Study Group

Ref ID 2043 **RID:** 562 1984 Nov 22

QUALITY

A. Selection bias (systematic differences between the comparison groups)

A4 Based on your answers t, in your opinion was selection bias present? If so, what is the likely direction of its effect?:

Low risk of bias

Direction =

B. Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)

B4 Based on your answers to the above, in your opinion was performance bias present? If so, what is the likely direction of its effect?:

Low risk of bias

Direction =

C. Attrition bias (systematic differences between the comparison groups with respect to loss of participants)

C4 Based on your answers to the above, in your opinion was attrition bias present? If so, what is the likely direction of its effect?:

Low risk of bias

Direction =

D. Detection bias (bias in how outcomes are ascertained, diagnosed or verified)

D6 Based on your answers to the above, in your opinion was detection bias present? If so, what is the likely direction of its effect?:

Unclear risk of bias

Direction =

Overall Study Quality -Strengths and Weaknesses:

See Ref ID 2010
This is a 11 year follow-up of the VA study.
99.9% patients completed 9 years follow-up, 91% completed 10 years and 73% completed 11 years.

DETAILS

# of patients: N=686 (n=332 medical and n=354 surgery)

Prevalence (Diagnostic):

Patient Characteristics

Interventions/ Test/ Factor being investigated surgery

Comparisons medical. Note:
Twenty patients randomly assigned to bypass surgery did not have an operation. 94% of those who underwent surgery did so within 3 months after random assignment. Of the 354 patients randomly assigned to medical treatment, 133 (38%) had bypass surgery during an average follow-up of 11.2 years. Of the 133, 22 had left main coronary artery disease and crossed over to surgery on an elective basis in accordance with a protocol amendment. 35 (11%) of the 312 patients randomly assigned to surgery who had coronary artery bypass grafting

	have had repeat grafting.
Length of Study/ Follow-up	7 years and 11 years
Outcome measures studied	Primary ouctome: survival rate
Results	
Effect Size	Results: Results reported in graphs. For the entire group At 7 years Survival: medical vs. surgery 70% vs. 77%; p=0.04 At 11 years 57% vs. 58% [Excluding patients with LM disease] At 7 years Survival: medical vs. surgery 72% vs. 77%; p==0.26 11 years 58% vs. 58%; p=0.813 At 7 years Sub group- 3 vessel disease Survival: Medical vs. surgery 63% vs. 75%; p=0.06 The difference in the cumulative survival rates diminished after 7 years, resulting in only a 6% difference at 11 years. At 7 years neither patients with single vessel disease nor those with double vessel disease had a significant difference in survival associated with treatment, although at 11 years surgically treated patients with two vessel disease had a marginally significant disadvantage in survival (p=0.045). At 7 years neither patients with single vessel disease nor those with double vessel disease had a significant difference in survival associated with treatment, although at 11 years surgically treated patients with two vessel disease had a marginally significant disadvantage in survival (p=0.045) At 7 years Patients with impaired left ventricular function Survival: medical vs. surgery (63% vs. 74%, respectively; p=0.049); At 11 years Survival: medical vs. surgery 49% and 53%, respectively (p=0.249). Patients with normal ventricular function At 7 years Survival: medical vs. surgery 84% vs. 80% At11years Survival: medical vs. surgery 71% vs. 64%, (p=ns) High angiographic risk (three vessel disease and impaired left ventricular function) At 7 years Survival: medical vs. surgery 52% vs. 76% (p=0.0002) At 11 years Survival: medical vs. surgery 38% vs. 50% (p=0.026) Clinically defined high risk (at least two of the following: resting ST depression, history of MI, or history of hypertension)

At 7 years
Survival: medical vs. surgery
52% vs. 72% (p=0.003)
At 11 years
Survival: medical vs. surgery
36% vs. 49% (p=0.015)

Combined angiographic and clinical high risk
At 7 years
Survival: medical vs. surgery
36% vs. 76% (p=0.002)
At 11 years
Survival: medical vs. surgery
24% vs. 54% (p=0.005)

Patients with impaired left ventricular function
At 7 years
Survival: medical vs. surgery
63% vs. 74% (p=0.049)
At 11 years
Survival: medical vs. surgery
49% vs. 53%

For patients in the low-risk
At 7 years
Survival: medical vs. surgery
88% vs. 81% ;(p=0.093)
At 11 years
Survival: medical vs. surgery
73% vs. 63% (p=0.066)

Source of funding: see Ref ID 2101

Does the study answer the question?/Further Comments Yes. The surgical treatment policy resulted in a non significant survival disadvantage throughout the 11 years in subgroups with normal ventricular function, low angiographic risk, and low clinical risk, and a statistically significant disadvantage at 11 years in patients with two vessel disease.
The authors conclude that among patients with stable ischemic heart disease, those with a high risk of dying benefit from surgical treatment, but beyond 7 years the survival benefit gradually diminishes.

Alderman EL;Bourassa MG;Cohen LS;Davis KB;Kaiser GG;Killip T;Mock MB;Pettinger M;Robertson TL;

Ten-year follow-up of survival and myocardial infarction in the randomized Coronary Artery Surgery Study

Ref ID 1941 **RID:** 622 1990 Nov

QUALITY

A. Selection bias (systematic differences between the comparison groups)

A4 Based on your answers t, in your opinion was selection bias present? If so, what is the likely direction of its effect?:

Low risk of bias

Direction =

B. Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)

B4 Based on your answers to the above, in your opinion was performance bias present? If so, what is the likely direction of its effect?:

Low risk of bias

Direction =

C. Attrition bias (systematic differences between the comparison groups with respect to loss of participants)

C4 Based on your answers to the above, in your opinion was attrition bias present? If so, what is the likely direction of its effect?:

Low risk of bias

Direction =

D. Detection bias (bias in how outcomes are ascertained, diagnosed or verified)

D6 Based on your answers to the above, in your opinion was detection bias present? If so, what is the likely direction of its effect?:

Low risk of bias

Direction =

Overall Study Quality -Strengths and Weaknesses:

Strengths: randomised (stratified randomisation). Baseline comparisons made. Intention to treat analysis reported.
Limitations: Allocation concealment not reported.
This is a 10 year follow-up of the CASS trial

DETAILS

# of patients:	N=780 (medical (n=390) AND surgery (n=390))
Prevalence (Diagnostic):	
Patient Characteristics	See Ref ID 2047
Interventions/ Test/ Factor being investigated	Surgery
Comparisons	Medical therapy.
Length of Study/ Follow-up	10 years
Outcome measures studied	Primary and secondary outcomes not stated. Outcome assessed : Survival rate, death.

Results

Effect Size

Results:
All patients: medical (n=390) vs. surgery (n=390)
Survival rate (%): 79% vs. 82 ;(p=0.25)
Angina + EF >0.5: medical (n=254) vs. n=surgery (n=260)
Survival rate (%):86% vs. 82%; P=0.30
Angina+ EF < 0.5: medical (n=54) vs. surgery (n=52)
Survival rate (%): 59% vs. 80; p=0.01
Age (yr): medical (n=163) vs. surgery (n=163)
Survival rate (%): 72% vs. 76%
Angina
None: medical (n=84) vs. surgery (n=86)
Survival rate (%): 70% vs. 81%;p=0.10
CCS 1: medical (n=47) vs. surgery (n=66)
Survival rate (%): 84 vs. 75; p=0.25
CCS 2: medical (n=243) vs. surgery (n=217)
Survival rate (%):80% vs. 84%; p=0.23
One vessel >70%: medical (n=107) vs. surgery (n=107)
Survival rate (%): 82% vs. 85%; p=0.44
Two vessel >70%: medical (n=148) vs. surgery (n=160)
Survival rate (%):79% vs. 83%; p=0.43
Three vessel >70%: medical (n=135) vs. surgery (n=123)
Survival rate (%): 75% vs. 76%; p=0.70
LAD >70%: medical (n=275) vs. surgery (n=277)
Survival rate (%): 78 % vs. 82%; p=0.26

Outcome: medical (n=390) vs. surgery (n=390)
Death
MI: 20 vs. 13
Sudden death: 32 vs. 23
Complications of CABG: 4 vs. 7
Other cardiovascular: 6 vs. 12
Non cardiovascular: 21 vs. 18
Unclassifiable: 1 vs. 1
Total: 84 vs. 73

Note 10 year crossover (%)*
40% in medical and 7% in surgery group.
*Crossover refers to surgical treatment in patients randomised to medicine and continued medical treatment without surgery in patients randomised to surgery.

Source of funding:

see Ref ID 2047

Does the study answer the question?/Further Comments

Yes. For CASS patients as a whole, there was no significant differences in medical vs. surgical 10 year survival (medical, 79% vs. surgical, 82%; p=0.25).
Patients who had a normal ejection fraction and mild stable angina, had longer event free survival (medical, 76% vs. surgery, 66%; p=0.024) with medical treatment than with surgery.
Patients who had an ejection fraction of between 0.35 and 0.5 with stable mild angina, exhibited an 80% 10 year survival in those assigned to surgery, which substantially exceeded the 59% survival for medically randomised patients (p=0.01).
Event free survival in patients with CCS class I angina was better for those patients randomised to medical therapy than to surgery compared with patients with class2 angina.
No significant survival or event rate benefits were observed for patients with one, two or three vessel disease.

Bhayana JN;Gage AA;Takaro T;

Long-term results of internal mammary artery implantation for coronary artery disease: a controlled trial by the participants of the Veterans Administration Coronary Bypass Surgery Cooperative Study Group

Ref ID 2084 **RID:** 574 1980 Mar

QUALITY

A. Selection bias (systematic differences between the comparison groups)

A4 Based on your answers t, in your opinion was selection bias present? If so, what is the likely direction of its effect?:

Unclear/unknown risk **Direction =**

B. Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)

B4 Based on your answers to the above, in your opinion was performance bias present? If so, what is the likely direction of its effect?:

Low risk of bias **Direction =**

C. Attrition bias (systematic differences between the comparison groups with respect to loss of participants)

C4 Based on your answers to the above, in your opinion was attrition bias present? If so, what is the likely direction of its effect?:

High risk of bias **Direction =**

D. Detection bias (bias in how outcomes are ascertained, diagnosed or verified)

D6 Based on your answers to the above, in your opinion was detection bias present? If so, what is the likely direction of its effect?:

Unclear risk of bias **Direction =**

Overall Study Quality -Strengths and Weaknesses:

Strengths: randomised, baseline comparisons made.
Weakness: allocation concealment not reported. Loss to follow-up not reported. Intention to treat analysis not reported.

DETAILS

# of patients: N=146 (n=75 in medical group and n=71 in surgical group)

Prevalence (Diagnostic):

Patient Characteristics

Male patients with chronic stable angina admitted to 16 participating Veterans Administration hospitals were screened
Inclusion criteria: history of stable angina of 6 months duration with medical treatment for at least 3 months ; no MI during the 6 months preceding admission ;

no cardiac decompensation for at least 3 weeks ; ECG evidence of old MI or S-T segment changes consistent with myocardial ischemia or a positive exercise stress test

Exclusion: uncontrolled diabetes ; unstable angina ; diastolic pressure >100mm Hg after therapy ; any disease limiting longevity ; ventricular aneurysm, diffusely abnormal or very poor myocardial contractility, marked elevation of left ventricular end-diastolic pressure, or a markedly diminished ejection fraction

Baseline characteristics

	Medical No(%)	Surgical No(%)	Total No(%)
New York Heart Association Functional Class			
I	1(1.3)	0(0)	1 (0.7)
II	25(33.3)	14 (19.7)	39 (26.7)
III	45(60)	49(69)	94(64.4)
IV	3 (4)	5 (7)	8 (5.5)
Unknown	1 (1.3)	3(4.2)	4 (2.7)
History of previous MI*			
None	17 (22.7)	24(33.8)	41(28.1)
One	58 (77.3)	45(63.4)	103(70.5)
Duration of angina*			
0-5	2 (2.7)	0(0)	2 (1.4)
6-24	27 (36)	27(39.1)	54 (37.5)
>=25	46 (61.3)	42 (60.9)	88 (61.2)
History of diabetes*			
No	61(81.3)	57(80.3)	118(80.8)
Yes	14(18.7)	12(16.9)	26(17.8)
No. diseased vessels*			
One	14(18.7)	11(15.9)	25(17.4)
Two	23(30.7)	29(42)	52(36.1)
Three	38(50.7)	29(42)	67(46.5)
Total	75(52.1)	69(47.9)	144(100)
Left Main lesion			
	6 (8)	5 (7.4)	

* unknown in 2 surgical patients

The differences in the incidence of double and triple vessel disease between the two groups were not statistically significant. The incidence of significant left main coronary artery disease was nearly the same in both groups.

Interventions/ Test/ Factor being investigated

surgery. (implantation of internal mammary artery in to the left ventricular myocardium). The patients in the surgery group also received appropriate medical treatment including drugs.

Comparisons

medical.There was no standardised protocol for medical therapy, which included the administration of nitrates (short and long acting), BB and anti arrhythmic drugs.

Length of Study/ Follow-up

up to 12 years (median 9.3 years)

Outcome measures studied

Primary outcome: survival

Results

Effect Size

Survival : medical vs. surgery
41% vs. 42%
Death in implant patients

	Medical No(%)	Surgical No(%)	Total No(%)
Cardiac	36(82)	33(81)	69(81)
Noncardiac	2(4)	3(7)	5(6)
Unknown	6(14)	5(12)	11(13)

Source of funding:	supported by the Veterans Administration Cooperative Studies Program, Medical Research Service, Veterans Administration Central Office, Washington DC
Does the study answer the question?/Further Comments	Yes. At the end of follow-up extending up to 12 years (mean 9.3 years), cumulative survival for both groups was similar.

Boden WE;O'Rourke RA;Teo KK;Hartigan PM;Maron DJ;Kostuk WJ;Knudtson M;Dada M;Casperson P;Harris CL;Chaitman BR;Shaw L;Gosselin G;Nawaz S;Title LM;Gau G;Blaustein AS;Booth DC;Bates ER;Spertus JA;Berman DS;Mancini GB;Weintraub WS;COURAGE Trial Research Grou

Optimal medical therapy with or without PCI for stable coronary disease

Ref ID 483 **RID:** 535 2007 Apr 12

QUALITY

A. Selection bias (systematic differences between the comparison groups)

A4 Based on your answers t, in your opinion was selection bias present? If so, what is the likely direction of its effect?:

Unclear/unknown risk **Direction =**

B. Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)

B4 Based on your answers to the above, in your opinion was performance bias present? If so, what is the likely direction of its effect?:

Low risk of bias **Direction =**

C. Attrition bias (systematic differences between the comparison groups with respect to loss of participants)

C4 Based on your answers to the above, in your opinion was attrition bias present? If so, what is the likely direction of its effect?:

Low risk of bias **Direction =**

D. Detection bias (bias in how outcomes are ascertained, diagnosed or verified)

D6 Based on your answers to the above, in your opinion was detection bias present? If so, what is the likely direction of its effect?:

Low risk of bias **Direction =**

Overall Study Quality -Strengths and Weaknesses:

Strengths: Randomisation method reported (permuted block design within strata –prior CABG/no prior CABG and by medical centre), sample size calculation reported, Blind outcome assessment (clinical outcome adjudicated by an independent committee whose members were unaware of treatment assignments). 9% of patients were lost to follow-up in the two groups (107 in the PCI group and 97 in the medical therapy group, p=0.51). Vital status was not ascertained in 194 patients (99 in the PCI group and 95 in the medical therapy group). Intention to treat analysis reported.

Weaknesses: Allocation concealment not reported.

DETAILS

# of patients:

n=2287 (n=1149 in PCI group and n=1138 in medical therapy)

Prevalence (Diagnostic):

Patient Characteristics

Baseline characteristics:
Characteristic: PCI (n=1149); medical therapy group (n=1138)
Age: 61.5±10.1; 61.8±9.7
Angina CCS class –no (%)
Class 0- 135 (12); 148 (13)
Class 1- 340 (30); 341 (30)
Class2 -409 (36); 425 (37)
Class 3- 261 (23); 221 (19)
Duration of angina months (medina): 5; 5
Diabetes: 367 (32); 399 (35)
Previous PCI- 174 (15); 185 (16)
Previous CABG- 124 (11); 124 (11)
Vessels with disease- no (%)
1-□361 (31); 343 (30)
2-□446 (39); 439 (39)
3-□341 (30); 355 (31)
Proximal LAD disease- 360 (31); 417 (37)
Ejection fraction- 60.8±11.2; 60.9±10.3

*Medical anti ischemic therapy in both groups included long acting metoprolol, amlodipine, and isosorbide mononitrate, alone or in combination, along with either lisinopril or losartan as standard secondary prevention. All patients received aggressive therapy (simvastatin alone or in combination with ezetimibe) to lower low-density lipoprotein cholesterol levels with a target level of 60 to 85 mg per decilitre.

Inclusion criteria: Patients with stable coronary artery disease and those in whom initial CCS class IV angina subsequently stabilised medically were included in the study. Entry criteria included stenosis of at least 70% in at least one proximal epicardial coronary artery and objective evidence of myocardial ischemia or at least one coronary stenosis of at least 80% and classic angina without provocative testing. Exclusion criteria included persistent CCS class IV angina, a markedly positive stress test, refractory heart failure or cardiogenic shock, an ejection fraction of less than 30%, revascularisation within the previous 6 months, and coronary anatomy not suitable for PCI.

Medication received by the participants:
At baseline
Medication: PCI group vs. CABG group
ACE inhibitor: 58% vs. 60%
ARB: 4% vs. 5%
Statin: 86% vs. 89%
Other anti lipid: 8% vs. 8%
Aspirin: 96% vs. 95%
BB: 85% vs. 89%
CCB: 40% vs. 43%

	Nitrates: 62% vs. 72% At 5 years Medication: PCI group vs. CABG group ACE inhibitor: 66% vs. 62% ARB: 11%vs.16% Statin: 93% vs. 93% Other anti lipid: 49% vs. 54% Aspirin: 95% vs. 94% BB: 85% vs. 86% CCB: 42% vs. 52% Nitrates: 40 %vs. 57%
Interventions/ Test/ Factor being investigated	PCI (angioplasty and stents) and optimal medical therapy * drug eluting stents were not approved for clinical use until the final 6 months of the study, so few patients received these devices.DES used in 31 patients
Comparisons	Optimal medical therapy alone.
Length of Study/ Follow-up	Follow-up-median 4.6 years (2.5 to 7 years)
Outcome measures studied	Primary outcome measure: composite death from any cause and non fatal MI. Secondary outcomes: composite of death, MI and stroke and hospitalisation for unstable angina with negative biomarkers.
Results	
Effect Size	Of the 1149 patients in the PCI group, 46 never underwent a procedure because the patients either declined treatment or had coronary anatomy unsuitable for PCI, as determined on clinical reassessment. In 27 patients the operator was unable to cross any lesions. Results: Outcome: PCI vs. Medical group Death: 85 vs. 95 (p=0.38) Cardiac death: 23 vs. 25 Total MI: 143 vs. 128 (p=0.33) Stroke: 22 vs. 14 (p=0.19) Hospitalisation for ACS: 135 vs. 125 (p=0.56) Angina free –no (%)- 316 (74) vs. 296 (72) (p=0.35) Revascularisation (PCI or CABG): 228 vs. 348 (p<0.001)* *Values exclude the initial PCI procedure in patients who were originally assigned to the PCI group.
Source of funding:	
Does the study answer the question?/Further Comments	Supported by the Cooperative studies program of the U.S. Department of Veterans Affairs Office of Research and Development, in collaboration with the Canadian Institutes of Health Research; and by unrestricted research grants from Merck, Pfizer, Bristol-Myers Squibb, Fujjsawa, Kos Pharmaceuticals, Data scope, Astrazeneca, Key Pharmaceutical, Sanofi-Aventis, First Horizon, and GE Heathcare. Yes. As an initial management strategy in patients with stable coronary artery disease, PCI did not reduce the risk of death, MI, or other major cardiovascular events when added to optimal medical therapy.

Bourassa MG;Knatterud GL;Pepine CJ;Sopko G;Rogers WJ;Geller NL;Dyrda I;Forman SA;Chaitman BR;Sharaf B;Davies RF;Conti CR;

Asymptomatic cardiac ischemia pilot (ACIP) study: Improvement of cardiac ischemia at 1 year after PTCA and CABG

Ref ID 2336 **RID:** 697 1995

QUALITY

A. Selection bias (systematic differences between the comparison groups)

A4 Based on your answers t, in your opinion was selection bias present? If so, what is the likely direction of its effect?:

Unclear/unknown risk **Direction =**

B. Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)

B4 Based on your answers to the above, in your opinion was performance bias present? If so, what is the likely direction of its effect?:

Low risk of bias **Direction =**

C. Attrition bias (systematic differences between the comparison groups with respect to loss of participants)

C4 Based on your answers to the above, in your opinion was attrition bias present? If so, what is the likely direction of its effect?:

Low risk of bias **Direction =**

D. Detection bias (bias in how outcomes are ascertained, diagnosed or verified)

D6 Based on your answers to the above, in your opinion was detection bias present? If so, what is the likely direction of its effect?:

Low risk of bias **Direction =**

Overall Study Quality -Strengths and Weaknesses: see Ref ID 1751

DETAILS

# of patients: N=558 (n=183 in angina guided therapy; n=183 in ischemia guided therapy; n=92 in revascularisation).

Prevalence (Diagnostic):

Patient Characteristics see Ref ID 1751

Interventions/ Test/ Factor being investigated	surgery
Comparisons	medical (angina guided therapy and ischemia guided therapy).
Length of Study/ Follow-up	1 year
Outcome measures studied	Primary outcome: complete suppression of ischemic episodes on the 48 hour AECG obtained at the 12 week visit (84 to 182 days) after enrolment or approximately 8 weeks after revascularisation. Secondary outcomes included other measures related to ischemia from the 48 hour AECG, ACIP protocol ETT, and clinical outcomes.
Results	
Effect Size	Results: Outcome: PTCA (n=92) vs. CABG (n=75) CCS class: (%) None: 71% vs. 81% Class I: 10% vs. 13% Class II: 16% vs. 5% Class III: 3% vs. 0 Class IV: 0 vs. 0 Outcome: PTCA (N=92) vs. CABG (n=78) Death: 0 vs. 0 MI: 3 vs. 1 PTCA: 9 vs. 1 (p=0.02) CABG: 7 vs. 0 (p=0.02) Note: Of 192 patients assigned to undergo revascularisation in the ACIP study, 94 had PTCA attempted, 79 had CABG performed, and 19 did not have any revascularisation procedure performed because the patient or treating physician refused after enrolment. Three patients, 2 in the PTCA group and 1 in the CABG group, who had their procedures done after 12 week visit were excluded from the analysis. Thus, in this report is based on 92 patients in whom PTCA was attempted and 78 patients in whom CABG was performed.
Source of funding:	see Ref ID 1751
Does the study answer the question?/Further Comments	Yes. Surgical patients had a lower incidence of clinical events (deasth, non fatal MI, and non protocol revascularisation).

Chamberlain DA;Fox K.A.;Henderson RA;Julian DG;

Coronary angioplasty versus medical therapy for angina: The second randomised intervention treatment of angina (RITA-2) trial

Ref ID 3544 **RID:** 699 1997

QUALITY

A. Selection bias (systematic differences between the comparison groups)

A4 Based on your answers t, in your opinion was selection bias present? If so, what is the likely direction of its effect?:

Unclear/unknown risk

Direction =

B. Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)

B4 Based on your answers to the above, in your opinion was performance bias present? If so, what is the likely direction of its effect?:

Low risk of bias

Direction =

C. Attrition bias (systematic differences between the comparison groups with respect to loss of participants)

C4 Based on your answers to the above, in your opinion was attrition bias present? If so, what is the likely direction of its effect?:

Low risk of bias

Direction =

D. Detection bias (bias in how outcomes are ascertained, diagnosed or verified)

D6 Based on your answers to the above, in your opinion was detection bias present? If so, what is the likely direction of its effect?:

Low risk of bias

Direction =

Overall Study Quality -Strengths and Weaknesses:

Strengths: multicentre (20 centres in UK and Ireland), stratified blocked randomisation. sample size calculation reported. Intention to treat analysis reported. Loss to follow-up- 5.1% in PTCA and 3.3% in medical group (N=478 PTCA an n=497 at 2.7 yrs) Blind outcome assignment.
Weakness: allocation concealment not reported.*
*This study is a median 2.7 yrs follow-up of the RITA-2 trial.

DETAILS

# of patients: n=1018 -PTCA (n=504) and medical (n=514).

Prevalence (Diagnostic):

Patient Characteristics

Baseline characteristics:
Characteristic: PTCA (n=504) vs. medical (n=514)
Diseased vessels
1 : 311 vs. 300
2: 163 vs. 175
3: 30 vs. 39
Recent unstable angina: 47 vs. 52
Angina grade
None: 24 vs. 47
1: 116 vs. 157
2: 180 vs. 154
3: 62 vs. 61
4: 43 vs. 43

	on diabetic treatment: 48 vs. 42 Age(yrs) <50: 101 vs. 106 50-59: 180 vs. 197 60-69: 190 vs. 181 >70: 31 vs. 29 Left ventricular score: 5: 276 vs. 269 6-9: 194 vs. 201 >10: 27 v. 36 Patients assigned to medical treatment were prescribed anti anginal medication for symptom relief, with a later myocardial revascularisation procedure reserved for patients whose symptoms were not adequately controlled by optimal medical therapy. This usually included a BB, a CCB, or a long acting nitrate in maximally tolerated doses, or a combination of these. All patients in both groups were treated with aspirin unless contraindicated.
Interventions/ Test/ Factor being investigated	PTCA.
Comparisons	medical treatment.
Length of Study/ Follow-up	2.7 years
Outcome measures studied	Primary endpoint was defined as the combined frequency of death (from all causes) and definite non fatal MI. The cause of death was classified as cardiac and non cardiac.
Results	
Effect Size	The intended randomised PTCA was performed in 471 (93%) of patients. Reasons for not undergoing PTCA in other 33 were: lesion regression (12), symptomatic improvement (4), disease progression (10, of whom 9 underwent CABG), patient refused (7). PTCA was complicated by emergency CABG in seven patients (1.5%), including two in whom stents were inserted. In the medical group, 101 patients subsequently underwent PTCA of whom 13 also needed CABG. Results: Outcome: PTCA vs. medical Deaths: 11 vs. 7 Cardiac death: 5 vs. 3 Non fatal MI: 21 vs. 10 Subsequent intervention PTCA: 62 vs. 101 CABG: 40 vs. 30 Unstable angina: 21 vs. 21 Stroke: 0 vs. 4 Throughout the follow-up there was substantial improvement in reported angina in both groups, but this improvement was significantly greater in the PTCA group. This treatment difference was greater early on, with a 16.5% excess of grade2+ angina in the medical group at 3 months ($p<0.001$). After 2 years, the medical group had only a 7.6% excess of grade 2+ angina ($p=0.02$).
Source of funding:	supported by a grant from the British heart foundation and the medical research council
Does the study answer the question?/Further Comments	Yes. After 2.7 years, the PTCA group had a significantly greater risk of death or non fatal MI. Angina improved in both groups, but more so in the PTCA group.

Davies RF;Goldberg AD;Forman S;Pepine CJ;Knatterud GL;Geller N;Sopko G;Pratt C;Deanfield J;Conti CR;

Asymptomatic Cardiac Ischemia Pilot (ACIP) study two-year follow-up: outcomes of patients randomized to initial strategies of medical therapy versus revascularization

Ref ID 1651 **RID:** 669 1997 Apr 15

QUALITY

A. Selection bias (systematic differences between the comparison groups)

A4 Based on your answers t, in your opinion was selection bias present? If so, what is the likely direction of its effect?:

Low risk of bias **Direction =**

B. Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)

B4 Based on your answers to the above, in your opinion was performance bias present? If so, what is the likely direction of its effect?:

Low risk of bias **Direction =**

C. Attrition bias (systematic differences between the comparison groups with respect to loss of participants)

C4 Based on your answers to the above, in your opinion was attrition bias present? If so, what is the likely direction of its effect?:

Low risk of bias **Direction =**

D. Detection bias (bias in how outcomes are ascertained, diagnosed or verified)

D6 Based on your answers to the above, in your opinion was detection bias present? If so, what is the likely direction of its effect?:

Low risk of bias **Direction =**

Overall Study Quality -Strengths and Weaknesses:

Strengths*: randomised, baseline characteristics reported. Intention to treat analysis reported. Follow-up: 97% complete at 2 years. Blind outcome assessment.
Weaknesses: allocation concealment not reported. Small sample size.
This is a 2 year follow-up of the ACIP study.

DETAILS

# of patients: N=558 (n=183 in angina guided therapy; n=183 in ischemia guided therapy; n=92 in revascularisation).

Prevalence (Diagnostic):

Patient Characteristics	See Ref ID 1751
Interventions/ Test/ Factor being investigated	1) Phramacologic therapy for angina (angina guided therapy) 2) Pharmacologic therapy to suppress both angina and ECG evdince of ischemia (ischemia guided strategy)
Comparisons	3) Revascularisation with either angioplasty or CABG within 4 weeks of entry according to physician and patients preference (revascularisation strategy).
Length of Study/ Follow-up	2 years
Outcome measures studied	Primary outcome: Death, MI, recurrent hospitalisation for cardiac disease and non protocol, revascularisation.

Results

Effect Size

Results:
Outcome: Angina guided (n=183) vs. Ischemia guided (n=183) vs. Revascularisation (n=192)
Death: 12 (6.6%) vs. 8 (4.4%) vs. 2 (1.1%)
Death or MI: 22 vs. 16 vs. 9
Death, MI, or hospitalisation: 76 vs. 70 vs. 44
Non protocol revascularisation:
PTCA: 19 vs. 15 vs. 12
CABG: 37 vs. 42 vs. 13

Subgroups:
Outcome: Angina guided vs. Ischemia guided vs. Revasc
Proximal LAD with > 50% stenosis
Death or MI: 10 vs. 9 vs. 2
Death, MI or hospitalisation: 36 vs. 25 vs. 12
No LAD stenosis
Death or MI: 12 vs. 7 vs. 7
Death, MI or hospitalisation: 40 vs. 43 vs. 32
No. of vessels with > 50% stenosis
One vessel
Death or MI: 2 vs. 4 vs. 2
Death, MI or hospitalisation: 9 vs. 16 vs. 15
Two vessel:
Death or MI: 7 vs. 5 vs. 5
Death, MI or hospitalisation: 27 vs. 20 vs. 19
Three vessel:
Death or MI: 13 vs. 7 vs. 2
Death, MI or hospitalisation: 40 vs. 34 vs. 10

Note: Protocol revascularisation-
Within the revascularisation strategy, PTCA was selected for 102 patients and CABG for 90 patients. 8 patients selected for PTCA subsequently refused the procedure, and 2 had the procedure outside of the specified time window (which was 6 weeks for staged PTCA, 4 weeks otherwise). This left 92 patients who underwent protocol PTCA. 11 patients selected for CABG subsequently refused the procedure, and 1 had the procedure outside of the 4 week time window. This left 78 patients who underwent CABG.

Source of funding:	This study was funded by the National Heart, Lung, and Blood Institute, Cardiac diseases Branch, Division of Heart and Vascular disease, National Institutes of
Does the study answer the question?/Further Comments	Yes. A strategy of initial revascularisation appeared to improve the prognosis of this population compared with angina guided therapy. The rate of death, MI or recurrent hospitalisation was 41.8% in the angina guided strategy, 38.5% in the ischemia guided strategy, and 23.1% in the revascularisation strategy ($p<0.001$). Pair wise testing (not reported separately in the paper) significant differences

between the revascularisation and angina guided strategies for each comparison.

However the authors report that a larger long term study is needed to confirm this benefit and to adequately test the potential of more aggressive drug therapy.

Detre K;Murphy ML;Hultgren H;

Effect of coronary bypass surgery on longevity in high and low risk patients. Report from the V.A. Cooperative Coronary Surgery Study

Ref ID 4097 **RID:** 680 1977

QUALITY

A. Selection bias (systematic differences between the comparison groups)

A4 Based on your answers t, in your opinion was selection bias present? If so, what is the likely direction of its effect?:

Low risk of bias **Direction =**

B. Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)

B4 Based on your answers to the above, in your opinion was performance bias present? If so, what is the likely direction of its effect?:

Low risk of bias **Direction =**

C. Attrition bias (systematic differences between the comparison groups with respect to loss of participants)

C4 Based on your answers to the above, in your opinion was attrition bias present? If so, what is the likely direction of its effect?:

Low risk of bias **Direction =**

D. Detection bias (bias in how outcomes are ascertained, diagnosed or verified)

D6 Based on your answers to the above, in your opinion was detection bias present? If so, what is the likely direction of its effect?:

Low risk of bias **Direction =**

Overall Study Quality -Strengths and Weaknesses:

This is a 4 year follow-up of the VA study. Sub group analysis reported.

see Ref ID 2101

DETAILS

# of patients:	n=596 (n=310 medical and n=286 surgery)
Prevalence (Diagnostic):	
Patient Characteristics	see Ref ID 2101
Interventions/ Test/ Factor being investigated	surgery
Comparisons	medical
Length of Study/ Follow-up	4 years
Outcome measures studied	Survival rate
Results	
Effect Size	Results: Entire group: medical (n=354) vs. surgery (n=332) Mortality: 17% vs. 14% Outcome: medical (n=44) vs. surgery (n=46) Mortality (sub group Left main coronary artery disease): 36% vs. 7% Entire group without L.M group: medical (n=310) vs. surgery (n=286) Mortality: 14% vs. 15% Survival rate : medical vs. surgery Sub group 3 vessels, abnormal L.V.F.: 74% vs. 87% 2 and 3 vessels, abnormal LVF: 78% vs. 84% 1 vessel, abnormal LVF and 1, 2, 3 vessels normal LVF: 95% vs. 92%
Source of funding:	see Ref ID 2101
Does the study answer the question?/Further Comments	Yes. The only sub-group which clearly benefited from surgery was the L.M. lesion.

Detre KM;Takaro T;Hultgren H;Peduzzi P;

Long-term mortality and morbidity results of the Veterans Administration randomized trial of coronary artery bypass surgery

Ref ID 4138 **RID:** 653 1985

QUALITY

A. Selection bias (systematic differences between the comparison groups)

A4 Based on your answers t, in your opinion was selection bias present? If so, what is the likely direction of its effect?:

Unclear/unknown risk

Direction =

B. Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)

B4 Based on your answers to the above, in your opinion was performance bias present? If so, what is the likely direction of its effect?:

Low risk of bias

Direction =

C. Attrition bias (systematic differences between the comparison groups with respect to loss of participants)

C4 Based on your answers to the above, in your opinion was attrition bias present? If so, what is the likely direction of its effect?:

Low risk of bias

Direction =

D. Detection bias (bias in how outcomes are ascertained, diagnosed or verified)

D6 Based on your answers to the above, in your opinion was detection bias present? If so, what is the likely direction of its effect?:

Unclear risk of bias

Direction =

Overall Study Quality -Strengths and Weaknesses:

See Ref ID 2101
This is a 11.2 years follow-up of the VA study

DETAILS

# of patients:	N=686 (n=354 medical and n=332 surgery)
Prevalence (Diagnostic):	
Patient Characteristics	See Ref ID 2101
Interventions/ Test/ Factor being investigated	surgery
Comparisons	medical treatment
Length of Study/ Follow-up	mean11.2 years
Outcome measures studied	Death, Non fatal MI.

Results

Effect Size

Results:
Overall 30 day mortality was 5.8%. The incidence of peri operative MI based on the development of new Q waves was 9.9%.

For 686 patients, including those with left main disease, the mortality difference was significant at 7 years; 30% medical vs. 23% surgical (p=0.043). By 11 years the surgical mortality curve converged to that of the medical, 43% vs. 42%, because of the accelerated surgical mortality beyond 7 years, from an average annual rate of 3.3% to 4.8%. Acceleration in the medical treatment group did not occur. Similar trends were observed in the patients without left main disease, but the small surgical advantage at 7 years did not reach statistical significance.
Sub group analysis: There was a non significant trend for lower mortality with surgery at 7 years in the sub group of patients with three vessel disease: 37% with medical vs. 25% with surgical treatment (p=0.061).
The cumulative mortality rate accelerated in the surgical group after 7 years, resulting in only a 6% difference at 11 years. At 7 years neither patients with single or double vessel disease showed a significant treatment difference, although by 11 years surgical patients with two vessel disease had a significantly higher mortality (p=0.045).

At 7, but not at 11 years there was a significant difference in mortality between the two treatment groups for patients with impaired left ventricular function: 37% in medical vs. 26% in surgical patients (p=0.049); mortality rates at 11 years were 51% vs. 47% respectively (p0.249). Mortality rates in patients with normal left ventricular function were not significantly different between medical and surgery respectively at 7 years (16% vs. 20%) or 11 years (29% vs. 36%).

Myocardial infarction: The 5 year rates were 14% with medical and 15% with surgical therapy (p=0.428).

Left main disease: The cumulative mortality rate of 48 patients with left main disease randomised to surgical treatment was 21% at 7 years and 41% at 11 years. Comparison with the assigned medical group was not made , since 47% of the original 43 medical patients had bypass surgery and 445 died, leaving only 4 adhering medical patients at 7 years.

Cross over: at 11.2 years follow-up, 133 of 354 patients randomised to medical treatment had bypass surgery, a cross over rate of 3.4% annually. Of these, 22 had left main disease and crossed over to surgery on an elective basis in accordance with a protocol amendment.

Source of funding:

supported by the veterans administration co operative studies program, medical research service, veterans administration central office, Washington DC

Does the study answer the question?/Further Comments

Yes. The 11 year cumulative mortality rates for all patients and for the 595 patients without left main disease were not significantly different in the two treatment groups. The 5 year non fatal MI rates for both the groups were virtually same.

Favarato ME;Hueb W;Boden WE;Lopes N;Nogueira CR;Takiuti M;Gois AF;Borges JC;Favarato D;Aldrighi JM;Oliveira SA;Ramires JA;

Quality of life in patients with symptomatic multivessel coronary artery disease: a comparative post hoc analyses of medical, angioplasty or surgical strategies-MASS II trial

Ref ID 501 RID: 580 2007 Apr 4

QUALITY

A. Selection bias (systematic differences between the comparison groups)

A4 Based on your answers t, in your opinion was selection bias present? If so, what is the likely direction of its effect?:

Unclear/unknown risk

Direction =

B. Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)

B4 Based on your answers to the above, in your opinion was performance bias present? If so, what is the likely direction of its effect?:

Unclear/unknown risk

Direction =

C. Attrition bias (systematic differences between the comparison groups with respect to loss of participants)

C4 Based on your answers to the above, in your opinion was attrition bias present? If so, what is the likely direction of its effect?:

Unclear/unknown risk

Direction =

D. Detection bias (bias in how outcomes are ascertained, diagnosed or verified)

D6 Based on your answers to the above, in your opinion was detection bias present? If so, what is the likely direction of its effect?:

low risk of bias

Direction =

Overall Study Quality -Strengths and Weaknesses:

Randomised trial, but no details of randomisation or allocation concealment in current paper. This is the MASS II study 1 year data (referenced to another publication). Only those completing 12 month quality of life data included in this analysis.

DETAILS

# of patients:

542 in all: CABG 175; PCI 180 and medical therapy (MT) 187

Prevalence (Diagnostic):

Patient Characteristics

Inclusion: Multivessel coronary disease and preserved ventricular function; suitable for medical therapy or revascularisation; stable angina or other evidence of ischaemia.
Exclusion: left main stenosis 50% or more; single-vessel coronary disease; previous coronary revascularisation; age 80 years or more.
Mean age around 59 years
300/542 (55%) female
167/542 (31%) current or past smoker
239/542 (44%) myocardial infarction
323/542 (60%) hypertension
159/542 (29%) diabetes

Interventions/ Test/ Factor being investigated	Coronary Artery Bypass Graft (CABG), Percutaneous coronary Intervention (PCI) or Medical Theray (MT). All patients had an optimal stepped care regimen (nitrates, aspirin, beta-blockers, calcium channel blockers, ACE inhibitors or a combination of these, plus statins and a low-fat diet on an individual basis); CABG and PCI groups had these in addition to MT.
Comparisons	PCI vs. CABG vs. Medical treatment
Length of Study/ Follow-up	1 year
Outcome measures studied	Primary outcome: incidence of cardiac mortality, MI or refractory angina requiring revascularisation/angioplasty. Secondary outcome: Health-related quality of life using Medical Outcome 36-item Short Form Health Survey (SF-36).
Results	Outcomes at 12 months

	CABG	PCI	Medical therapy	p
Death	6 (3.9%)	9 (4.4%)	3 (1.9%)	not stated
Acute MI	6 (3.0%)	17 (8.3%)	8 (3.9%)	not stated
Angina-free	88%	79%	46%	p<0.001
Additional interventions	0.5%	13.3%	10.8%	p<0.001
SF-36 domains:				
Role physical	48.37	50.00	40.26	0.0416
Role emotional	66.08	63.48	62.63	0.6623
Mental health	70.69	70.43	68.13	0.4120
Vitality	71.33	67.37	61.59	0.0001
Physical functioning	71.51	68.29	62.63	0.0005
Bodily pain	72.24	70.10	64.92	0.0215
General health	76.59	71.32	69.58	0.0007
Social functioning	81.89	81.82	77.05	0.0661

Effect Size	
Source of funding:	Zerbini Foundation, Sao Paulo, Brazil
Does the study answer the question?/Further Comments	Large randomised controlled trial (MASS II). Compared to those underoing PCI or maintained on medical therapy, patients underoing CABG had the highest chance of being angina-free and the lowest need for additional interventions; and on the SF-36 quality of life scale they had the best vitality, physical functioning and general health.

Folland ED;Hartigan PM;Parisi AF;

Percutaneous transluminal coronary angioplasty versus medical therapy for stable angina pectoris: outcomes for patients with double-vessel versus single-vessel coronary artery disease in a Veterans Affairs Cooperative randomized trial. Veterans Affairs AC

Ref ID 9144 **RID:** 659 1997 Jun

QUALITY

A. Selection bias (systematic differences between the comparison groups)

A4 Based on your answers t, in your opinion was selection bias present? If so, what is the likely direction of its effect?:

Low risk of bias **Direction =**

B. Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)

B4 Based on your answers to the above, in your opinion was performance bias present? If so, what is the likely direction of its effect?:

Low risk of bias **Direction =**

C. Attrition bias (systematic differences between the comparison groups with respect to loss of participants)

C4 Based on your answers to the above, in your opinion was attrition bias present? If so, what is the likely direction of its effect?:

Unclear/unknown risk **Direction =** type 2 error likely - i.e. not able to assess small difference due to low sample size

D. Detection bias (bias in how outcomes are ascertained, diagnosed or verified)

D6 Based on your answers to the above, in your opinion was detection bias present? If so, what is the likely direction of its effect?:

Low risk of bias **Direction =**

Overall Study Quality -Strengths and Weaknesses:

Strengths: randomisation (stratified, but details not given), detailed baseline comparisons, blinding of outcome assessors, sample size calculations
Weaknesses: Allocation concealment not reported, small sample size of double-vessel disease patient (underpowered), pilot study
*This study includes the single-vessel disease sample from the ACME study as a comparison group (ref id 1900)

DETAILS

# of patients: N=328 (double-vessel disease with PTCA n=51, double-vessel disease with Medical Treatment n=51, single vessel disease PCTA n=115, single-vessel

Prevalence (Diagnostic):

Patient Characteristics Randomisation took place according to 4 randomisation strata: 1a = single-vessel disease (<99% stenosis) THIS GROUP IS THE SAME AS THE ORIGINAL GROUP (ref id 1900), 1b = single-vessel disease, 100% occlusion, 2a = double-vessel disease, both vessels amenable to PTCA; and 2b = double-vessel disease , only one vessel amenable to PTCA. Baseline characteristics were comparable

between patients assigned to PTCA and Medical Treatment (details not given) within all randomisation strata. However there were some differences between randomisation strata. Baseline characteristics of randomised patients by randomisation strata:

	Double-vessel Disease		Single-Vessel Disease	
	Group 2a	Group 2b	Group 1a	Group 1b
	(n=64)	(n=37)	(n=212)	(n=15)
Index lesions/patient*	2.2‡	1.4	1.1	1.2
Prior MI (%)	38‡	57	31	67
Angina free (%)	17.2	18.9	8.5	33.3
Left ventricular ejection fraction:	0.68	0.64	0.70	0.60
QOL score:	101	96.8	96.8	104.1

* Number of lesions intended for coronary angioplasty in the same patient. MI = myocardial infarction.
‡ Significant differences between group 2a and 2b.

Inclusion criteria: Clinical requirements were either a history of angina, a strikingly positive exercise-tolerance test (ST-segment depression ≥3 mm), or a myocardial infarction within the past three months. Angiographic requirements were at least 70% diameter stenosis in the proximal ⅔ of one or two major coronary arteries. Exclusion criteria: The main clinical exclusions were medically refractory unstable angina, previous coronary artery revascularisation and primary cardiac diagnosis other than coronary artery disease. Patients were also excluded for left main coronary artery stenosis ≥50%, ≥70% stenosis of more than two major coronary arteries (three –vessel disease) or a left ventricular ejection fraction ≤30%.

Interventions/ Test/ Factor being investigated

PTCA within 3 days of randomisation

Comparisons

PTCA vs Medical Therapy in Double-vessel and Single-vessel disease

Length of Study/ Follow-up

1st follow-up at 6 months then patients were followed up by mailed questionnaire or telephone call or both for up to 6 years

Outcome measures studied

Clinical outcome measures: changes in angina frequency during each 30-day follow-up time period compared to baseline values and percent of patients free from angina during the last month of follow-up. Angiographic outcome was the change in mean percent diameter stenosis of the index lesions. Proportion of people with the following events at follow-up: PTCA, cornonary artery bypass, graft surgery, hospital admission, acute myocardial infarction and death.

Results

Effect Size

Treatments received during first 6 months in 328 randomized patients

	Double-vessel Disease (groups 2a and 2b)		Single-Vessel Disease (groups 1a and 1b)	
	PTCA (n=51)	Medical (n=50)	PTCA (n=115)	Medical (n=112)
PTCA				
Initial	51	7	110	13
Repeat	11	1	17	1
CABG				
Total	3	1	7	0
Emergency	0	0	3	0

Adverse events:

	Double-vessel Disease (groups 2a and 2b)		Single-Vessel Disease (groups 1a and 1b)	
	PTCA	Medical	PTCA	Medical
Death (all)				

1st 6 months	2	1	1	1
Subsequent follow-up*	7	9	15	14
Death (procedural)				
1st 6 months	0	0	1	1
Subsequent follow-up	N/A	N/A	N/A	N/A
MI (all)				
1st 6 months	2	6	5	3
Subsequent follow-up	4	0	9	5
MI (procedural)				
1st 6 months	1	1	4	0
Subsequent follow-up	N/A	N/A	N/A	N/A
Unstable angina (no. Of hospital admissinon)				
1st 6 months	9	6	12	10
Subsequent follow-up	9	14	9	24

*subsequent follow-up: at a median 60 months, mean 57 months, minimum 1 day, maximum 95 months

Symptoms and Quality of Life at 6 Months:

	Double-vessel Disease (groups 2a and 2b)			Single-Vessel Disease (groups 1a and 1b)		
	PTCA	p Value	Medical	PTCA	p Value	Medical
Angina freq	-7	0.75	-6	-16	0.05	-7
Angina free at 6 mo (%):	53	0.09	36	63	0.02	48
QOL	+1.3	0.32	+4.4	+7.1	0.01	+1.5

Source of funding:

The Cooperative Studies Program of the US Department of veterans Affairs, Washington, DC

Does the study answer the question?/Further Comments

Yes. It suggests that the advantages in symptoms and quality of life in patients with PTCA over Medical treatment patients experienced by men with single-vessel disease (as reported in this study as well as the 3 previous studies by the same research group ref ids 1900, 1741 and 1538) may be relatively diminished for patients with double- vessel disease.

Frick MH;Harjola PT;Valle M;

Coronary bypass surgery in stable angina pectoris. A randomized study of the effects on morbidity, mortality and employment

Ref ID 4140 **RID:** 479 1985

QUALITY

A. Selection bias (systematic differences between the comparison groups)

A4 Based on your answers t, in your opinion was selection bias present? If so, what is the likely direction of its effect?:

Unclear/unknown risk

Direction =

B. Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)

B4 Based on your answers to the above, in your opinion was performance bias present? If so, what is the likely direction of its effect?:

Low risk of bias

Direction =

C. Attrition bias (systematic differences between the comparison groups with respect to loss of participants)

C4 Based on your answers to the above, in your opinion was attrition bias present? If so, what is the likely direction of its effect?:

Low risk of bias

Direction =

D. Detection bias (bias in how outcomes are ascertained, diagnosed or verified)

D6 Based on your answers to the above, in your opinion was detection bias present? If so, what is the likely direction of its effect?:

Low risk of bias

Direction =

Overall Study Quality -Strengths and Weaknesses:

Strengths: randomised, baseline comparisons made. No loss to follow-up
Weakness: allocation concealment not reported

DETAILS

# of patients:

N=100 (n=50 medical and n=50 surgery)

Prevalence (Diagnostic):

Patient Characteristics

Baseline characteristics:
Characteristics: medical (n=50) ; surgery (n=50)
Age (yrs): 47 ±0.9; 46±0.9
Duration of angina (months): 37±5.0; 39 ±5.2*
Patients with past MI: 14 (28%); 22 (49%)
Two vessel disease: 10 (20%); 13 (29%)
Three vessel disease: 40 (80%); 32 (71%)
Left main stenosis: 8 (16%); 5 (11%)
Left ventricular ejection fraction: 67±1.4; 66±1.6*
*mean±SE

The characteristics of randomised patients did not differ significantly.

Interventions/ Test/ Factor being investigated

surgery

Comparisons	medical therapy. The medical therapy of both randomised groups was adjusted to give maximum benefit to the patients.
Length of Study/ Follow-up	5 years
Outcome measures studied	Primary and secondary outcomes not stated. Outcomes assessed- death, angina status, employment
Results	
Effect Size	Results: Outcome : medical vs. surgery Death: 10** vs. 2* *2 patients' dies before the surgery after randomisation ** All of the 10 patients died suddenly (less than 1 hour from the onset of symptoms). Classification of angina pectoris*: Follow-up: medical vs. surgical 6 months: 3.2±0.8 vs. 1.7±0.8 1yr: 3.5±0.6 vs. 1.8±1 2 yrs: 3.3±0.8 vs. 1.9±1.0 3 yrs: 3.2±0.9 vs 2.0±1.0 4 yrs: 3.3±0.7 vs. 1.9±0.9 5 yrs: 3.2±0.7 vs. 1.9±1.0 *Angina was graded as: 1= no angina; 2= angina by walking uphill/upstairs; 3=angina by rapid walking on the level; 4= angina by slow walking on the level; 5=angina at rest. Note: 2 patients did not consult to the surgery and 2 patients died after randomisation but before the scheduled operation, leaving 45 patients in the surgery group.
Source of funding:	not reported
Does the study answer the question?/Further Comments	Yes. More than 40% of patients in the surgery group were free from symptoms over the 5 years. The annual mortality of surgical patients was 0.8% as compared with 4% in the medical patients ($p<0.05$).

Frye RL;August P;Brooks MM;Hardison RM;Kelsey SF;MacGregor JM;Orchard TJ;Chaitman BR;Genuth SM;Goldberg SH;Hlatky MA;Jones TL;Molitch ME;Nesto RW;Sako EY;Sobel BE;

A randomized trial of therapies for type 2 diabetes and coronary artery disease

Ref ID 7 **RID:** 856 2009 Jun 11

QUALITY

A. Selection bias (systematic differences between the comparison groups)

A4 Based on your answers t, in your opinion was selection bias present? If so, what is the likely direction of its effect?:

Unclear/unknown risk

Direction =

B. Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)

B4 Based on your answers to the above, in your opinion was performance bias present? If so, what is the likely direction of its effect?:

Low risk of bias

Direction =

C. Attrition bias (systematic differences between the comparison groups with respect to loss of participants)

C4 Based on your answers to the above, in your opinion was attrition bias present? If so, what is the likely direction of its effect?:

Low risk of bias

Direction =

D. Detection bias (bias in how outcomes are ascertained, diagnosed or verified)

D6 Based on your answers to the above, in your opinion was detection bias present? If so, what is the likely direction of its effect?:

Low risk of bias

Direction =

Overall Study Quality -Strengths and Weaknesses:

Strengths: Large scale randomised control trial (randomisation method not reported), intention to treat analysis, power calculation for 5 year follow-up reported, baseline comparisons were made
Weaknesses: No allocation concealment reported, not all of the patients enrolled suffered from stable angina.

DETAILS

# of patients: 2368 (378 CABG and 798 PCI and 1192 Medical Therapy)

Prevalence (Diagnostic):

Patient Characteristics

Baseline characteristics before randomisation (N=2368):

Age years (mean, SD)	62.4; 8.9
Male (%)	70.4
Angina Status (%)	
None (%)	17.9
Stable CCS 1	14.3
Stable CCS 2	28.8
Stable CCS 3	7.5
Stable CCS 4	1.2
Unstable Angina	9.5
Duration of diabetes (%)	
< 5 years	33.3
5 – 10 years	23.5
10 - 20 years	29.2
≥ 20 years	14.1

Inclusion criteria: Diagnosis of both types 2 diabetes and coronary artery disease. All patients had to be candidates for elective percutaneous coronary intervention (PCI) or coronary-artery bypass grafting (CABG). Exclusion criteria: Patients were excluded if they required immediate revascularization or had left main coronary disease, a creatinine level of more than 2.0 mg per deciliter (177 µmol per liter), a glycated haemoglobin level of more than 13.0% class III or IV heart failure, or hepatic dysfunction or if they had undergone PCI or CABG within the previous 12 months.

Interventions/ Test/ Factor being investigated

Two surgical interventions (CABG and PCI)

Comparisons

Surgical intervention (either CABG or PCI) compared to medical treatment (either insulin-sensitization or insulin-provision)

Length of Study/ Follow-up

5 years

Outcome measures studied

The primary end point was death from any cause and the principal secondary end point was a composite of death, myocardial infarction, or stroke (major cardiovascular events).

Results

Effect Size

	Revascularization	Med Therapy	p-value
Rates of survival	88.3%	87.8%	=.97
Freedom from major cardiovascular events	77.2%	75.9%	=.70
Medication at 3 years follow-up:			
Metformin	43.1%	42.3%	=.72
Any thiazolidinedione	32.8%	33.2%	=.85
Rosiglitazone	28.8%	29.4%	=.76
Sulfonylurea	35.5%	35.5%	=1.00
Insulin	42.8%	46.2%	=.13
Beta-blocker	83.9%	87.9%	=.01
ACE or ARB	91.2%	92.0%	=.50
Nonsublingual nitrate	15.7%	26.3%	<.01
Aspirin	93.5%	94.2%	=.49
Clopidogrel or diclopidine	20.7%	21.0%	=.86
Statin	94.6%	95.4%	=.48

Within the CABG stratum patients who were assigned to the revascularization group had significantly fewer major cardiovascular events than did patients in the CABG stratum who were assigned to the medical-therapy group (percentage free from events: 77.6 CABG vs. 69.5 Med Therapy, p=.01).
Note. The patients for whom CABG was prespecified as the intended method of revascularization had more extensive coronary disease, with significantly more three-vessel disease, proximal disease of the left anterior descending artery, and chronic coronary occlusions than the patients for whom PCI was intended.

Source of funding:

National Institute of Health with additional support from industry. Industry sponsors did not have access to outcome data at any time during the trial and did not

Does the study answer the question?/Further Comments	Yes, but only specific to the subgroup of patients with diabetes. There was no significant difference in the rates of death and major cardiovascular events between patients undergoing prompt revascularization and those undergoing medical therapy or between strategies of insulin sensitization and insulin provision.

Guinn GA;Mathur VS;

Surgical versus medical treatment for stable angina pectoris: prospective randomized study with 1- to 4-year follow-up

Ref ID 4092 **RID:** 645 1976

QUALITY

A. Selection bias (systematic differences between the comparison groups)

A4 Based on your answers t, in your opinion was selection bias present? If so, what is the likely direction of its effect?:

Low risk of bias **Direction =**

B. Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)

B4 Based on your answers to the above, in your opinion was performance bias present? If so, what is the likely direction of its effect?:

Low risk of bias **Direction =**

C. Attrition bias (systematic differences between the comparison groups with respect to loss of participants)

C4 Based on your answers to the above, in your opinion was attrition bias present? If so, what is the likely direction of its effect?:

Low risk of bias **Direction =**

D. Detection bias (bias in how outcomes are ascertained, diagnosed or verified)

D6 Based on your answers to the above, in your opinion was detection bias present? If so, what is the likely direction of its effect?:

Low risk of bias **Direction =**

Overall Study Quality -Strengths and Weaknesses:	Strengths: Randomised. No loss to follow-up. Baseline comparisons made. Intention to treat analysis reported. Limitations: allocation concealment not reported.

DETAILS

# of patients:	N=116 (n=56 surgery and n=60 medical)
Prevalence (Diagnostic):	
Patient Characteristics	Baseline characteristics: All the patients' were men. The groups were comparable with regard to age, duration of angina pectoris, consumption of nitroglycerin, incidence of hypertension, diabetes mellitus, previous MI, congestive heart failure, and electrocardiographic abnormalities. The 2 groups had a similar distribution of coronary arteries involved and normal or abnormal LVEDP. Inclusion criteria: chronic stable angina to atleast 3 months of intensive medical treatment, with significant coronary artery stenosis, ie, 70% or more, in atleast one major coronary artery.
Interventions/ Test/ Factor being investigated	surgery
Comparisons	medical treatment
Length of Study/ Follow-up	34 months. (range 9 to 46 months)
Outcome measures studied	Primary and secondary outcomes not stated. Outcomes assessed: death, MI, angina status, exercise test.
Results	
Effect Size	Results: Outcome: surgery (n=56) vs. medical (n=60) MI: 5 (9%) vs. 11 (18%); p=ns Death: 3 vs. 7 * Status Asymptomatic: 38 (68%) vs. 5 (8%); p<0.01 Improved: 13 (23%) vs. 35 (58%); p<0.05 Required operation later: 1 (2%) vs. 4 (7%); p=ns The deaths in the surgery group occurred within 30 days and were due to acute MI in 2 patients; the third died after discharge, and the diagnosis is uncertain. These 3 patients had had three vessel disease. All 7 deaths in the medical group were from cardiac causes. In the group dying while under medical treatment, 3 had three vessel disease, 3 had 2 vessel disease, and 1 had 1 vessel disease. Note: One patient refused operation after randomisation. 4 patients in the non surgical group underwent ACB at 4, 13, 24, and 30 months respectively, because of unstable angina refractory to maximum medical treatment. The data of these patients were included with the nonsurgical group for statistical analysis until the time of ACB.
Source of funding:	not reported
Does the study answer the question?/Further Comments	Yes. Important results show that although most patients in both groups were improved, more surgical patients were asymptomatic (68% vs. 8%). Survival was similar in the two groups.

Hartigan PM;Giacomini JC;Folland ED;Parisi AF;

Two- to three-year follow-up of patients with single-vessel coronary artery disease randomized to PTCA or medical therapy (results of a VA cooperative study). Veterans Affairs Cooperative Studies Program ACME Investigators. Angioplasty Compared to Medicin

Ref ID 1538 **RID:** 517 1998 Dec 15

QUALITY

A. Selection bias (systematic differences between the comparison groups)

A4 Based on your answers t, in your opinion was selection bias present? If so, what is the likely direction of its effect?:

Unclear/unknown risk **Direction =**

B. Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)

B4 Based on your answers to the above, in your opinion was performance bias present? If so, what is the likely direction of its effect?:

Low risk of bias **Direction =**

C. Attrition bias (systematic differences between the comparison groups with respect to loss of participants)

C4 Based on your answers to the above, in your opinion was attrition bias present? If so, what is the likely direction of its effect?:

Low risk of bias **Direction =**

D. Detection bias (bias in how outcomes are ascertained, diagnosed or verified)

D6 Based on your answers to the above, in your opinion was detection bias present? If so, what is the likely direction of its effect?:

Unclear / unknown risk **Direction =**

Overall Study Quality -Strengths and Weaknesses:

Strengths: randomisation, detailed baseline comparisons were made in the original study (1900) and also follow-up group data, intention to treat analysis used, analysis of missing cases, searches were carried out to follow-up those patients that were not interviewed or did not undergo exercise testing for death, myocardial infarction and revascularization and authors used power calculation for total number of cardiovascular events.
Weaknesses: no blinding of outcome assessors, with technological advances the original PTCA method was already an older procedure
*This study reports extended follow-up of the ACME study (ref id 1900)

DETAILS

# of patients:

N=212 (n=107 to medical therapy ; n=105 to PTCA)

Prevalence (Diagnostic):

Patient Characteristics

For detailed medical baseline comparing PTCA and Med Therapy refer to ref id 1900. The current extended follow-up study shows baseline comparing the whole original group to those with ETT data at 2/3 years and those interviewed at 2/3 years follow-up.

Population	ETT at 2/3 years (n=132)	Interviewed at 2/3 years (n=175)	Total Study (n=212)
Age	60 ± 9	61 ± 8	60 ± 9
Diabetes (%)*	13	18	18
Angina in the last month (%)	92	92	92
No. of episodes:	20 ± 37	19 ± 34	17 ± 31
Average stenosis	78 ± 12	79 ± 12	78 ± 12
Ejection fraction	69±9	68±10	68±10

* A higher than expected proportion of diabetic patients did not have a 2/3-year exercise test. The proportion in the interviewed subgroup was not affected.
Inclusion criteria (see ref. ID 1900):

Interventions/ Test/ Factor being investigated

PTCA

Comparisons

PTCA vs Medical Treatment

Length of Study/ Follow-up

2 to 3 years (mean time to inteview follow-up was 2.4 years and mean time to follow-up exercise test was 3.0 years)

Outcome measures studied

Patients were interviewed about their angina during the last 30 days, current cardiac medication, employment and hospitalisations. At 2 to 3 years after randomization, patients underwent exercise testing (on medications).

Results

Effect Size

No (%) of patients angina free and mean no. of episodes at each stage of the follow-up for the original group (ref. id 1900), 6 months follow-up and extended follow-up:

	PTCA	Medical Treat	P Value
Original study:			
Six-month follow-up (N=198)	96	102	
No. (%) of patients angina free	61(64)	47(46)	= .01
Mean no. of episodes	4 ± 12	7 ± 16	= .15
Patients who had an extended follow-up interview:			
Baseline (N=175)	85	90	
No. (%) of patients angina free	7 (84)	7(8)	= .91
Mean no. of episodes	22 ± 44	15 ± 21	= .22
Six-month follow-up (N=168)	80	88	
No. (%) of patients angina free	50(63)	43(49)	= .08
Mean no. of episodes	5 ± 13	7 ± 17	= .35
Three-year follow-up (N=175)	85	90	
No. (%) of patients angina free	53(62)	42(47)	= .04
Mean no. of episodes	3 ± 9	12± 40	= .04

Cardiovascular events over entire follow-up (events, hospitalisations and

interventions):

	PCTA	Medical therapy	P Value
	(N=105)	(N=107)	
Events:			
Death	5	7	=.58
Myocardial infarction	10	7	
Hospitalisations:			
No. of patients hospitalised	64	69	=.60
Total cardiac hospitalisation days	664	960	=.17
Interventions (no. patients [procedures]):			
0-6 mos			
Coronary angioplasty	16(19)	11(13)	=.30
Coronary bypass	7(7)	0(0)	=.001
Total 0-36 mos			
Coronary angioplasty	31(35)	34(42)	=.72
Coronary bypass	13(13)	12(12)	=.72

Source of funding: The Cooperative Studies Program Research Service, Department of Veterans Affairs, Washington, DC

Does the study answer the question?/Further Comments Yes. At 3 years a significantly greater number of patients continue to be angina free in the PTCA group than in the medically assigned patients, with the proportions not different from those shown at the 6 months follow-up. There were no differences in mortality or rate of myocardial infarction between the PTCA and medical therapy groups in this study. The total number of events was small. The need for bypass surgery which was greater in the PTCA group at 6 months was no different in the 2 groups at the late follow-up.

Henderson RA;Pocock SJ;Clayton TC;Knight R;Fox KA;Julian DG;Chamberlain DA;Second Randomized Intervention Treatment of Angina (RITA;

Seven-year outcome in the RITA-2 trial: coronary angioplasty versus medical therapy

Ref ID 1051 **RID:** 660 2003 Oct 1

QUALITY

A. Selection bias (systematic differences between the comparison groups)

A4 Based on your answers t, in your opinion was selection bias present? If so, what is the likely direction of its effect?:

Unclear/unknown risk **Direction =**

B. Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)

B4 Based on your answers to the above, in your opinion was performance bias present? If so, what is the likely direction of its effect?:

Low risk of bias **Direction =**

C. Attrition bias (systematic differences between the comparison groups with respect to loss of participants)

C4 Based on your answers to the above, in your opinion was attrition bias present? If so, what is the likely direction of its effect?:

Low risk of bias

Direction =

D. Detection bias (bias in how outcomes are ascertained, diagnosed or verified)

D6 Based on your answers to the above, in your opinion was detection bias present? If so, what is the likely direction of its effect?:

Low risk of bias

Direction =

Overall Study Quality -Strengths and Weaknesses:

Strengths – multicentre (20 centres in UK and Ireland), stratified blocked randomisation. sample size calculation reported. Intention to treat analysis reported. Loss to follow-up was 1.8% (18 patients). The 5 year follow-up rate was 99.1%. Blind outcome assignment.
Weakness: allocation concealment not reported.*
*This study is a 7 yrs follow-up of the RITA-2 trial

DETAILS

# of patients:

n=1018 .PTCA- N=504 and N=514 Medical.

Prevalence (Diagnostic):

Patient Characteristics

60% patients had single vessel disease, 53% had angina grade 2 or worse, 18% were female, and the median age was 58 years. At randomisation 53% were receiving two or more anti anginal drugs, 13% were taking lipid lowering medication, 47% had had a previous MI, and 9% were treated for diabetes. The PTCA and medical treatment groups were similar with regard to all these baseline features.

Inclusion-exclusion criteria: Patients with arteriographically proven coronary artery disease were considered for the trial if the supervising cardiologist thought that continued medical therapy and PTCA were both acceptable options. Patients had to be over 18 years of age, but there was no upper age limit. Patients with previous myocardial revascularisation, significant left main stem disease, recent ACS, hemodynamically significant valve disease, or life threatening non cardiac disease likely to have a major influence on survival were excluded.

Interventions/ Test/ Factor being investigated

PTCA

Comparisons

Medical therapy

Length of Study/ Follow-up

median 7 years

Outcome measures studied

Primary endpoint was the 5 year rate of death and definite MI.

Results

Effect Size

Results:
Outcome: PTCA (n=504) vs. medical (n=514)
Death (all causes) : 43 vs. 43
Cardiac death: 13 vs. 22
Non fatal MI: 32 vs. 23
Patients with non –randomised intervention (total no. of procedures in brackets)*
CABG: 64 (65) vs. 63 (63)
Non randomised PTCA: 86 (106) vs. 139 (174)

At 5 years the prevalence of angina grade 2 or worse in the PTCA group remained steady at 15% whereas in the medical group the prevalence of angina was reduced to 21.4%. The 5 year treatment difference is thus much smaller, 6.4% in favour of PTCA (95% CI 1.5% to11.3%, P=0.011).

There was a trend for the 90 patients with diabetes mellitus to be at greater risk of death or MI (hazard ratio 1.17, 95% CI 0.56 to 2.43).

*Since randomisation, 64 patients randomised to PTCA (12.7%) and 63 (12.3%) patients randomised to medical treatment have had CABG. This includes the seven emergency CABG after randomised to PTCA and nine CABG performed instead of the intended randomised PTCA. In the PTCA group, additional non-randomised PTCA was required in 86 patients, 13 of whom also had CABG and 17 of whom required two or more such PTCA's. In the medical group, 139 patients subsequently had a first PTCA, of whom 20 also needed CABG during follow-up. In total, PTCA and medical groups had 106 and 174 non-randomised PTCA during follow-up, and stents were implanted during 36% of these procedures in each group.

Source of funding:

the trial was supported by grants from the British Heart Foundation (BHF) and Medical research council. Additional support was provided by Advanced

Does the study answer the question?/Further Comments

Yes. Authors conclusion: Over a median seven years follow-up, initial policies of PTCA and medical therapy in patients considered suitable for either treatment were comparable with regard to risk of death and nonfatal MI, but an initial policy of PTCA was associated with a lower prevalence of angina.

Hueb W;Lopes N;Gersh BJ;Soares PR;Ribeiro EE;Pereira AC;Favarato D;Rocha AS;Hueb AC;Ramires JA;

Ten-Year Follow-Up Survival of the Medicine, Angioplasty, or Surgery Study (MASS II). A Randomized Controlled Clinical Trial of 3 Therapeutic Strategies for Multivessel Coronary Artery Disease

Ref ID 15922 **RID:** 1192 2010 Aug 23

QUALITY

A. Selection bias (systematic differences between the comparison groups)

A4 Based on your answers t, in your opinion was selection bias present? If so, what is the likely direction of its effect?:

Unclear/unknown risk

Direction = More patients in PCI group had had MI and fewer were current or past smokers; other characteristics similar at baseline;

B. Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)

B4 Based on your answers to the above, in your opinion was performance bias present? If so, what is the likely direction of its effect?:

Low risk of bias

Direction =

C. Attrition bias (systematic differences between the comparison groups with respect to loss of participants)

C4 Based on your answers to the above, in your opinion was attrition bias present? If so, what is the likely direction of its effect?:

Low risk of bias

Direction =

D. Detection bias (bias in how outcomes are ascertained, diagnosed or verified)

D6 Based on your answers to the above, in your opinion was detection bias present? If so, what is the likely direction of its effect?:

low risk of bias

Direction =

Overall Study Quality -Strengths and Weaknesses:

Large randomised controlled trial; no loss to follow up. Randomisation and allocation concealment unclear but referenced to another paper.

DETAILS

# of patients:

611 total: 203 medical therapy (MT), 205 PCI, 203 CABG

Prevalence (Diagnostic):

Patient Characteristics

Inclusion: Proximal multivessel coronary stenosis >70% and documented ischaemia; suitable for medical therapy or revascularisation.
Exclusion: refractory angina or acute MI requiring emergency revascularisation; ventricular aneurysm requiring surgical repair; left ventricular ejection fraction below 40%; previous coronary revascularisation; single-vessel coronary disease; normal or minimal coronary artery disease; congenital heart disease; valvular heart disease; cardiomyopathy; unable to understand or cooperate with protocol or return for follow up; left main stenosis 50% or more; suspected or known pregnancy; contraindication to PCI or CABG.

Mean age around 60 years
188/611 (31%) female
187/611 (31%) current or past smoker
269/611 (44%) myocardial infarction
365/611 (60%) hypertension
179/611 (29%) diabetes

Interventions/ Test/ Factor being investigated	PCI vs.CABG vs. MT
Comparisons	1 way ANOVA compared between the three groups and multiple comparison tests or multivariate analysis for pairwise comparisons between PCI, CABG and MT.
Length of Study/ Follow-up	minimum 9 years; maximum 15 years; mean 11.4 years; vital status up to 10 year visit at least
Outcome measures studied	Primary outcome: incidence of overall mortality, MI or refractory angina requiring revascularisation/angioplasty. Secondary outcomes: angina status, cardiac death, stroke/cerebrovascular accident
Results	Outcomes at 10 years CABG PCI Medical therapy p Death 51 (25.1%) 49 (24.1%) 63 (31.0%) 0.089 Cardiac death 22 (10.8%) 29 (14.1%) 42 (20.7%) 0.019 Additional interventions 15 (7.4%) 85 (41.9%) 80 (39.4%) p<0.001 Non-fatal MI 21 (10.3%) 27 (13.2%) 42 (20.7%) 0.016 Cerebrovascular accident 17 (8.4%) 11 (5.4%) 14 (6.9%) 0.550 Event-free survival p<0.0001 Relative risk for event-free survival: CABG compared with PCI RR 0.53 (95% CI 0.39 to 0.72), p<0.001 CABG compared with MT RR 0.43 (95% CI 0.32 to 0.58), p<0.001 PCI compared with MT RR 0.79 (95% CI 0.62 to 1.01) no difference Angina-free 130 (64%) 120 (59%) 88 (43%) not stated CABG compared with PCI: not significant CABG compared with MT: p<0.001 PCI compared with MT: p<0.001
Effect Size	
Source of funding:	Zerbini Foundation, Sao Paulo, Brazil
Does the study answer the question?/Further Comments	Yes. Large randomised controlled trial (MASS II). Compared to those underoing PCI or maintained on medical therapy, patients underoing CABG had the highest event-free survival and the lowest need for additional intervention; the MT group had the lowest chance of being free of angina

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Hueb W;Soares PR;Gersh BJ;CÚsar LA;Luz PL;Puig LB;Martinez EM;Oliveira SA;Ramires JA;

The medicine, angioplasty, or surgery study (MASS-II): a randomized, controlled clinical trial of three therapeutic strategies for multivessel coronary artery disease: one-year results

Ref ID 4637 **RID:** 504 2004

QUALITY

A. Selection bias (systematic differences between the comparison groups)

A4 Based on your answers t, in your opinion was selection bias present? If so, what is the likely direction of its effect?:

Unclear/unknown risk

Direction = More patients in PCI group had had MI and fewer were current or past smokers; other characteristics similar at baseline;

B. Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)

B4 Based on your answers to the above, in your opinion was performance bias present? If so, what is the likely direction of its effect?:

Low risk of bias

Direction =

C. Attrition bias (systematic differences between the comparison groups with respect to loss of participants)

C4 Based on your answers to the above, in your opinion was attrition bias present? If so, what is the likely direction of its effect?:

Low risk of bias

Direction =

D. Detection bias (bias in how outcomes are ascertained, diagnosed or verified)

D6 Based on your answers to the above, in your opinion was detection bias present? If so, what is the likely direction of its effect?:

low risk of bias

Direction =

Overall Study Quality -Strengths and Weaknesses:

Randomised trial, but no details of randomisation or allocation concealment in current paper. This is the MASS II study 1 year data.

DETAILS

# of patients:

611 in total: 203 CABG; 205 PCI; 203 medical therapy (MT)

Prevalence (Diagnostic):

Patient Characteristics

Inclusion: Proximal multivessel coronary stenosis >70% and documented ischaemia; suitable for medical therapy or revascularisation.
Exclusion: unstable angina or acute MI requiring emergency revascularisation; ventricular aneurysm requiring surgical repair; left ventricular ejection fraction below 40%; previous coronary revascularisation; single-vessel coronary disease; congenital heart disease; valvular heart disease; cardiomyopathy; unable to understand or cooperate with protocol or return for follow up; left main stenosis 50% or more; suspected or known pregnancy; contraindication to PCI or CABG.
Mean age around 60 (9) years
188/611 (31%) female
187/611 (31%) current or past smoker
269/611 (44%) myocardial infarction
365/611 (60%) hypertension

	179/611 (29%) diabetes
Interventions/ Test/ Factor being investigated	CABG vs. PCI vs. MT
Comparisons	1 way ANOVA compared between the three groups and multiple comparison tests or multivariate analysis for pairwise comparisons between PCI, CABG and MT.
Length of Study/ Follow-up	Minimum 1 year
Outcome measures studied	Primary outcome: incidence of overall mortality, MI or refractory angina requiring revascularisation/angioplasty. Secondary outcomes: angina status, stroke/cerebrovascular accident
Results	Outcomes at 1 year CABG PCI Medical therapy p Death 8 (4.0%) 9 (4.5%) 3 (1.5%) 0.23 Cardiac death 8 (4.0%) 9 (4.5%) 3 (1.5%) 0.23 Additional interventions 1 (0.5%) 25 (12.3%) 16 (8.0%) p<0.0001 Acute MI 4 (2.0%) 16 (8.3%) 10 (5.0%) 0.01 Cerebrovascular accident 3 (1.5%) 2 (1.0%) 3 (1.5%) 0.29 Event-free survival 13 (6.4%) 50 (24.4%) 29 (14.3%) p<0.0001 Angina-free 120 (59%) 107 (52%) 74 (36%) CABG compared with PCI: p=0.16 CABG compared with MT: p<0.0001 PCI compared with MT: p=0.001 Reduction in the rate of positive exercise tests: 36% 18% 5% CABG compared with baseline: p<0.0001 PCI compared with baseline: p=0.0005 MT compared with baseline: p=0.45
Effect Size	
Source of funding:	Zerbini Foundation, Sao Paulo, Brazil
Does the study answer the question?/Further Comments	Large randomised controlled trial (MASS II). Compared to those underoing PCI or maintained on medical therapy, patients underoing CABG had the highest event-free survival and the lowest need for additional intervention; the MT group had the lowest chance of being free of angina

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Hueb WA;Bellotti G;de Oliveira SA;Arie S;de Albuquerque CP;Jatene AD;Pileggi F;

The Medicine, Angioplasty or Surgery Study (MASS): a prospective, randomized trial of medical therapy, balloon angioplasty or bypass surgery for single proximal left anterior descending artery stenoses

Ref ID 4242 **RID:** 662 1995

QUALITY

A. Selection bias (systematic differences between the comparison groups)

A4 Based on your answers t, in your opinion was selection bias present? If so, what is the likely direction of its effect?:

Unclear/unknown risk

Direction =

B. Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)

B4 Based on your answers to the above, in your opinion was performance bias present? If so, what is the likely direction of its effect?:

Low risk of bias

Direction =

C. Attrition bias (systematic differences between the comparison groups with respect to loss of participants)

C4 Based on your answers to the above, in your opinion was attrition bias present? If so, what is the likely direction of its effect?:

Low risk of bias

Direction =

D. Detection bias (bias in how outcomes are ascertained, diagnosed or verified)

D6 Based on your answers to the above, in your opinion was detection bias present? If so, what is the likely direction of its effect?:

Unclear risk of bias

Direction =

Overall Study Quality -Strengths and Weaknesses:

Strengths: Randomised. Baseline comparisons made. ITT reported.
Limitations: allocation concealment not reported. Blinding of outcome assessors not reported.Number of patients lost to follow-up not reported.
This study is a 3 year follow-up of the MASS-I study (for patients with stable angina and single proximal left anterior descending coronary artery stenosis).

DETAILS

# of patients:

N=214 (n=70 bypass surgery, n=72 balloon angioplasty, n=72 medical treatment)

Prevalence (Diagnostic):

Patient Characteristics

Variables: medical therapy (n=72); PTCA (N=72); Mammary bypass surgery
Age (yr): 58±7; 54±9; 58±11
Male gender: 59; 58; 58
Hypertension (%): 38; 34; 30
Diabetes (%): 20; 15; 18

Patients with stable angina and single vessel disease with at least 80% diameter stenosis in the left anterior descending artery before the first diagonal branch were included. Angioplasty had to be considered technically feasible in every case. Patients with unstable angina, prior infarction, significant valvular disease,

	cardiomyopathy, left ventricular dysfunction, a previous coronary intervention or prior open heart surgery were excluded.
Interventions/ Test/ Factor being investigated	(1) Balloon angioplasty (2) Surgical revascularisation (bypass grafting using the left internal mammary artery)
Comparisons	Medical therapy. Patients received treatment according to a predefined approach that included aspirin, nitrates, beta-blockers, ad calcium channel blocking agents, unless contraindicated o eliminate symptoms of angina.
Length of Study/ Follow-up	3.5±1.5 years.
Outcome measures studied	The pre-defined primary study endpoint was the combined incidence of cardiac death, MI or refractory angina requiring revascularisation. Surgical revascularisation, but not repeat coronary angioplasty, was considered an endpoint for patients assigned to coronary angioplasty. Secondary outcomes were angina functional class at the lat follow-up visit, employment status and positive exercise test results.
Results	Primary endpoints- Medical therapy: In the medical therapy group, 2 patients sustained an uncomplicated MI, 4 were referred for bypass surgery, and three were referred for angioplasty because of refractory angina. There were no deaths r strokes. Bypass surgery: Of the 70 patients assigned to left internal mammary artery bypass surgery, one patient had a periopertaive infarction, and one died on the way to the hospital after the onset of chest pain 43 months after bypass surgery. No patient required angioplasty and there were no strokes. Coronary angioplasty: Angioplasty was clinically successful in 96% of the 72 patients initially assigned to coronary angioplasty. It was not possible to dilate the stenosis in three patients, two of whom had a periprocedural MI and were referred for emergency by pass surgery. During the follow-up period, 27 patients assigned to this group (37.5%) had repeat angiography because of refractory angina and 21 underwent one or more additional angioplasty procedures. Eight patients had refractory angina requiring elective bypass surgery. No patient was referred to bypass surgery solely as a result of 6month follow-up angiography. One patient assigned to angioplasty died suddenly at home 8 months after the procedure. There were no strokes. Angina-There was a marked suppression of angina in patients randomised to both revascularisation strategies: 68 patients assigned to bypass surgery (98%) and 58randomisedto coronary angioplasty (82%) were totally asymptomatic at the last follow-up visit an average of 3 years after enrolment. In contrast, only 23 patients randomised to medical treatment (32%) were asymptomatic at the 3 year follow-up visit ($p<0.01$ for bypass surgery vs. coronary angioplasty;$p<0.01$ for coronary angioplasty vs. medical treatment). No patient in any randomised group had limiting angina (functional class III or IV) at the last follow-up visit.
Effect Size	
Source of funding:	Research grant from E.J. Zerbin Foundation, Sao Paulo, Brazil.
Does the study answer the question?/Further Comments	Yes. At an average follow-up period of 3 years, a primary endpoint had occurred in only 2 patients (3%) assigned to bypass surgery compared with 17 assigned to angioplasty (24%) and 12 assigned to medical therapy (17%) ($p=0.0002$, angioplasty vs. bypass surgery; $p=0.006$, bypass surgery vs. medical treatment; $p=0.28$, angioplasty vs. medical treatment).There was no difference immortality or infarction rates among the groups. However , no patient allocated to bypass surgery needed revascularisation, compared with 8 and 7 patients assigned, respectively, to coronary angioplasty and medical treatment($p=0.09$) Both revascularisation techniques resulted in greater symptomatic relief.

Hueb WA;Soares PR;Almeida D;Arie S;Cardoso RHA;Wajsbrot DB;Cesar LAM;Jatene AD;Ramires JAF;

Five-year follow-up of the medicine, angioplasty, or surgery study (MASS): A prospective, randomized trial of medical therapy, balloon angioplasty, or bypass surgery for single proximal left anterior descending coronary artery stenosis

Ref ID 2916 **RID:** 542 1999

QUALITY

A. Selection bias (systematic differences between the comparison groups)

A4 Based on your answers t, in your opinion was selection bias present? If so, what is the likely direction of its effect?:

Unclear/unknown risk **Direction =**

B. Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)

B4 Based on your answers to the above, in your opinion was performance bias present? If so, what is the likely direction of its effect?:

Low risk of bias **Direction =**

C. Attrition bias (systematic differences between the comparison groups with respect to loss of participants)

C4 Based on your answers to the above, in your opinion was attrition bias present? If so, what is the likely direction of its effect?:

Low risk of bias **Direction =**

D. Detection bias (bias in how outcomes are ascertained, diagnosed or verified)

D6 Based on your answers to the above, in your opinion was detection bias present? If so, what is the likely direction of its effect?:

Unclear risk of bias **Direction =**

Overall Study Quality -Strengths and Weaknesses:

Strengths: Randomised, Baseline comparisons made. Number of patients lost to follow-up not reported. ITT reported.
Limitations: allocation concealment not reported. Blinding of outcome assessors not reported.
This study is a 5 year follow-up of the MASS-I study (for patients with stable angina and single proximal left anterior descending coronary artery stenosis).

DETAILS

# of patients: N=214 (n=70 bypass surgery, n=72 balloon angioplasty, n=72 medical treatment)

Prevalence (Diagnostic):

Patient Characteristics	Patients with stable angina whose angiograms showed a single stenotic lesion in the proximal third of the LAD, before the diagonal branch, were selected. Eligible patients had no prior intervention by coronary bypass or PTCA. The artery had to have≥ 80% luminal stenosis by visual evaluation, and the lesion length had to measure ≤12 mm to be adequate to receive the 3.0-mm or larger catheter balloon. The specific angiographic criteria for exclusion from the study were (1) lesions .12.0 mm in length, (2) a ≤2.5-mm involvement in the artery ostium or artery diameter, or (3) an occluded, tortuous, or calcified artery. Patients with a ≥50% stenosis of the left main coronary artery were also excluded. The clinical criteria for inclusion were (1) the presence of stable angina, (2) absence of previous infarction, and (3) normal left ventricular ejection fraction (LVEF). The endocardial contours were traced during systole and diastole of a normal sinus beat, and a global left ventricular ejection fraction was obtained by use of the area length method. The LVEF calculation was obtained by the area measurement method. Patients with associated valve disease, cardiomyopathy, ventricular dysfunction, or previous cardiac interventions were not included. The study also excluded patients who could not undergo periodic examinations or repeated angiography or who refused any one of the indicated treatments. The study design allowed for patients to cross over from one treatment to another, based on occurrence of symptoms, at any time during the study. Baseline characteristics of study patients according to treatment group: Variable: medical treatment (n=72); PTCA (n=72); surgery (n=70) Age (yr): 58±7; 54±9; 58±11 Male: 59; 58; 58 Hypertension (%): 38; 34; 30 Diabetes (%): 20; 15; 18
Interventions/ Test/ Factor being investigated	(1) Balloon angioplasty. The PTCA procedure was carried out under a standard technique. All patients received 100mg aspirin and calcium channel blockers. (2) Surgical revascularisation. The Left internal mammary artery was used for anastomosis with the LAD in all patients. . All 3 groups uniformly received the following drugs: calcium channel antagonists, Beat-blockers, nirates, and antiplatelet agents.
Comparisons	Medical therapy. Patients assigned to medical therapy received agents indicated for the prevention and relief of angina symptoms including B-blockers, nitrates, calcium antagonists and antiplatelet agents
Length of Study/ Follow-up	5 years
Outcome measures studied	The primary endpoint was defined as one of the following events: cardiac related death, acute MI, and refractory angina requiring revascularisation.

Results

Effect Size	Cardiac related deaths: There were 4 deaths in the PTCA group; 2 deaths in the group submitted to surgery and 2 deaths in the medically treated group (p=0.622). The cumulative survival rates at 5 years were 94.3%, 97.1%, and 97.1% for patients assigned to PTCA, surgery, and medical treatment respectively. Medical therapy: In this group, 3 of 72 patients had uncomplicated acute MI; 8 were referred to surgery and 4 to angioplasty because they showed signs of unstable angina. Two cardiac and 4 non cardiac deaths were recorded. The cardiac deaths were related to acute MI and the non cardiac deaths to cancer (3 patients) and stroke (1 patient). Bypass surgery: In the 70 patients referred to surgery, 1 patient had a perioperative acute MI. There were no in-hospital deaths in this group of patients; however, 1 patient died on his way to the hospital as result of unstable angina after 43 months of out-

patient follow-up, and 1 patient had cardiogenic shock and died during evolution of an acute MI. Non fatal MI was observed in 3 patients and stroke in 1 patient. None of these patients required angioplasty during the follow-up period.

Coronary angioplasty:
A successful outcome was reported in 95.8% of the 72 patients randomly assigned to the angioplasty group. During the follow-up period, 27 (39.1%) of the 69 patients in this group underwent repeat catheterisation for unstable angina and 21 (30.3%) required 1 or 2 additional angioplasty procedures for treatment of restenosis. Eight patients had unstable angina and were electively referred to cardiac surgery; none of these patients required surgery during the first 6 months of follow-up. Four patients died during follow-up; 1 died suddenly at home and the other 3 died during acute MI. Non cardiac deaths occurred in 2 patients: 1 died of a stroke and the other of AIDS. Non fatal MI occurred in 4 patients during the follow-up period.

Anginal symptoms:
Patients treated by surgical bypass were the most likely to be free of anginal symptoms at the conclusion of the study, where as a marked increased was observed in anginal symptoms among patients randomly assigned to medical therapy. Only 17 (25.8%) patients in the medically treated group were free of such symptoms at the end of the study, compared with 48 (72.7%) and 44 (64.7%) of the surgery and angioplasty groups, respectively. A statistically significant benefit was found for angioplasty as compared with medical therapy ($p<0.001$). None of the study patients of all the groups had refractory angina (functional class III or IV) at final follow-up.

Source of funding:

E.J. Zerbini Foundation, Sao Paulo, Brazil.

Does the study answer the question?/Further Comments

Yes. After a 5 year follow-up, combined events (acute MI or death and presence of refractory angina) were reported in only 6 patients referred for surgery compared with 29 patients treated with angioplasty and 17 patients who only received medical treatment ($p=0.001$). However, no differences were noted in relation to the occurrence of cardiac related death in the 3 treatment groups ($p=0.622$).No patient assigned to surgery needed repeat operation, whereas 8 patients assigned to angioplasty and 8 patients assigned to medical treatment required bypass after the initial random assignment. Surgery and angioplasty reduced anginal symptoms considerably. However, all 3 treatments effectively improved limiting angina.

Hultgren HN;Peduzzi P;Detre K;Takaro T;

The 5 year effect of bypass surgery on relief of angina and exercise performance

Ref ID 2016 **RID:** 655 1985 Dec

QUALITY

A. Selection bias (systematic differences between the comparison groups)

A4 Based on your answers t, in your opinion was selection bias present? If so, what is the likely direction of its effect?:

Unclear/unknown risk

Direction =

B. Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)

B4 Based on your answers to the above, in your opinion was performance bias present? If so, what is the likely direction of its effect?:

Low risk of bias

Direction =

C. Attrition bias (systematic differences between the comparison groups with respect to loss of participants)

C4 Based on your answers to the above, in your opinion was attrition bias present? If so, what is the likely direction of its effect?:

High risk of bias

Direction =

D. Detection bias (bias in how outcomes are ascertained, diagnosed or verified)

D6 Based on your answers to the above, in your opinion was detection bias present? If so, what is the likely direction of its effect?:

Low risk of bias

Direction =

Overall Study Quality -Strengths and Weaknesses:

See Ref ID 2101.
This is a1 year and 5 year follow-up of the VA study. Since the Angina questionnaire (AQ) and exercise testing were not implemented at baseline, only about half the patients randomised in the 1972 to 1974 cohort had a baseline evaluation. Approximately 90% of both the 1 year and 5 year survivors had a follow-up AQ. Only about 60% of the 1 year and 5 year survivors had exercise tests.

DETAILS

# of patients:	N= 341 (n=176 medical group and n=165 surgical group).
Prevalence (Diagnostic):	
Patient Characteristics	See Ref ID 2101. Not reported seperately for this group of patients.
Interventions/ Test/ Factor being investigated	Surgery
Comparisons	Medical treatment
Length of Study/ Follow-up	Follow-up 1 year and 5 year.

Outcome measures studied

Severity of angina and exercise performance

Results

Effect Size

Results:
Severity of angina:
At 1 year: The percentage of surgical patients with mild or absent angina was 78%, nearly triple the rate of 28% observed at entry. The corresponding rates in the medical group showed little change: 38% at 1 year and 32% at entry. At 5 years the percentage of surgical patients with mild or absent angina decreased from the 1 year rate 78% to 64%, while the medical group exhibited a small increase from 38% to 49%.
Analysis of the change in angina indicated that 49% of surgical patients were markedly improved at 1 year compared with only 12% of medical patients. Also 56% of medical patients had a worsened or no changed symptoms at 1 year compared with only 13% of surgical patients. At 5 years the percentage of surgical patients who remained markedly improved decreased to 41% and the percentage with worsened or unchanged symptoms nearly doubled from 12% at 1 year to 17% at 5 years.

Exercise test results reported graphically: At 1 year surgical patients had fewer tests stopeed by angina compared with medical patients (28% vs. 64%), a higher estimated oxygen consumption (26 vs. 21 ml/kg/min) and treadmill exercise duration (7.33 vs. 4.9 min). At 5 years exercise performance of surgical patients remained superior to that of medical patients, but the treatment difference was smaller.

Angina questionnaire: An AQ scoring system was devised using the specific items on the questionnaire. The score consisted of two components: 1) a severity score (range 0 to 9) based on the frequency of angina, the presence of rest or nocturnal angina, and the type of activity producing angina; and 2) a medication score (range 0 to 9) based on the use of nitroglycerin, propranolol and long acting nitrates. The combined score (range 0 to 18) provided an overall measure of the severity of angina, i.e., the higher the score the more severe the angina. The score was shown to be reproducible upon testing 50 patients by two independent observers. The validity of the score was reinforced by comparison with exercise performance, a more objective measure of physical performance than commonly used classification systems.

Source of funding:

see Ref ID 2101

Does the study answer the question?/Further Comments

Yes. Benefits of surgery were substantially superior to medical treatment at 5 years.

Kaiser C;Kuster GM;Erne P;Amann W;Naegeli B;Osswald S;Buser P;Schlapfer H;Brett W;Zerkowski HR;Schindler C;Pfisterer M;Investigators TIME;

Risks and benefits of optimised medical and revascularisation therapy in elderly patients with angina--on-treatment analysis of the TIME trial

Ref ID 957 **RID:** 518 2004 Jun

QUALITY

A. Selection bias (systematic differences between the comparison groups)

A4 Based on your answers t, in your opinion was selection bias present? If so, what is the likely direction of its effect?:

Low risk of bias

Direction =

B. Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)

B4 Based on your answers to the above, in your opinion was performance bias present? If so, what is the likely direction of its effect?:

Unclear/unknown risk

Direction =

C. Attrition bias (systematic differences between the comparison groups with respect to loss of participants)

C4 Based on your answers to the above, in your opinion was attrition bias present? If so, what is the likely direction of its effect?:

Low risk of bias

Direction =

D. Detection bias (bias in how outcomes are ascertained, diagnosed or verified)

D6 Based on your answers to the above, in your opinion was detection bias present? If so, what is the likely direction of its effect?:

Low risk

Direction =

Overall Study Quality -Strengths and Weaknesses:

Strengths: randomised, low attrition bias (on-treatment analysis so no loss to follow up)
Weaknesses: the potential for bias is substantial because both treatment groups contain failures of the other treatment. In addition the patient number is relatively low.No allocation concealment as on-treatment analysis. No intention to treat analysis as it is an ontreatment analysis.

This is a 1 year follow-up of the TIME trial (sub group- for elderly patients)

DETAILS

# of patients:

n= 174 Revasc (112 originally assigned to INV and 62 initially in MED gp)
n= 123 MED (86 initially assigned to MED and 41 initially in INV but no revasc (no

Prevalence (Diagnostic):

Patient Characteristics

Baseline characteristics:
Criteria, MED(n=127), REVASC(n=174), P value
Age (yrs (SD)), 80.3(3.7) ; 79.6(3.5), 0.09
Women (%), 48 ; 40 ; 0.18
History of AMI (%), 44 ; 49 ; 0.41
History of PCI/CABG (%), 18 ; 16 ; 0.63
>=2 risk factors (%) 54 ; 58 ; 0.52
>= 2 comorbidities (%) 32 ; 23 ; 0.11
Angina CCS class (SD) 3.0(0.9) ; 3.1(0.8) ; 0.13
Anti-anginal drugs (SD) 2.5(0.6) ; 2.5(0.7) ; 0.92

	LVEF(% (SD)) 52.6(11.8) ; 52.6(13) ; 0.99 General Health – SF36 (SD) ; 56.4(16.9) ; 52.5(18.3) ; 0.06 Vitality – SF36 (SD) ; 48.5(20.9) ; 44.7(21.6) ; 0.14 Duke Activity Status Index (SD) ; 13.6(11.2) ; 12.2(11.4) ; 0.2
Interventions/ Test/ Factor being investigated	Revascularisation vs Medical therapy alone
Comparisons	For this "on-treatment" analysis, all patients with revascularisation attempted during the one year observation period were compared to all patients with medical therapy alone with regards to symptoms, QoL and MACE up to one year after randomisation.
Length of Study/ Follow-up	1 year follow up
Outcome measures studied	Primary endpoint: quality of life (assessed by standardised questionnaires) and freedom from MACE (death, nonfatal MI, or hospitalisation for uncontrolled symptoms or acute coronary syndrome with or without need for revascularisation)
Results	
Effect Size	Effect of therapy on symptoms and QoL: With the exception of vitality, these parameters were significantly less improved by MED therapy than by REVASC therapy, despite the fact that there was also a significant treatment effect in this group vs baseline. MED patients needed more anti-anginal drugs after 1yr than REVASC CCS $p<0.0003$ ROSE $p=0.005$ Antianginal drugs $p<0.0001$ General health $p=0.002$ Vitality $p=0.02$ Duke Activity Status Index $p=0.003$ Effect of therapy on MACE: Hazard ratio REVASC vs MED* P value Death 1.31(0.58-2.99) 0.52 Cardiac death 1.02(0.41-2.51) 0.98 Death and/or MI 1.77(0.91-3.41) 0.009 MACE 1.10(0.69-1.76) 0.69 *adjusted for sex, age, CCS class and heart rate at rest
Source of funding:	grants from the Swiss Heart Foundation and the Adumed Foundation, Switzerland
Does the study answer the question?/Further Comments	Yes. The aim of the “on treatment” analysis was to more fully describe the effects of optimised medical therapy and revasc on angina severity, measures of QoL and MACE. The main findings were that the mortality of MED patients was similar to that of REVASC patients of the same advanced age, indicating that mortality is increased in these elderly CAD patients whatever treatment they receive. The early mortality hazard of invasive management was mainly due to the high mortality of CAD patients assigned to invasive management who could not be revascularised, rather than to the PCI or CABG surgery itself. Overall, revascularisation led to a significant improvement in angina severity and measures of QoL, compared to the optimised medical therapy

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Killip T;Passamani E;Davis K;

Coronary artery surgery study (CASS): a randomized trial of coronary bypass surgery. Eight years follow-up and survival in patients with reduced ejection fraction

Ref ID 2022 **RID:** 656 1985 Dec

QUALITY

A. Selection bias (systematic differences between the comparison groups)

A4 Based on your answers t, in your opinion was selection bias present? If so, what is the likely direction of its effect?:

Low risk of bias **Direction =**

B. Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)

B4 Based on your answers to the above, in your opinion was performance bias present? If so, what is the likely direction of its effect?:

Low risk of bias **Direction =**

C. Attrition bias (systematic differences between the comparison groups with respect to loss of participants)

C4 Based on your answers to the above, in your opinion was attrition bias present? If so, what is the likely direction of its effect?:

Low risk of bias **Direction =**

D. Detection bias (bias in how outcomes are ascertained, diagnosed or verified)

D6 Based on your answers to the above, in your opinion was detection bias present? If so, what is the likely direction of its effect?:

Low risk of bias **Direction =**

Overall Study Quality -Strengths and Weaknesses: See Ref ID 2047

This is a 8 years follow-up of the CASS trial.

DETAILS

# of patients: n=780 [Surgery (n=390) and. Medical (n=390)] [n=160 patients with ejection fraction less than 0.50 but >0.35.]. Patients with ejection fraction of less than 0.35

Prevalence (Diagnostic):

Patient Characteristics See Ref ID 2047

Interventions/ Test/ Factor being investigated	surgery
Comparisons	medical
Length of Study/ Follow-up	8 years
Outcome measures studied	Survival rate.

Results

Effect Size	Results: After 8 years follow-up, 87% of the patients assigned to surgical treatment and 84% of those assigned to medical treatment remained alive. Single vessel disease: Survival after 7 years was 92% for patients assigned to surgery and 90% for those in medical group. 2 vessel disease: After 7 years, medical and surgical survival was 88% for both medical and surgery group. 3 vessel disease: After 7 years, 88% of patients in surgery and 83% in medical group were alive. Patients with ejection fraction less than 0.50: Over 7 year's follow-up, 36 deaths occurred in patients with ejection fraction <0.50 of these, 11 were in patients assigned to surgical therapy and 25 in those assigned to medical treatment. After 7 years, survival in the surgical group was 84%, where as that in the medical group was 70%, a highly significant difference (p=0.012). Note: One patient assigned to surgical therapy died while awaiting surgery 4 days after randomisation. Six patients assigned to surgical therapy initially refused this treatment. None of the surgically assigned patients died as a result of the procedure. During the follow-up interval, 22 of the medically assigned patients underwent CABG at an annual rate of 3.8%. In patients with triple vessel disease, the annual rate of crossover was 4.8%. There was one operative death in a patient initially assigned to medical therapy who crossed over to surgery.
Source of funding:	See Ref ID 2047
Does the study answer the question?/Further Comments	Yes. After 8 years, survival curves were not significantly different between medical and surgical groups; 87% of patients assigned to surgical and 84% of those assigned to medical treatment were alive. A significant advantage favouring surgical assignment was observed in patients with 3 vessel disease and reduced ejection fraction (<0.50 but >0.35).

Kloster FE;Kremkau EL;Ritzmann LW;Rahimtoola SH;R÷sch J;Kanarek PH;

Coronary bypass for stable angina: a prospective randomized study

Ref ID 4110 **RID:** 601 1979

QUALITY

A. Selection bias (systematic differences between the comparison groups)

A4 Based on your answers t, in your opinion was selection bias present? If so, what is the likely direction of its effect?:

Unclear/unknown risk

Direction =

B. Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)

B4 Based on your answers to the above, in your opinion was performance bias present? If so, what is the likely direction of its effect?:

Low risk of bias

Direction =

C. Attrition bias (systematic differences between the comparison groups with respect to loss of participants)

C4 Based on your answers to the above, in your opinion was attrition bias present? If so, what is the likely direction of its effect?:

High risk of bias

Direction =

D. Detection bias (bias in how outcomes are ascertained, diagnosed or verified)

D6 Based on your answers to the above, in your opinion was detection bias present? If so, what is the likely direction of its effect?:

Unclear risk of bias

Direction =

Overall Study Quality -Strengths and Weaknesses:	strengths: randomised, baseline comparisons made. Loss to follow-up not reported Weakness: allocation concealment not reported. ITT not reported.

DETAILS

# of patients:	N=100 (n=49 medical and n=51 surgery)
Prevalence (Diagnostic):	
Patient Characteristics	Baseline characteristics: variable: medical (n=49) ; surgery (n=51) Age: 51.6 yrs; 52.4 yrs Angina classification: all class III ; all class III Inclusion criteria: Chronic disabling angina pectoris for 1 year, 62 years of age or less, no episodes of unstable angina or MI within 6 months, no clinical evidence of heart failure or cardiomegaly on x-ray study, absence of other major disabling illnesses, and willingness and availability to participate in a long term research study. Entry in to the study was closed after 5 years in December 1976, with 100 patients in the study.
Interventions/ Test/ Factor being investigated	surgery (aortocoronary bypass)

Comparisons	Medical therapy consisted of bed rest, oxygen, sedation, analgesics, and propanolol during the initial part of the study and as standard medical therapy evolved over the years, included the aggressive use of propranalol, sublingual isosorbide dinitrate and nitroglycerin ointment to maximum tolerated levels.
Length of Study/ Follow-up	medical (mean 38.1±2.9 months) and surgery (36.6±3.1 months)
Outcome measures studied	Primary outcome: major cardiac events.
Results	
Effect Size	Results: At 5 years Outcome: medical vs. surgery Death : 5 vs. 4* MI: 8 vs. 10 Stroke: 2 vs. 1 *all medical patients died from cardiac causes. Of these one had one vessel, 2 had 2 vessel and 2 had 3 vessel disease. In the surgery group, one died during the operation, and one at 6 weeks. Two occurred at 18 and 41 months after. All patients' had 3 vessel disease. Functional class: At 6 months, 44 medical patients without terminating events, 23 had improved to Class II (52%) and 35 of the remaining 42 surgical patients (83%) were improved or asymptomatic. There was a highly significant difference between the two groups at that point ($p<0.01$). At 3 years , 14 out of 27 medical patients (50%) without terminating events remained in class II, and 24 of 34 surgical patients (71%) were in class I or II; there was a significant difference in class between the two groups. Vein grafts: 43 of the 51 surgical patients underwent repeat coronary angiography 6 months after the operation to evaluate patency of the venous graft. Of the 8 patients not undergoing repeat angiography, two were dead , three had interim MI, one had chronic active hepatitis, one moved out of state, and one refused.
Source of funding:	Supported in part by a grant and by a program project grant from the National Heart, Lung, and Blood institute
Does the study answer the question?/Further Comments	Yes. The bypass resulted in greater functional improvement than medical therapy. The likelihood of death and MI was unchanged by operation.

Loeb HS;Pifarre R;Sullivan H;Palac R;Croke RP;Gunnar RM;

Improved survival after surgical therapy for chronic angina pectoris: one hospital's experience in a randomized trial

Ref ID 2090 **RID:** 559 1979 Aug

QUALITY

A. Selection bias (systematic differences between the comparison groups)

A4 Based on your answers t, in your opinion was selection bias present? If so, what is the likely direction of its effect?:

Unclear/unknown risk **Direction =**

B. Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)

B4 Based on your answers to the above, in your opinion was performance bias present? If so, what is the likely direction of its effect?:

Unclear/unknown risk **Direction =**

C. Attrition bias (systematic differences between the comparison groups with respect to loss of participants)

C4 Based on your answers to the above, in your opinion was attrition bias present? If so, what is the likely direction of its effect?:

Unclear/unknown risk **Direction =**

D. Detection bias (bias in how outcomes are ascertained, diagnosed or verified)

D6 Based on your answers to the above, in your opinion was detection bias present? If so, what is the likely direction of its effect?:

Unclear **Direction =**

Overall Study Quality -Strengths and Weaknesses:

Strength: intention to treat analysis used
Weaknesses: randomisation and allocation concealment methods not reported ; loss to follow up unclear ; small sample size; crossover of patients (13/60 patients assigned to the medical therapy underwent surgery and 3/61 patients assigned to surgical treatment declined surgery)

DETAILS

# of patients:

N= 60 to medical treatment
N=61 to surgical treatment

Prevalence (Diagnostic):

Patient Characteristics

Inclusion: Male patients were considered for study if they had clinically stable angina pectoris for at least 6 months and been under medical treatment for at least 3 months.
Exclusion : Patients with acute MI or unstable angina within the prior 6 months were excluded. Excluded patients with significant left main coronary obstruction. Other reasons for exclusion were uncontrolled hypertension or diabetes, severe heart failure, and other significant cardiac or noncardiac disease likely to influence longevity

Clinical feature:Medical (%); Surgical (%); p value
History
Prior MI : 50 ; 54 ; ns
Hypertension:38 ; 38 ; ns

	Congestive heart failure: 12 ; 7 ;ns Diabetes mellitus:17 ;15 ; ns Blood pressure Systolic >= 150mmHg:23 ; 20 ; ns Diastolic >- 100mm Hg:18 ; 7 ; <0.05 Cardiothoracic ratio <= 0.50:14 ; 12 ; ns Serum cholesterol: 32 ;18 ; ns >=280mg% Age years (SE of mean):52(1); 51(1); ns
Interventions/ Test/ Factor being investigated	Consenting patients underwent coronary arteriography and left ventriculography. Patients were randomised to medical or surgical therapy only if a significant obstruction was demonstrated in a major coronary vessel, and if aortocoronary bypass surgery was considered to be feasible according to the appearance of the distal vessels and the quality of ventricular function. Medical therapy was not standardised in either patient group but was determined by individual patient need according to current clinical practice. Likewise, saphenous vein aortocoronary bypass was performed by standard surgical techniques commonly practiced at that time.
Comparisons	surgical intervention (aortocoronary bypass) vs medical therapy
Length of Study/ Follow-up	up to 6 years
Outcome measures studied	survival
Results	
Effect Size	Crossover: 13/60 patients assigned to the medical therapy underwent aortocoronary bypass either because patient insisted or because physician felt that increased severity of symptoms warranted surgical intervention. 3/61 patients assigned to surgical treatment declined surgery Survival at 6 years (ITT analysis) Results presented as graph Year 1 ; 2 ; 3 ; 4 ; 5 ; 6 P< NS ; NS ; 0.03 ; 0.02 ; 0.02 ; 0.04 N(surgical gp) 58 ; 57 ; 55 ; 47 ; 28 ; 10 N(medical gp) 53 ; 50 ; 45 ; 36 ; 22 ; 6 Survival at 6 years (crossover patients excluded) Figures read from graph Year 1 ; 2 ; 3 ; 4 ; 5 ; 6 P< NS ; NS ; 0.02 ; 0.02 ; 0.01 ; 0.03 N(surgical gp) 58 ; 55 ; 54 ; 53 ; 45 ; 27 ; 10 N(medical gp) 47 ; 41 ; 39 ; 34 ; 27 ; 17 ; 5
Source of funding:	supported in part by the Medical Research Service of the Veterans Administration Edward Hines Jr Medical Center, Hines, Illinois
Does the study answer the question?/Further Comments	Results of this study differ from the preliminary results from the Veterans study primarily because of higher mortality in the medical group. The medical mortality in the groups are in keeping with other reports of the natural history of patients with angina pectoris, and they propose that the population of patients they randomised closely simulates the usual type of patients with chronic angina being considered for surgical treatment.

Lopes NH;Paulitsch FS;Gois AF;Pereira AC;Stolf NA;Dallan LO;Ramires JA;Hueb WA;

Impact of number of vessels disease on outcome of patients with stable coronary artery disease: 5-year follow-up of the Medical, Angioplasty, and bypass Surgery study (MASS)

Ref ID 210 **RID:** 582 2008 Mar

QUALITY

A. Selection bias (systematic differences between the comparison groups)

A4 Based on your answers t, in your opinion was selection bias present? If so, what is the likely direction of its effect?:

Unclear/unknown risk **Direction =** baseline characteristics given by 1m 2 or 3 vessel disease, not by treatment allocation

B. Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)

B4 Based on your answers to the above, in your opinion was performance bias present? If so, what is the likely direction of its effect?:

Low risk of bias **Direction =**

C. Attrition bias (systematic differences between the comparison groups with respect to loss of participants)

C4 Based on your answers to the above, in your opinion was attrition bias present? If so, what is the likely direction of its effect?:

Low risk of bias **Direction =**

D. Detection bias (bias in how outcomes are ascertained, diagnosed or verified)

D6 Based on your answers to the above, in your opinion was detection bias present? If so, what is the likely direction of its effect?:

low risk of bias **Direction =**

Overall Study Quality -Strengths and Weaknesses: Large randomised controlled trial; randomisation and allocation concealment unclear.Baseline characteristics given by groups based on number of vessels involved ratehr than treatment group allocation.

DETAILS

# of patients: 825 (CABG 273: PCI 277: medical therapy [MT]:275)

Prevalence (Diagnostic):

Patient Characteristics Inclusion: Proximal multivessel coronary stenosis >70% and documented ischaemia; suitable for medical therapy or revascularisation.
Exclusion: not stated in this paper.

Single vessel 2vessel 3

vessel	p value				
Age		57 (10)	58 (9)	60 (9)	p<0.0001
Male (%)		70.5	67.5	70.3	0.7109
Current smoker (%)		37.3	35.9	32.4	0.4298
Hypertension (%)		35.5	57.3	61.1	p<0.0001
Diabetes (%)		31.3	37.9	38.8	0.1700
Randomisation:					
CABG (%)		32.7	33.6	32.9	
PCI (%)		33.6	33.6	33.5	0.9995
Medical therapy (MT) (%)		33.6	32.8	33.5	
Vessel territory (%)					
Left anterior descending		100	95	98	
Left circumflex		0	79	89	
Right coronary artery		0	75	82	

Interventions/ Test/ Factor being investigated

CABG vs. PCI vs. medical therapy (MT)

Comparisons

To compare the impact of number of vessels disease on the mortality and event-free survival; analysis stratified by treatment allocated

Length of Study/ Follow-up

5 years (mean 1702 (452) days; median 1840 days

Outcome measures studied

Primary outcome measure: combined incidence of mortality, MI or refractory angina requiring revascularisation

Results

Outcomes at 5 years:

All treatments:	Single vessel (SVD)	2vessel (2VD)	3 vessel (3VD)	p value
Cumulative survival	95.5%	91.5%	87.4%	p=0.004 3VD vs. 2VD and SVD
Event-free survival	76%	72%	71%	not significant

Event-free survival:	CABG	PCI	Medical therapy	p
Single vessel disease	94%	75%	58%	p<0.001
2 vessel disease	86%	64%	63%	p<0.001
3 vessel disease	87%	65%	64%	p<0.001

Hazard ratios for composite endpoint:

Single vessel disease
- PCI:CABG 9.56 (95% CI 3.37 to 27.18), p<0.001
- MT:CABG 4.78 (95% CI 1.62 to 14.12), p=0.005

2 vessel disease
- PCI:CABG 3.27 (95% CI 1.64 to 6.52), p=0.001
- MT:CABG 3.11 (95% CI 1.55 to 6.22), p=0.001

3 vessel disease
- PCI:CABG 2.91 (95% CI 1.66 to 5.11), p<0.001
- MT:CABG 2.49 (95% CI 1.41 to 4.38), p=0.002

Effect Size

Source of funding:	not stated
Does the study answer the question?/Further Comments	Large randomised controlled trial. Mainly comparing single, 2 vessel and 3 vessel disease. Event-free survival higher among patients with CABG than PCI or medical therapy. NB This paper includes the patients in the MASS II study (papers Hueb 2004, Soares 2006, Favarato 2007, Hueb 2007, Hueb 2010) so beware double counting. Results given as cumulative survival and hazard ratios.

Maron DJ;Spertus JA;Mancini GB;Hartigan PM;Sedlis SP;Bates ER;Kostuk WJ;Dada M;Berman DS;Shaw LJ;Chaitman BR;Teo KK;O'Rourke RA;Weintraub WS;Boden WE;COURAGE Trial Research Group;

Impact of an initial strategy of medical therapy without percutaneous coronary intervention in high-risk patients from the Clinical Outcomes Utilizing Revascularization and Aggressive DruG Evaluation (COURAGE) trial

Ref ID 9127 **RID:** 677 2009 Oct 15

QUALITY

A. Selection bias (systematic differences between the comparison groups)

A4 Based on your answers t, in your opinion was selection bias present? If so, what is the likely direction of its effect?:

Unclear/unknown risk **Direction =**

B. Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)

B4 Based on your answers to the above, in your opinion was performance bias present? If so, what is the likely direction of its effect?:

Low risk of bias **Direction =**

C. Attrition bias (systematic differences between the comparison groups with respect to loss of participants)

C4 Based on your answers to the above, in your opinion was attrition bias present? If so, what is the likely direction of its effect?:

Low risk of bias **Direction =**

D. Detection bias (bias in how outcomes are ascertained, diagnosed or verified)

D6 Based on your answers to the above, in your opinion was detection bias present? If so, what is the likely direction of its effect?:

Low rsik of bias **Direction =**

Overall Study Quality -Strengths and Weaknesses:	Strengths: Randomisation method reported (permuted block design within strata –prior CABG/no prior CABG and by medical centre), sample size calculation reported, Blind outcome assessment (clinical outcome adjudicated by an independent committee whose members were unaware of treatment assignments). Intention to treat analysis reported. Weaknesses: Allocation concealment not reported. * Author reported weakness: Selection bias, because the patients with high risk clinical or angiographic features were less likely to be referred by their cardiologists for enrolment in the COURAGE trial. This study is a post hoc analysis of COURAGE trial with high risk patients.

DETAILS

# of patients:	N=2287 (all COURAGE trial participants). High risk – n=264 (n=132 in OMT and n=132 in PCI+OMT). 2 patients randomised to PCI did not receive PCI because of
Prevalence (Diagnostic):	
Patient Characteristics	Baseline characteristics of high risk patients: 264 high risk patients, of these 146 had CCS class III angina with a first onset of symptoms ≤ 2 months before enrolment, 100 had had an ACS ≤ 2 weeks before enrolment, and 18 had both conditions. Characteristic: OMT (n=132) ; PCI +OMT(n=132) Age (years): 61±11; 60±11 Men: 113 (86%); 112 (85%) White: 111 (84%); 111 (84%) Diabetes mellitus: 43 (33%); 44 (34%) Previous MI: 65 (49%); 57 (44%) Previous PCI: 23 (17%) ; 15 (12%) Previous CABG: 17 (13%);16 (12%) New onset class III angina: 69; 77 Stabilised acute coronary syndrome: 53; 47 New onset class III angina plus stabilised ACS: 10; 8 1 vessel disease: 46 (35%) ;44 (33%) 2 vessel disease: 52 (40%);56 (42%) 3 vessel disease: 32 (“5%); 31 (23%) 2 vessel disease with proximal left anterior descending: 19 (37%); 11 (20%) 3 vessel disease with proximal anterior descending: 10 (31%); 10 (32%) Ejection fraction (%): 59±10; 61±11 Patients with ejection fraction ≤50%: 32 (24%); 32 (24%)
	Inclusion in the post hoc analysis of patients who had the following high risk clinical characteristics: 1)CCS class III angina with a first onset of symptoms ≤2 months before randomisation 2) ACS ≤2 weeks before randomisation without revascularisation or rehospitalisation for recurrent ACS or 3)both conditions.
Interventions/ Test/ Factor being investigated	PCI +OMT
Comparisons	OMT.Both groups received OMT consistent with established practice guidelines for patients with chronic stable angina.
Length of Study/ Follow-up	Median- 4.6yrs

Outcome measures studied

The primary outcome measure was the composite of death from any cause or nonfatal. The secondary outcomes were angina related health status; the composite of death or MI, with peri-PCI, MI excluded; the individual outcomes of death and MI; hospitalisation for ACS; the composite of death, MI, and ACS; the rates of subsequent revascularisation

Results

Effect Size

Results:
The rate of death or MI in high risk patients (both treatment groups combined) was 56% greater than in the non-high risk patients during a median 4.6 years of follow-up.
Outcome: OMT (n=132) vs. PCI+OMT (n=132)
Death: 12 (9%) vs. 12 (9%); p=0.98
MI: 25 (19%) vs. 22 (17%); p=0.66
ACS: 22 (17%) vs. 27 (20%); p=0.39
During the follow-up period, a greater number of revascularisation procedures were performed in the OMT group, most of which were performed within 1 year of enrolment. During the first year of follow-up, 40 OMT patients crossed over to the revascularisation group compared to 21 PCI patients who underwent repeat revascularisation procedures (30% vs. 15%; p=0.003). During the entire follow-up period 56 OMT patients crossed over to revascularisation compared to 41 assigned to initial PCI who required a repeat procedure (42% vs. 30%;p=0.02). The clinical indications for crossover among the OMT patients were angina unresponsive to medical therapy (61%), MI (13%), the need for coronary artery bypass grafting (13%), ischemia (5%), and other (9%). The indications for repeat revascularisation in the PCI group were re-stenosis (37%), angina unresponsive to medical therapy (20%), MI (17%), ischemia (15%), and the need for coronary artery bypass grafting (10%). Most revascularisation in both treatment groups during the follow-up period were PCI procedures.

At baseline the high risk patients had a significantly worse angina-related health status than patients without high risk features. This difference disappeared after 1 month, and no significant difference between the high risk and non high risk patients was detectable during the subsequent 3 years of follow-up. Among the high-risk patients, the baseline Seattle Angina Questionnaire scores within the treatment groups were similar at baseline. The angina frequency and quality of life scores in the OMT group were significantly worse at any other point compared to the scores in the PCI group. At 3 years the scores for these domains were better in the OMT group. A repeated measures analysis was done to assess the effect of the treatment assignment over time-the angina related health status was not significantly different between the 2 treatment groups (p=0.25 for angina frequency, p =0.35 for quality of life).

Source of funding:

see RefID 483

Does the study answer the question?/Further Comments

Yes.High risk patients randomised to OMT alone as the initial management strategy, they did not experience a greater rate of death or MI or have a poorer quality of life than patients randomised to initial PCI plus OMT. However, high risk patients assigned to OMT alone crossed over to revascularisation at a high rate-30% by 1 year and 42% by the end of the study.
Authors report that the lack of benefit from angina related health status from PCI was unexpected. Possible explanations include crossover from OMT to revascularisation, aggressive use of anti-ischemic medications in the OMT group, the positive effect of OMT on endothelial function, and the unavailability of drug-eluting stents.

Mathur VS;Guinn GA;

Prospective randomized study of coronary bypass surgery in stable angina. The first 100 patients

Ref ID 4090 **RID:** 558 1975

QUALITY

A. Selection bias (systematic differences between the comparison groups)

A4 Based on your answers t, in your opinion was selection bias present? If so, what is the likely direction of its effect?:

Direction =

B. Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)

B4 Based on your answers to the above, in your opinion was performance bias present? If so, what is the likely direction of its effect?:

Direction =

C. Attrition bias (systematic differences between the comparison groups with respect to loss of participants)

C4 Based on your answers to the above, in your opinion was attrition bias present? If so, what is the likely direction of its effect?:

Direction =

D. Detection bias (bias in how outcomes are ascertained, diagnosed or verified)

D6 Based on your answers to the above, in your opinion was detection bias present? If so, what is the likely direction of its effect?:

Direction =

Overall Study Quality -Strengths and Weaknesses:

Strengths: Randomised control trial (randomisation method not reported), baseline comparisons made, no loss to follow-up
Weaknesses: No allocation concealment, small sample size, evaluations carried out by the first author, overall very high number of smokers in the study (see publication year)
* Study seems to report the same findings as those in ref. id 4089 with 28 additional cases

DETAILS

# of patients: 100 (50 angiography 50 medical treatment)

Prevalence (Diagnostic):

Patient Characteristics

Baseline characteristics:

	Surgery (n=50)	Med Therapy (n=50)
Age years (median)	54	53
Diabetes (%)	34	24
Myocardial infarction (%)	84	80

	Smokers (%) 90 84
	Inclusion / exclusion criteria – see also ref id 4089: Male patients with stable angina pectoris believed to be due to arteriosclerotic heart disease. All patients had received at least 12 weeks of treatment and their symptoms had to continue to be disabling. Exclusion criteria: All patients received left ventriculography, selective coronary arteriography and atrial pacing and patients without critical disease (more than 70% obstruction) were excluded. Other exclusions were any of the following – significant valvular disease; surgically resectable ventricular aneurysm; critical stenosis of left main coronary artery; severe distal arterial disease rendering the arteries non-bypassable; or poor left ventricular function with an ejection fraction below 15%. Also later excluded were data from 2 patients – one from the surgical group who changed his mind after randomisation and from another in the medical group who needed surgery after 4 months of medical treatment.
Interventions/ Test/ Factor being investigated	Surgical intervention – a saphenous-vein aortocoronary bypass to all the major bypassable vessels with critical stenosis.
Comparisons	Surgical intervention (revasculisation) vs medical treatment
Length of Study/ Follow-up	8 to 34 months – median 24 months
Outcome measures studied	Subjective assessment of current symptoms, frequency of adverse events and complications were recorded (death, myocardial infarction etc)
Results	
Effect Size	Subjective assessment of current symptomatic status*: Surgery Med Therapy p-value Asymptomatic 70% 8% <.01 Improved 18% 64% ns Same or worse 4% 16% ns *Note: Unlike in ref id 4089 in the current article percentages are calculated from the original cohort and include those who have died and 2% in each group who were excluded from the analysis. Adverse events: Surgery Med Therapy p-value Death no. (%) 3(6) 5(10) ns Myocardial infarction no. (%) 3 (6) 9(18) n
Source of funding:	Not stated in current study
Does the study answer the question?/Further Comments	Yes. The frequency of adverse outcomes was not significantly different between the surgical and the medical treatment intervention group. Subjective assessments of asymptomatic together with improvements were 88% in surgical patients and 72% in medically treated patients. Significantly more patients subjectively rated themselves at asymptomatic in the surgical group (70%) compared to the non-operative group (8%).

Mathur VS;Guinn GA;

Prospective randomized study of the surgical therapy of stable angina

Ref ID 4099 **RID:** 861 1977

QUALITY

A. Selection bias (systematic differences between the comparison groups)

A4 Based on your answers t, in your opinion was selection bias present? If so, what is the likely direction of its effect?:

Unclear/unknown risk

Direction =

B. Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)

B4 Based on your answers to the above, in your opinion was performance bias present? If so, what is the likely direction of its effect?:

Low risk of bias

Direction =

C. Attrition bias (systematic differences between the comparison groups with respect to loss of participants)

C4 Based on your answers to the above, in your opinion was attrition bias present? If so, what is the likely direction of its effect?:

Unclear/unknown risk

Direction =

D. Detection bias (bias in how outcomes are ascertained, diagnosed or verified)

D6 Based on your answers to the above, in your opinion was detection bias present? If so, what is the likely direction of its effect?:

Unclear risk of bias

Direction =

Overall Study Quality -Strengths and Weaknesses:

Strengths: stratified randomisation, n=5 lost to follow-up.
Weakness: small sample size, allocation concealment not reported, ITT not reported.

DETAILS

# of patients:

N=116 (n=56 surgery, n=60 medical)

Prevalence (Diagnostic):

Patient Characteristics

Baseline characteristics:
The clinical features were remarkably similar in the two groups.
Median age in both the groups was 54 years.
Variable: surgery (n=56) vs. n= medical (n=60)
History of diabetes: 47 (84%) vs. 47 (78%)
No. of major vessels with 70% obstruction
One vessel: 9 (16%) vs. 9 (15%)
Two vessels: 26 (29%) vs. 20 (33%)
Three or more vessels: 31 (55%) vs. 31 (52%)

	Inclusion criteria: all patients with symptoms of angina pectoris were screened for possible inclusion in the study. The patients whose symptoms were stable for 12 weeks and who continued to remain disabled inspite of medical treatment were approached for possible participation in the study, provided no significant valvular disease was suspected and no previous cardiac surgery had been performed. The symptoms were considered disabling in relation to the patients own usual activities and habits. Patients with hypertension or history of congestive heart failure were considered eligible provided the major symptoms were angina pectoris. Exclusion criteria: Patients with the following features were excluded prior to randomisation: 1) absence of critical disease in a major coronary artery. The critical disease was defined as 70% or greater luminal narrowing as judged from the diameter. 2) Presence of critical disease in left main coronary artery.3) Valvular disease with nay gradient across the valve or regurgitation more than 1+ (in a scale of 1+ to 4+). 4) surgically resectable ventricular aneurysm. 5) Severe distal coronary arterial disease rendering all the arteries with critical disease nonbypassable. 6) Generalised poor left ventricular function with an ejection fraction below 15%.
Interventions/ Test/ Factor being investigated	Surgery. Saphenous vein graft. All patients in both groups were advised regarding diet and weight control, abstinence from smoking and participation in regular exercise program. Anginal symptoms were treated with frequent doses of nitrates, and propranolol was added whenever symptoms persisted.
Comparisons	Medical treatment.
Length of Study/ Follow-up	median 38 months (range 13 to 52 months)
Outcome measures studied	Primary and secondary outcomes not stated. Outcomes assessed: death, non fatal MI, relief of angina symptoms.
Results	
Effect Size	Results: Outcome: surgery (n=55)* vs. medical (n=60); p-value Asymptomatic***: 34 (62%) vs. 4 (7%);p<0.01 Improved since entry: 15 (27%) vs. 38 (63%); p<0.05 Unchanged or worse: 2 (4%) vs. 8 (13%); ns Current disability Mild: 14 (25%) vs. 32 (53%); p<0.05 Moderate: 1 (2%) vs. 12 (20%); ns Severe: 2 (4%) vs. 2 (3%); ns Dead**: 3 (5%) vs. 7 (12%); ns Non fatal MI: 6 (11%) vs. 10 (17%); ns Unstable angina****: 8 (14%) vs. 24 (40%); p<0.05 *one surgery patients not operated was not included in this analysis. The status of the patients in the non surgical group who were later operated was analysed only for the period prior to surgery. **there were 3 operative deaths but no other cardiac deaths during the follow-up period in the surgical group. There were 7 deaths, all cardiac, in the medical group; 5 in the first year, one in the second year, and one in the third year. *** A patient was considered asymptomatic if he was able to carry out unrestricted activities without being limited by any cardiac symptoms and without having to take nitroglycerin. Improvement was based on the subjective assessment by the patient corroborated by his description of physical activities he was able to perform prior to entering the study and those he could perform later. **** There were 9 episodes of unstable angina in 8 surgical patients and 36 episodes in 24 non surgical patients (p<0.01). Note:- Adherence to the assigned group: Except for one patient who was randomised to the surgical group but changed his mind after randomisation and was not operated, all others followed the group assignment. Of the 60 patients in the non surgical group, 4 patients subsequently underwent surgery during the follow-up period. All of them failed to respond to maximum tolerated medical therapy and were operated after developing repeated

episodes of unstable angina. Two of them were operated 4 and 13 months of medical treatment and two others were operated at other institutions 24 and 30 months after randomisation. None of these 5 patients were lost to follow-up.

Source of funding: Not reported

Does the study answer the question?/Further Comments Yes. Significantly more patients in the surgery group were asymptomatic compared to medical group. The incidence of death and MI was higher in the medical group throughout the follow-up period although the difference did not achieve statistical significance.

Mathur VS;Guinn GA;Anastassiades LC;Chahine RA;Korompai FL;Montero AC;Luchi RJ;

Surgical treatment for stable angina pectoris. Prospective randomized study

Ref ID 4089 **RID:** 529 1975

QUALITY

A. Selection bias (systematic differences between the comparison groups)

A4 Based on your answers t, in your opinion was selection bias present? If so, what is the likely direction of its effect?:

Unclear/unknown risk **Direction =**

B. Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)

B4 Based on your answers to the above, in your opinion was performance bias present? If so, what is the likely direction of its effect?:

Low risk of bias **Direction =**

C. Attrition bias (systematic differences between the comparison groups with respect to loss of participants)

C4 Based on your answers to the above, in your opinion was attrition bias present? If so, what is the likely direction of its effect?:

Low risk of bias **Direction =**

D. Detection bias (bias in how outcomes are ascertained, diagnosed or verified)

D6 Based on your answers to the above, in your opinion was detection bias present? If so, what is the likely direction of its effect?:

Unclear / unknown risk **Direction =**

Overall Study Quality -Strengths and Weaknesses:

Strengths: Randomised control trial (randomisation method not reported), baseline comparisons made, no loss to follow-up
Weaknesses: No allocation concealment, small sample size, evaluations carried out by the first author, measure of subjective assessment not described (validity / reliability unclear), overall very high number of smokers in the study (see publication year)

DETAILS

# of patients:

72 (36 angiography 36 medical treatment)

Prevalence (Diagnostic):

Patient Characteristics

Baseline characteristics:

	Surgery (n=36)	Med Therapy (n=36)
Age years (±SE)	50.8±1.3	52.1±1.1
Duration of symptomatic disease (months)	44.2±6.4	43.9±8.2
Diabetes no. (%)	14(39)	8(22)
Myocardial infarction no. (%)	29(81)	26(72)
Smokers no. (%)*	33(92)	29(81)

* Note – no. and % smokers reported in discussion section.
Inclusion criteria: Patients with stable angina pectoris believed to be due to arteriosclerotic heart disease without previous cardiac operations were screened. All patients had received at least 12 weeks of treatment and their symptoms had to continue to be disabling. Symptoms had to be refractory to maximal propranolol and nitrate therapy. Cardiac catheterization including left ventriculography and selective coronary angiography was carried out and 'critical stenosis' was defined as greater than 70% luminal narrowing in a major coronary artery.
Exclusion criteria: Any of the following – valvular disease with any gradient across the valve or regurgitation more than 1+ in scale of 1+ to 4+; surgically resectable ventricular aneurysm; critical stenosis of left main coronary artery; severe distal arterial disease rendering the arteries non-bypassable; or poor left ventricular function with an ejection fraction below 15%.

Interventions/ Test/ Factor being investigated

Surgical intervention – a saphenous-vein aortocoronary bypass to all the major bypassable vessels with critical stenosis.

Comparisons

Surgical intervention (revasculisation) vs medical treatment

Length of Study/ Follow-up

17 to 34 months – median 28 months

Outcome measures studied

Outcome measures studied: Subjective assessment of current symptoms, frequency of adverse events and complications were recorded (death, myocardial infarction etc)

Results

Effect Size

Subjective assessment of current symptomatic status:

	Surgery (n=35)*	Med Therapy (n=35)*	p-value
Asymptomatic	14(39)	8(22)	<.01
Improved	7(20)	19(54)	<.10
Same or worse	1 (3)	7(20)	ns

*Note: In the group assigned to surgery, one patient changed his mind after randomization and his data were excluded. In the medical treatment group one was treated surgically four months after randomisation and his data are also excluded from the analysis.
Adverse events:

	Surgery (n=35)	Med Therapy (n=35)	p-

	value		
	Death no. (%)	3(9)	5(14)
	ns		
	Myocardial infarction		
	no. of events no. patients (%)	3; 2 (6)	7; 7 (20)
	ns		

Source of funding: The Veterans Administration Hospital, Euston, TX.

Does the study answer the question?/Further Comments Yes. The frequency of adverse outcomes was not significantly different between the surgical and the medical treatment intervention group. However, due to the small sample size any differences would be unlikely to be detected. There was a trend for subjective improvements to be higher in the medical treatment than in the surgical group.

Murphy ML;Hultgren HN;Detre K;Thomsen J;Takaro T;

Treatment of chronic stable angina. A preliminary report of survival data of the randomized Veterans Administration cooperative study

Ref ID 812 **RID:** 519 1977 Sep 22

QUALITY

A. Selection bias (systematic differences between the comparison groups)

A4 Based on your answers t, in your opinion was selection bias present? If so, what is the likely direction of its effect?:

Low risk of bias **Direction =**

B. Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)

B4 Based on your answers to the above, in your opinion was performance bias present? If so, what is the likely direction of its effect?:

Low risk of bias **Direction =**

C. Attrition bias (systematic differences between the comparison groups with respect to loss of participants)

C4 Based on your answers to the above, in your opinion was attrition bias present? If so, what is the likely direction of its effect?:

Low risk of bias **Direction =**

D. Detection bias (bias in how outcomes are ascertained, diagnosed or verified)

D6 Based on your answers to the above, in your opinion was detection bias present? If so, what is the likely direction of its effect?:

Low risk of bias

Direction =

Overall Study Quality -Strengths and Weaknesses:

Strengths: Randomised, baseline comparisons made, numbers loss to follow-up not reported. Intention to treat analysis reported.
Limitations: allocation concealment not reported.
This is a study reports analysis of overall survival in patients in the VA cooperative study, excluding patients with left main coronary artery disease (n=90).

DETAILS

# of patients:

n=686 (in the VA study). In this study n=586 (after excluding patients with left main coronary artery disease). (n=310 medical and n=286 surgery)

Prevalence (Diagnostic):

Patient Characteristics

Baseline characteristics: (Of 596 patients after excluding n=90 patients with severe left main coronary disease)
Characteristic: Medical (n=310) vs. surgery (n=286)
NYHA classes II &III: 94.2%; 95.4%
Duration of angina >25 months: 50; 51.8
History of previous MI: 59.3%; 64%
History of diabetes: 12.9%; 12.2%
Left ventricular contraction abnormality: 68.7%; 64%
Ejection fraction <45%: 28.1%; 24.1%

The average of the medical group was 51 years (range 27-67 yrs) and that of the surgical group 50 years (range 30-66 yrs).

Interventions/ Test/ Factor being investigated

surgery.

Comparisons

medical

Length of Study/ Follow-up

36 months

Outcome measures studied

Overall survival

Results

Effect Size

Results reported graphically difficult to interpret.
36 months:
Survival: 87% vs. 88%
At 36 months, the medical treatment group of patients with triple vessel disease and an abnormal left ventricle showed an 82% survival, and the surgery group a survival of 86%.

Source of funding:

see Ref ID 2101

Does the study answer the question?/Further Comments

Yes. At 36 months, there was no statistically significant difference between in survival between patients treated medically and those treated with saphneous vein bypass grafting.

Parisi AF;Folland ED;Hartigan P;

A comparison of angioplasty with medical therapy in the treatment of single-vessel coronary artery disease. Veterans Affairs ACME Investigators

Ref ID 1900 **RID:** 494 1992 Jan 2

QUALITY

A. Selection bias (systematic differences between the comparison groups)

A4 Based on your answers t, in your opinion was selection bias present? If so, what is the likely direction of its effect?:

Unclear/unknown risk **Direction =**

B. Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)

B4 Based on your answers to the above, in your opinion was performance bias present? If so, what is the likely direction of its effect?:

Low risk of bias **Direction =**

C. Attrition bias (systematic differences between the comparison groups with respect to loss of participants)

C4 Based on your answers to the above, in your opinion was attrition bias present? If so, what is the likely direction of its effect?:

Low risk of bias **Direction =**

D. Detection bias (bias in how outcomes are ascertained, diagnosed or verified)

D6 Based on your answers to the above, in your opinion was detection bias present? If so, what is the likely direction of its effect?:

Low risk of bias **Direction =**

Overall Study Quality -Strengths and Weaknesses:

Strengths: Randomised, baseline comparison made, intention to treat analysis used, no patients lost to follow up. Weakness: Randomisation method not clearly described.Allocation concealment not reported.

DETAILS

# of patients: n=212 (n=105 to PCTA and n=107 to medical therapy)

Prevalence (Diagnostic):

Patient Characteristics

Base-line characteristics

	Med Therapy	PTCA
Age	63	62
Diabetes (%)	19	17
Angina-free for past 30 days (%)	8	9
Mean percent stenosis:		
Right coronary artery (no.)	80 (34)	79(42)
Left anterior descending coronary artery (no.)	78(38)	77(41)
Left circumflex coronary artery (no.)	75(32)	70(21)
Ejection fraction	65.1±1.3	64.9±1.1

Inclusion criteria: Clinical requirement was any of the following – stable angina pectoris, a strikingly positive exercise-tolerance test (ST-segment depression ≥3 mm), or a myocardial infarction within the past three month. The angiographic requirement was stenosis of 70-99 % of the diameter, assessed visually, in the proximal ⅔ of one major epicardial coronary artery or similar serial stenosis limited to the proximal ⅔ of the same artery or its branches. Patients with no ST-segment depression who had angina during the test could also be included if there was a reperfusing thallium defect in the region of the involved artery.

Interventions/ Test/ Factor being investigated

PTCA within 3 days of randomisation

Comparisons

Medical therapy ('stepped-care' approach: oral isosorbide dinitrate with sublingual prophylactic and therapeutic nitroglycerin, beta-blocking agents, calcium channel-blocking agents or a combination of these drugs)

Length of Study/ Follow-up

Six months after randomization (or at least three months after repeat PTCA)

Outcome measures studied

Primary outcomes: Exercise tolerance, frequency of angina attacks, the use of nitroglycerin between base line and the final month of the study. The secondary outcome: change in degree of stenosis in the originally identified index lesions and change in the score on a standard self-administered questionnaire designed to measure psychological-well-being and employment (The Psychological General Well-Being - PGWB - index).

Results

Effect Size

	Medical therapy (N=107)	PCTA (N=105)*	P Value
Total duration of exercise (min)	100	99	< .0001
Time to onset of angina (min)	37	24	< .01
Mean change in episodes /mo	98	94	= .06
Percent angina-free in 6th mo	102	96	< .01
Myocardial infarction	3	5	= .50
Death	1	0	= 1.0

The overall psychological-well-being score improved by 8.6 for patients in the PTCA group and 2.4 for patients in the medical therapy group (p=.03) from base-line values 72.7 and 72.0, respectively

*Note: In the group assigned to PTCA, two patients declined to undergo the procedure; on patient's physician refused to have the patient undergo it; in one case the pressure gradient across the index lesion was minimal; and in one case the index lesion disappeared between the time of angiography and of PCTA

Source of funding:

supported by the Cooperative Studies Program, Research Service, Department of Veteran Affairs, Washington DC

Does the study answer the question?/Further Comments

Yes. Study is relevant to the review protocol. Angina improved in both groups, but those who received PTCA improved more than those in the medical treatment group, difference was apparent by 1 month after treatment (twice as many angina free in PTCA) and also after 6 months (64% in PTCA vs 46% of Med Treat). Patients in PCTA had fewer angina attacks overall and improvement in psychological well-being (quality of life). There was a substantial reduction in the percent stenosis of the index lesions in PTCA group but not in the Med Treat group

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Passamani E;Davis KB;Gillespie MJ;Killip T;

A randomized trial of coronary artery bypass surgery. Survival of patients with a low ejection fraction

Ref ID 2035 **RID:** 572 1985 Jun 27

QUALITY

A. Selection bias (systematic differences between the comparison groups)

A4 Based on your answers t, in your opinion was selection bias present? If so, what is the likely direction of its effect?:

Low risk of bias **Direction =**

B. Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)

B4 Based on your answers to the above, in your opinion was performance bias present? If so, what is the likely direction of its effect?:

Low risk of bias **Direction =**

C. Attrition bias (systematic differences between the comparison groups with respect to loss of participants)

C4 Based on your answers to the above, in your opinion was attrition bias present? If so, what is the likely direction of its effect?:

Low risk of bias **Direction =**

D. Detection bias (bias in how outcomes are ascertained, diagnosed or verified)

D6 Based on your answers to the above, in your opinion was detection bias present? If so, what is the likely direction of its effect?:

Low risk of bias **Direction =**

Overall Study Quality -Strengths and Weaknesses:

Strengths: randomised (stratified randomisation). Baseline comparisons made. Follow-up (for patients with ejection fraction under 0.50): 100% for 54 months, 99% for 60 months, 84% for 72 months, and 51% for 84 months. Intention to treat analysis reported.
Limitations: Allocation concealment not reported.
This is a 7 year follow-up of the CASS trial (sub group analysis of

patients with ejection fraction under 0.50)

DETAILS

# of patients:

N=160 (n=82 medical group and n=78 surgical group)

Prevalence (Diagnostic):

Patient Characteristics

Baseline characteristics for patients with ejection fraction under 0.50
Characteristics: Medical group (n=82); surgical group (n=78)
Age (mean ±SD): 50±8; 51 ±8
Male: 94; 96
White: 98; 95
Angina
None: 41; 37
Class I: 11; 9
Class II: 45; 47
Class III or IV: 0; 0
Non exertional : 2 ;6
Diabetes mellitus: 12; 12
Stroke: 1; 1
Normal electrocardiogram: 13; 8
One vessel disease: 13; 8
Two vessel disease: 43; 36
Three vessel disease: 44; 54

Baseline characteristics of patients with ejection fraction under 0.50 and triple vessel disease:
Characteristics: medical (n=36); surgery (n=42)
Age (mean ±SD): 51 ±8; 51±8
Male: 89; 98
White: 97; 93
Angina
None: 42; 29
Class I: 14; 10
Class II: 44; 57
Class III or IV: 0; 0
Non exertional: 0; 5
Diabetes mellitus: 11; 10

Inclusion criteria: Class I or II angina with or without a history of MI, or well documented MI occurring more than 3 weeks before random assignment.
Exclusion criteria: Prior CABG; unstable or progressive angina; angina that was more severe than Class II; congestive heart failure (NYHA class III or IV); a co-existing illness that would have increased the likelihood of death within 5 years; and a variety of practical factors that might have limited active participation during follow-up, such as inaccessibility, psychological problems, or language barriers.

Interventions/ Test/ Factor being investigated

Surgery.

Comparisons

medical therapy.

Length of Study/ Follow-up

7 years

Outcome measures studied

Primary and secondary outcomes not specified. Outcomes assessed: death.

Results

Effect Size	Results: For patients with ejection fraction under 0.50 Outcome: medical (n=82) vs. surgery (=78) Death (all causes): 25 vs. 11 Coronary heart disease MI: 5 VS. 0 Sudden death: 13 vs. 5 Complications of bypass: 1 vs. 1 Other cardiovascular causes: 1 vs. 3 Non cardiovascular causes: 3 vs. 1 For Patients with ejection fraction under 0.50 and triple vessel disease: Outcome: Medical (n=36) vs. surgery (n=42) Death (all causes): 13 vs. 5 Coronary artery disease: 11 vs. 3 Note: Six patients assigned to surgical therapy initially refused it; 2 of the 6 subsequently reconsidered and underwent surgery. During the follow-up interval, 22 patients assigned to medical therapy underwent CABG, in most cases because of worsening symptoms. Thus 3.8% of patients assigned to medical therapy 'crossed over' to surgical therapy each year.
Source of funding:	Supported by research contracts of the National Heart, Lung, and Blood Institute, Bethesda, Maryland
Does the study answer the question?/Further Comments	Yes. Authors conclusion- Patients with triple vessel disease and ejection fraction higher than 0.34 but under 0.50 appear to have improved 7 year survival with elective bypass surgery.

Peduzzi P;

Eighteen-year follow-up in the Veterans Affairs Cooperative Study of Coronary Artery Bypass Surgery for stable angina

Ref ID 3510 **RID:** 495 1992

QUALITY

A. Selection bias (systematic differences between the comparison groups)

A4 Based on your answers t, in your opinion was selection bias present? If so, what is the likely direction of its effect?:

Low risk of bias **Direction =**

B. Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)

B4 Based on your answers to the above, in your opinion was performance bias present? If so, what is the likely direction of its effect?:

Low risk of bias **Direction =**

C. Attrition bias (systematic differences between the comparison groups with respect to loss of participants)

C4 Based on your answers to the above, in your opinion was attrition bias present? If so, what is the likely direction of its effect?:

Low risk of bias

Direction =

D. Detection bias (bias in how outcomes are ascertained, diagnosed or verified)

D6 Based on your answers to the above, in your opinion was detection bias present? If so, what is the likely direction of its effect?:

Low risk of bias

Direction =

Overall Study Quality -Strengths and Weaknesses:

See Ref ID 2101
This is a 18 year follow-up of the VA study. One patient lost to follow-up

DETAILS

# of patients: N=332 surgery, n=354 medical therapy.

Prevalence (Diagnostic):

Patient Characteristics See Ref ID 2101

Interventions/ Test/ Factor being investigated surgery

Comparisons medical

Length of Study/ Follow-up median follow-up 16.8 years.

Outcome measures studied survival rate, MI, free of angina

Results

Effect Size

Results:
Outcome: medical vs. surgery
Survival rate: 33% vs. 30% (p=0.60)
MI: 41% vs. 49%
Non fatal MI: 32% 44% (P=0.015)
Fatal MI: 14% vs. 13% (p=0.62)

Patients who were free of angina was significantly higher with surgical therapy only during the first 5 years of follow-up. Rates for medicine and surgery were 3% vs. 22% at 1 year (p<0.001), 4% vs. 12% at 5 years (p<0.001), 6% vs. 5% at 10 years, and 3% vs. 4% at 15 years.

Non adherence: Of the 354 medically assigned patients, 154 eventually had bypass surgery, and 24 of these patients also had a second operation. Operative mortality was 4.6% for the initial operation and 12.5% for repeat surgery. The cumulative rate of cross over from medical to surgical therapy was 62% at 18

years; median time to cross over was 5 years. Only 20 of the 332 surgically assigned patients did not have the bypass surgery. Of the 312 patients who had surgery, 67 (21%) have had repeat surgery. Operative mortality was 5.8% for the initial surgery and 11.9% for the second surgery. The cumulative rate of repeat surgery was 41% at 18 years; median time to repeat surgery was 9.7 years.

Source of funding: see 2101

Does the study answer the question?/Further Comments Yes. No significant difference between the two groups for mortality , MI and freedom from angina. Non Fatal infarction rates were lower with medical than with surgical therapy, but fatal infarction rates were similar.

Peduzzi P;Hultgren H;Thomsen J;Detre K;

Ten-year effect of medical and surgical therapy on quality of life: Veterans Administration Cooperative Study of Coronary Artery Surgery

Ref ID 4157 **RID:** 520 1987

QUALITY

A. Selection bias (systematic differences between the comparison groups)

A4 Based on your answers t, in your opinion was selection bias present? If so, what is the likely direction of its effect?:

Low risk of bias **Direction =**

B. Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)

B4 Based on your answers to the above, in your opinion was performance bias present? If so, what is the likely direction of its effect?:

Low risk of bias **Direction =**

C. Attrition bias (systematic differences between the comparison groups with respect to loss of participants)

C4 Based on your answers to the above, in your opinion was attrition bias present? If so, what is the likely direction of its effect?:

Low risk of bias **Direction =**

D. Detection bias (bias in how outcomes are ascertained, diagnosed or verified)

D6 Based on your answers to the above, in your opinion was detection bias present? If so, what is the likely direction of its effect?:

Low risk of bias

Direction =

Overall Study Quality -Strengths and Weaknesses:

See Ref ID 2101
This is a 10 year follow-up of the VA study.

DETAILS

# of patients:

N=686 (n=354 medical and n=332 surgery)

Prevalence (Diagnostic):

Patient Characteristics

see Ref ID 2101
Note: Of the 354 patients assigned to medical treatment, 14 (4%) crossed over to surgical treatment in the first year of follow-up, 77 (22%) in the first 5 years and 123 (35%) in the first 10 years; 22 of all patients who crossed over (18%) had left main disease. Only 20 patients (6%) assigned to surgery did not undergo bypass operation, whereas 35 of 312 operated patients (11%) underwent repeat bypass surgery in the first 10 years. Five operative deaths occurred in medical crossover patients (4%), all in the first 5 years. In the surgically assigned group, 18 operative deaths (6%) were associated with initial operation and 5 (14%) with reoperation

Interventions/ Test/ Factor being investigated

Surgery

Comparisons

medical therapy.

Length of Study/ Follow-up

10 years

Outcome measures studied

Primary outcome: NYHA class, angina score, exercise test.

Results

Effect Size

Results:
The mean baseline angina score was slightly higher in surgically assigned patients (9.9) than in medically assigned patients (9.3), but the difference was not significant. The magnitude of the scores indicated that the average medical and surgical patients had moderate angina at the time of the entry in to the study. At 1 year the mean score in the surgically treated patients was reduced by 50% and was significantly lower ($p<0.00001$) than that of medically treated patients (4.2 vs. 8.7). After 1 year the mean scores in surgical patients increased from 4.2 to 6.0 at 5 years and to 6.6 at 10 years. In medically assigned patients the mean scores gradually decreased with longer follow-up; 8.7, 7.8 and 6.5 at 1, 5 and 10 years, respectively. Although the scores remained significantly lower ($p<0.0001$) in surgically assigned patients at 5 years by 10 years the scores were nearly identical in the 2 treatment groups ($p=0.853$).
At both 1and 5 years surgically treated patients had significantly more improvement than medically treated patients ($p<0.0001$). By 10 years the rates of improvement were not significantly different in the 2 treatment groups (33% for surgically treated vs. 37% for medically treated patients, $p=0.799$).

Exercise testing: Values reported graphically.
Surgical patients had significantly better exercise performance than medical patients at 1 and 5 years, but not at 10 years. Improvement in exercise performance diminished after they first year in the surgical group.

Note: Angina: A physician administered angina questionnaire was developed to

record data on frequency of angina, daily medication use and level of activity producing angina over the preceding month. An angina scoring system was devised to provide an overall measure of the severity of angina. The score consisted of 2 components: a severity score and medication score. The severity score (range 0 to 9) measured the frequency of angina was based on use of nitroglycerin, propranalol and long acting nitrates. The combined score (range 0 to 18) provided an index of the overall severity of angina. Scores 7 or lower indicated mild angina and those indicated mild angina and those 12 or higher sever angina. The score was reproducible and was correlated with exercise performance.

Source of funding: see Ref ID 2101

Does the study answer the question?/Further Comments Yes. The benefit of surgery in relief of symptoms and improvement of exercise performance remained superior to that of medical therapy at 5 years, but at 10 years symptoms increased and exercise tolerance decreased to levels similar to those of the medically treated patients.

Peduzzi P;Kamina A;Detre K;

Twenty-two-year follow-up in the VA Cooperative Study of Coronary Artery Bypass Surgery for Stable Angina

Ref ID 4308 **RID:** 521 1998

QUALITY

A. Selection bias (systematic differences between the comparison groups)

A4 Based on your answers t, in your opinion was selection bias present? If so, what is the likely direction of its effect?:

Low risk of bias **Direction =**

B. Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)

B4 Based on your answers to the above, in your opinion was performance bias present? If so, what is the likely direction of its effect?:

Low risk of bias **Direction =**

C. Attrition bias (systematic differences between the comparison groups with respect to loss of participants)

C4 Based on your answers to the above, in your opinion was attrition bias present? If so, what is the likely direction of its effect?:

Low risk of bias **Direction =**

D. Detection bias (bias in how outcomes are ascertained, diagnosed or verified)

D6 Based on your answers to the above, in your opinion was detection bias present? If so, what is the likely direction of its effect?:

Low risk of bias

Direction =

Overall Study Quality -Strengths and Weaknesses:

This is a 22 year follow-up of the VA study.

Follow-up was essentially 100% complete through 18 years; 96% of patients followed for 19 years; 92% for 20 years, 85% for 21 years, and 78% for 22 years. The median follow-up time was 21.1 years; 18 patients (3%) were considered lost to follow-up. Of the original cohort of 686 patients, 178 (26%) are still alive.
See Ref ID 2101

DETAILS

# of patients: n=686 (n=354 medical and n=332 surgery)

Prevalence (Diagnostic):

Patient Characteristics see Ref ID 2101.

Interventions/ Test/ Factor being investigated Surgery

Comparisons medical

Length of Study/ Follow-up 22 years

Outcome measures studied Primary outcome: survival, incidence of MI, repeat revascularisation, and relief of angina.

Results

Effect Size

Results:
All patients Survival rate: medical vs. surgery
25% vs. 20% (p=0.24)

22 year cumulative probabilities of being alive:
Group (no. of patients): medical vs. surgery
All patients (n=686): 0.25 vs. 0.20
Left main (n=91): 0.11 vs. 0.10
Without left main (n=595): 0.27 vs. 0.22
Low angiographic risk (n=421): 0.31 vs. 0.24 (p<0.05)
High angiographic risk (n=168): 0.20 vs. 0.15
Low/mid clinical risk (n=411): 0.35 vs. 0.26 (p<0.05)
High clinical risk (n=177): 0.11 vs. 0.12

22 year cumulative probabilities of being free of MI:
Group (no. of patients): medical vs. surgery
All patients (n=686): 0.57 vs. 0.41 (p<0.05)
Left main (n=91): 0.46 vs. 0.43
Without left main (n=595): 0.59 vs. 0.40 (p<0.05)
Low angiographic risk (n=421): 0.61 vs. 0.37 (p<0.05)
High angiographic risk (n=168): 0.55 vs. 0.52
Low/mid clinical risk (n=411): 0.63 vs. 0.46(p<0.01)
High clinical risk (n=177): 0.48 vs. 0.37

MI:
All patients: medical (n=354) vs. surgery (n=332)
123/354 vs. 137/332

Left main
16/43 vs. 21/48
Low angiographic risk
72/211 vs. 89/210
High angiographic risk
34/97 vs. 27/71
Low/mid clinical risk
53/214 vs. 68/197
High clinical risk
39/94 vs. 31/83

Angina score: reported in graphs, difficult to interpret.

Note:
Cross overs- 160 of the 354 patients assigned to medical therapy crossed over to surgery in 22 years and 33 underwent a second operation. Operative mortality was 4.4% for the initial procedure and 9.1% for repeat surgery. The cumulative rate of crossover from medical to surgical therapy (adjusted for mortality and lost to follow-up in the life-table calculations), amounted to 49% during the first 11 years and 17% during the last 11 years, yielding an overall crossover rate of 66% at 22 years.
20 patients assigned to surgery did not undergo bypass operation. Of the 312 patients who did, 78 had a second procedure. Operative mortality was 5.8% for the initial operation and 10.3% for the second. Unlike medical crossovers, the need for reoperation tended to occur during the second 11 years of follow-up. The cumulative reoperation rate for this group was 16% during the first 11 years of follow-up and doubled to 32% during the last 11 years for an overall cumulative reoperation rate of 48% at 22 years.
The total number of bypass operations amounted to 393 in the surgically assigned group compared with 194 in the medically assigned group.

Severity of angina score: Severity of angina was measured by a reproducible angina score (range 0 to 9) based on the frequency of angina, presence of rest angina and type of activity producing angina recorded on an angina questionnaire.

Source of funding: see Ref ID 2101

Does the study answer the question?/Further Comments Yes. This trial provided strong evidence that initial bypass surgery did not improve survival for low risk patients, and that it did not reduce the overall risk of MI. Although there was an early survival benefit with surgery in high risk patients (up to a decade), long term survival rates became comparable in both treatment groups. In total, there were twice as many bypass procedures performed in the group assigned to surgery without any long term survival or symptomatic benefit.

Pfisterer M;Bertel O;Erne P;Goy JJ;

Trial of invasive versus medical therapy in elderly patients with chronic symptomatic coronary-artery disease (TIME): a randomised trial

Ref ID 1309 RID: 701 2001 Sep 22

QUALITY

A. Selection bias (systematic differences between the comparison groups)

A4 Based on your answers t, in your opinion was selection bias present? If so, what is the likely direction of its effect?:

Unclear/unknown risk

Direction =

B. Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)

B4 Based on your answers to the above, in your opinion was performance bias present? If so, what is the likely direction of its effect?:

Unclear/unknown risk

Direction =

C. Attrition bias (systematic differences between the comparison groups with respect to loss of participants)

C4 Based on your answers to the above, in your opinion was attrition bias present? If so, what is the likely direction of its effect?:

Low risk of bias

Direction =

D. Detection bias (bias in how outcomes are ascertained, diagnosed or verified)

D6 Based on your answers to the above, in your opinion was detection bias present? If so, what is the likely direction of its effect?:

Low risk

Direction =

Overall Study Quality -Strengths and Weaknesses:

See data extraction of Study ID 9142

DETAILS

# of patients:	See data extraction of Study ID 9142
Prevalence (Diagnostic):	
Patient Characteristics	See data extraction of Study ID 9142
Interventions/ Test/ Factor being investigated	coronary angiography followed by revascularisation (PCI or CABG) if feasible. Patients were included on basis of their clinical presentation and coronary angiography was done on a per-protocol basis only in the invasive group
Comparisons	Optimised medical strategy (increase in the number or dose of antianginal drugs with the aim to reduce pain as much as possible)
Length of Study/ Follow-up	6 months

Outcome measures studied

Primary endpoint: quality of life (assessed by standardised questionnaires) and freedom from MACE (death, nonfatal MI, or hospitalisation for uncontrolled symptoms or acute coronary syndrome with or without need for revascularisation)

Results

Effect Size

Measure of quality of Lifeβ

	INV	MED P*	MED without revasc P$
General health (SF36)	11.4(20)	3.8(18.7) ; 0.008	-1.1(17.3) ; <0.0001
Bodily pain (SF36)	31.3(32.2)	23.6(31.5) ; 0.12	17.1(29.1) ; 0.006
Vitality (SF36)	10.6(20.6)	6.1(22.4) ; 0.16	4.0(21.9) ; 0.04
Duke activity score index	7.2(14.1)	5.3(14.4) ; 0.17	4.0(12.1) ; 0.09
Rose score	-1.9(2.0)	-1.1(1.9) ; 0.008	-0.8(1.7) ; 0.0003
Angina pectoris class	-2.0(1.3)	-1.6(1.4) ; 0.01	-1.3(1.2) ; 0.0001
Number of anginal medications	-1.0(1.2)	-0.2(1.2) ; <0.0001	0.2(1.0) ; <0.0001

βscores are mean(SD)
*invasive vs medical
$invasive vs medical without revascularisation

MACE

	INV	MED	Pvalue
Death	13	6	0.15
Non-fatal infarction	12	17	0.46
Hospital admissions for ACS:			
Without revascularisation	5	18	0.006
With revascularisation	10	55	<0.0001
Total MACE	40	96	<0.0001

Source of funding:

See data extraction of Study ID 9142

Does the study answer the question?/Further Comments

Yes. This study showed that after 6 months, elderly patients with chronic angina benefit more from revascularisation than optimised medical therapy in terms of symptom relief and quality of life.

Pfisterer M;Buser P;Osswald S;Allemann U;Amann W;Angehrn W;Eeckhout E;Erne P;Estlinbaum W;Kuster G;Moccetti T;Naegeli B;Rickenbacher P;Trial of Invasive versus Medical therapy in Elderly patients (TIME) Investigators;

Outcome of elderly patients with chronic symptomatic coronary artery disease with an invasive vs optimized medical treatment strategy: one-year results of the randomized TIME trial

Ref ID 9142 **RID:** 694 2003

QUALITY

A. Selection bias (systematic differences between the comparison groups)

A4 Based on your answers t, in your opinion was selection bias present? If so, what is the likely direction of its effect?:

Unclear/unknown risk

Direction =

B. Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)

B4 Based on your answers to the above, in your opinion was performance bias present? If so, what is the likely direction of its effect?:

Unclear/unknown risk

Direction =

C. Attrition bias (systematic differences between the comparison groups with respect to loss of participants)

C4 Based on your answers to the above, in your opinion was attrition bias present? If so, what is the likely direction of its effect?:

Low risk of bias

Direction =

D. Detection bias (bias in how outcomes are ascertained, diagnosed or verified)

D6 Based on your answers to the above, in your opinion was detection bias present? If so, what is the likely direction of its effect?:

Low risk of bias

Direction =

Overall Study Quality -Strengths and Weaknesses:

Strengths: randomised, low attrition bias (8/155 (5%) did not complete treatment in invasive group; 2/150 (1%) did not complete treatment in optimal medical strategy group), intention to treat analysis used
Weaknesses: allocation concealment unclear ; patients selected solely on basis of their clinical presentation and not on angiographic findings; therefore there were crossovers in both directions within the first year: 28% of invasive gp assigned patients who did not need or could not be revascularised and 46% of optimal medical treatment assigned patients needed PCI or CABG surgery because of refractory symptoms.

This is a 1 year follow-up of the TIME trial

DETAILS

# of patients:

N=305 but 4 protocol violations so 301 randomised to optimised medical therapy (n=148) or invasive strategy (n=153) with coronary angiography followed by

Prevalence (Diagnostic):

Patient Characteristics

Baseline characteristics: Invasive (n=140); Optimised Medical (n=142)
Age, mean (SD),y 80(3.6);80(3.5)
Women n(%) 59(42.1);59(41.5)
Risk factors: Diabetes n(%) 29(20.9);32(22.5)
Symptoms
Angina CCS2 n(%) 28(20); 37(26)
Angina CCS3 n(%) 66(47); 67(47)

	Angina CCS4 n(%) 46(33); 38(27) Drug therapy Antianginal drugs Beta-blockers 116(83.5); 102(72.3) Calcium antagonist 70(51.1); 71(50) Long acting nitrates 103(74.6); 106(74.6) Molsidomine 54(39.4); 51(35.9) Potassium blockers 1(0.7); 8(5.6) Diuretics 51(37.2); 50(35.2) ACE inhibitors 29(21); 47(33.1) Lipid lowering drugs 117(84.8); 116(81.7) Aspirin 117(84.8); 116(81.7) Warfarin 17(12.4); 17(12) Heparin 25(18.2); 25(17.6) LVEF, mean (SD), % 53.8(11.9); 52.9(12.7) Angiographic findings of vessels diseased, % 0□11(8) 1□19(14) 2□26(19) 3□79(59) Left Main* 17(13) *left main disease counted in 2 or 3 vessel disease groups Inclusion criteria: age 75 and over, chronic angina with Canadian Cardiac Society class 2 and higher despite treatment with at least 2 antianginal drugs Exclusion criteria: acute myocardial infarction within the previous 10 days, concomitant valvular or other heart disease, predominant congestive heart failure, or no consent for a possible revascularisation procedure
Interventions/ Test/ Factor being investigated	coronary angiography followed by revascularisation (PCI or CABG) if feasible. Patients were included on basis of their clinical presentation and coronary angiography was done on a per-protocol basis only in the invasive group
Comparisons	Optimised medical strategy (increase in the number or dose of antianginal drugs with the aim to reduce pain as much as possible)
Length of Study/ Follow-up	1 year
Outcome measures studied	Primary endpoint: quality of life (assessed by standardised questionnaires) and freedom from MACE (death, nonfatal MI, or hospitalisation for uncontrolled symptoms or acute coronary syndrome with or without need for revascularisation)
Results	
Effect Size	Results: Outcome during 0-12 months: invasive(n=153) ;optimised medical (n=148); P valueβ; Hazard Ratio invasive vs optimised medical (95%CI)¥ P value No of deaths (%) 17(11.1);12(8.1) p=0.44; 1.51(0.72-3.16) p=0.28 No of cardiac deaths (%) 13(8.5);10(6.7) p=0.67; 1.36(0.59-3.10) p=0.47 No of myocardial infarctions* 14;20 p=0.37; 0.75(0.36-1.55) p=0.44 Patients with death or MI 26(17);29(19.6) p=0.65; 0.9(0.53-1.53) p=0.71 No of hospitalisation with revascularisation 16;71 p<0.001; 0.19(0.11-0.32) p<0.001 Total No of hospitalisation 28;106 p<0.001; 0.19(0.12-0.30) p<0.001 No of MACE 59;138 p<0.001; 0.31(0.21-0.45) p<0.001 Patients with MACE 39(25.5);95(64.2) p<0.001 *several patients had >1 events so % not included βFisher exact test and Wilcoxon rank sum test respectively. ¥univariate Cox proportional hazard model for time to first event Quality of Life Between-group comparisons at 12 months CCS class p=0.21 Rose Score p=0.93 No of antianginal drugs p<0.001 (in favour of invasive therapy)

General health (SF 36) p=0.75
Vitality (SF 36) p=0.35
Duke Activity Status Index p=0.07

Source of funding: Grants from the Swiss Heart Foundation Berne, ADUMED Foundation. Sponsored by the Working Group of Coronary Interventions and Acute Coronary Syndromes

Does the study answer the question?/Further Comments Yes. This study shows that 1 year outcomes in elderly patients with chronic angina are similar with regards to symptoms, quality of life and death or non fatal infarction with invasive vs optimised medical strategies. The invasive approach carries an early intervention risk while medical management poses an almost 50% chance of later hospitalisation and revascularisation.

Pfisterer M;Trial of Invasive versus Medical therapy in Elderly patients Investigators;

Long-term outcome in elderly patients with chronic angina managed invasively versus by optimized medical therapy: four-year follow-up of the randomized Trial of Invasive versus Medical therapy in Elderly patients (TIME)

Ref ID 4660 **RID:** 507 2004

QUALITY

A. Selection bias (systematic differences between the comparison groups)

A4 Based on your answers t, in your opinion was selection bias present? If so, what is the likely direction of its effect?:

High risk of bias **Direction =**

B. Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)

B4 Based on your answers to the above, in your opinion was performance bias present? If so, what is the likely direction of its effect?:

Unclear/unknown risk **Direction =**

C. Attrition bias (systematic differences between the comparison groups with respect to loss of participants)

C4 Based on your answers to the above, in your opinion was attrition bias present? If so, what is the likely direction of its effect?:

Low risk of bias **Direction =**

D. Detection bias (bias in how outcomes are ascertained, diagnosed or verified)

D6 Based on your answers to the above, in your opinion was detection bias present? If so, what is the likely direction of its effect?:

Low risk

Direction =

Overall Study Quality -Strengths and Weaknesses:

Strengths: randomised, Intention to treat analysis used.This is a follow-up study with low risk of attrition bias:out of 276 surviving patients at 1 yr follow up 60 died before long term follow up (21.2% of INV and 22.3% of MED)
Weaknesses: allocation concealment not reported. Loss between randomisation and treatment unclear.A major weakness is that patients were selected solely on basis of their clinical presentation and not on angiographic findings; therefore there were crossovers in both directions within the first year: 28% of invasive gp assigned patients who did not need or could not be revascularised and 46% of optimal medical treatment assigned patients needed PCI or CABG surgery because of refractory symptoms.

This is a 4 year follow-up of the TIME trial

DETAILS

# of patients:

N=305 but 4 protocol violations so 301 randomised to optimised medical therapy (n=148) or invasive strategy (n=153) with coronary angiography followed by

Prevalence (Diagnostic):

Patient Characteristics

Baseline characteristics: Invasive (n=140); Optimised Medical (n=142)
Age, mean (SD),y 80(3.6);80(3.5)
Women n(%) 59(42.1);59(41.5)
Risk factors: Diabetes n(%) 29(20.9);32(22.5)
Symptoms
Angina CCS2 n(%) 28(20); 37(26)
Angina CCS3 n(%) 66(47); 67(47)
Angina CCS4 n(%) 46(33); 38(27)
Drug therapy
Antianginal drugs
Beta-blockers 116(83.5); 102(72.3)
Calcium antagonist 70(51.1); 71(50)
Long acting nitrates 103(74.6); 106(74.6)
Molsidomine 54(39.4); 51(35.9)
Potassium blockers 1(0.7); 8(5.6)
Diuretics 51(37.2); 50(35.2)
ACE inhibitors 29(21); 47(33.1)
Lipid lowering drugs 117(84.8); 116(81.7)
Aspirin 117(84.8); 116(81.7)
Warfarin 17(12.4); 17(12)
Heparin 25(18.2); 25(17.6)
LVEF, mean (SD), % 53.8(11.9); 52.9(12.7)
Angiographic findings of vessels diseased, %
0 11(8)
1 19(14)
2 26(19)
3 79(59)
Left Main* 17(13)

*left main disease counted in 2 or 3 vessel disease groups

Inclusion criteria: age 75 and over, chronic angina with Canadian Cardiac Society class 2 and higher despite treatment with at least 2 antianginal drugs

Exclusion criteria: acute myocardial infarction within the previous 10 days, concomitant valvular or other heart disease, predominant congestive heart failure, or no consent for a possible revascularisation procedure.

Interventions/ Test/ Factor being investigated	coronary angiography followed by revascularisation (PCI or CABG) if feasible. Patients were included on basis of their clinical presentation and coronary angiography was done on a per-protocol basis only in the invasive group
Comparisons	Optimised medical strategy (increase in the number or dose of antianginal drugs with the aim to reduce pain as much as possible)
Length of Study/ Follow-up	median follow-up 4 years (survivors of the first year were contacted again after a median of 3.1 years by questionnaire, followed by queries to patients, relatives or treating physicians
Outcome measures studied	Primary endpoint: quality of life (assessed by standardised questionnaires) and freedom from MACE (death, nonfatal MI, or hospitalisation for uncontrolled symptoms or acute coronary syndrome with or without need for revascularisation)
Results	
Effect Size	Major events during long term follow up (between 1year and late follow up) INV(n=137) MED (n=139) P Hazard Ratio* P All death % 21.2 ; 22.3 ; 0.88 ; 0.68 ; 0.18 Cardiac death %, 13.9; 17.3; 0.51; 0.56; 0.10 Patients with nonfatal MI %, 4.4; 0.7; 0.07; 5.24; 0.13 Patients with late PCI/CABG %, 2.9; 2.9; 0.98; 1.41; 0.67 Patients with cardiac hospitalisation %, 20.4; 13; 0.11; 2.37; 0.01 Patients with major clinical events %, 45.3; 37.4; 0.22; 1.43; 0.08 * hazard ratios are adjusted for sex, age, family history of CAD, peripheral vascular disease, and baseline treatment differences.
Source of funding:	Grants from the Swiss Heart Foundation Berne, ADUMED Foundation, Aetas Foundation Sponsored by the Working Group of Coronary Interventions and Acute
Does the study answer the question?/Further Comments	Long term outcome findings of the TIME study suggest that, by intention to treat an INV strategy and MED strategy for elderly patients with chronic angina despite standard drug therapy have similar outcomes. Mortality rate is increased particularly in patients >80 years of age and in those with prior heart failure, reduced left ventricular function, 2 or more relevant comorbidities and no revascularisation within the first year. The benefit in symptom relief and improvement in well being is maintained with either strategy, but the early advantage of INV strategy disappears over time. The MED strategy involved however a larger number of nonfatal events, mostly hospitalisation and late revascularisations. Overall, elderly patients and their physicians may choose either an INV strategy with early symptoms relief and improvement in well-being, at the “cost” of an early investigations or revascularisation, or a MED strategy with a similar long term outcome but more drugs and >50% chance of late nonfatal events, mainly hospitalisations for refractory symptoms with the need for late revascularisation.

Pitt B;Waters D;Brown WV;van Boven AJ;Schwartz L;Title LM;Eisenberg D;Shurzinske L;McCormick LS;

Aggressive lipid-lowering therapy compared with angioplasty in stable coronary artery disease. Atorvastatin versus Revascularization Treatment Investigators

Ref ID 1482 **RID:** 551 1999 Jul 8

QUALITY

A. Selection bias (systematic differences between the comparison groups)

A4 Based on your answers t, in your opinion was selection bias present? If so, what is the likely direction of its effect?:

Unclear/unknown risk

Direction =

B. Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)

B4 Based on your answers to the above, in your opinion was performance bias present? If so, what is the likely direction of its effect?:

Low risk of bias

Direction =

C. Attrition bias (systematic differences between the comparison groups with respect to loss of participants)

C4 Based on your answers to the above, in your opinion was attrition bias present? If so, what is the likely direction of its effect?:

Low risk of bias

Direction =

D. Detection bias (bias in how outcomes are ascertained, diagnosed or verified)

D6 Based on your answers to the above, in your opinion was detection bias present? If so, what is the likely direction of its effect?:

Low risk of bias

Direction =

Overall Study Quality -Strengths and Weaknesses:

Strengths: open label randomised, multicentre, sample size calculation reported. Blind outcome assessment. No loss to follow-up.ITT reported
Limitations: allocation concealment not reported.
This study is a 18 month follow-up of the AVERT trial

DETAILS

# of patients:

N=341 (n=164 Atorvastatin and n=177 angioplasty)

Prevalence (Diagnostic):

Patient Characteristics

Baseline characteristics of patients:
Characteristics: Atorvastatin (n=164); angioplasty (n=177)
Male no (%): 130 (79); 157 (89)
White: 157 (96); 168 (95)
Age (yr): 59±0.8; 58±0.6
Mean ejection fraction (%): 61; 61
Angina pectoris- no. (%): 126 (77); 139 (79)
Diabetes: 28 (17); 26 (15)
CCS class 0 (asymptomatic)- no (%): 29 (18); 27 (15)
CCS class I: 74 (45); 70 (40)
Class II: 60 (37) ; 77 (44)
Class III: 1 (1); 2 (1)
Class IV: 0 ; 1 (1)
Single vessel- no (%): 94 (57); 99 (56)
Double vessel: 70 (43); 78 (44)

	Left anterior descending artery: 70 (43); 53 (30) Left circumflex coronary artery: 59 (36); 63 (36) Right coronary artery: 59 (36); 64 (36) Inclusion criteria: Patients with stable coronary artery disease, a serum level of low density lipoprotein (LDL) cholesterol of at least 115 mg per decilitre (3.0 mmol per litre), and a serum level of triglycerides of no more than 500 mg per decilitre (5.6 mmol per litre). The patients had stenosis of 50% or more in at least one coronary artery and had been recommended for treatment with PCI. The patients were asymptomatic or had CCS class I or II angina and were able to complete at least 4 minutes of a treadmill test conducted according to the Bruce protocol or a bicycle exercise test at 20W per minute without marked electrocardiographic changes indicative of ischemia. Major exclusion criteria were: Left main coronary artery disease, triple vessel disease, unstable angina or MI within the previous 2 weeks, and an ejection fraction of less than 40%.
Interventions/ Test/ Factor being investigated	Medical treatment with 80 mg Atorvastatin (Lipitor) per day.Patients in both groups were encouraged to take 1 aspirin/day and to optimise antianginal therapy
Comparisons	Angioplasty, followed by usual care, which include lipid-lowering treatment. There was no washout period for patients already receiving lipid lowering medication. [Usual care- diet, behaviour modification, or anti hyperlipidemic medication].
Length of Study/ Follow-up	18 months
Outcome measures studied	Primary and secondary outcomes not stated. Outcomes assessed-cdiac death, stroke, angina status, revascularisation, adverse events, quality of life.
Results	
Effect Size	Results: at 18 months Outcome: Atorvastatin (n=164) vs. Angioplasty (n=177) Revascularisation (PCI or CABG): 20 vs. 29 Improvement in angina symptoms: 67 vs. 95 Death from cardiac causes: 1 (0.6%) vs. 1 (0.6%) Non fatal MI: 4 (2.4%) vs. 5 (2.8%) Stroke: 0 vs. 0 Adverse events: 17 vs. 28* Worsening of angina (resulting in hospitalisation): 11 (6.7%) vs. 25 (14.1%) *Atrovastation group- none of the adverse events were considered to be related to atorvastatin group. Angioplasty group- 6/28 of the patients had events considered to be related to angioplasty procedure (thrombosis at access site, dissection, arteriovenous fistula, coronary occlusion, occlusion of iliac stenosis and femoral hematoma). Four of the patients had persistent elevation in the levels of aspirate or alanine aminotransferase.No patient in either treatment group had persistent elevation of creatinine kinase level. Quality of life: The patient's quality of life was assessed at baseline at 6 and 18 months after randomisation with the use of 36-item Medical Outcomes study short form general health survey. Both treatment groups had a mean increase in the summary scores for physical and mental health at both the 6 month and 18 month assessments, denoting an improvement in quality of life from baseline. Mean increases in scores ranged from 2.9 to 6.3; the increases were slightly larger in the angioplasty group. Note: One patient in the atorvastatin group never received atorvastatin, and 11 of the patients in the angioplasty group (6%) did not undergo revascularisation as assigned because of refusal by the patient (8 patients), disease progression (1, who underwent CABG), regression of the lesion (1), and a procedure that was unsuccessful because of technical difficulty (1); these patients remained in the study. Four of the patients in the atorvastatin group (2%) and 2 of the patients in the angioplasty group (1%) withdrew from the study because of an adverse event (mild impotence in one patient in the atorvastatin group) or a decision by the patient (3 patients in the atorvastatin group and 2 in the angioplasty group). In

addition 8 patients in the atorvastatin group discontinued the study treatment (2 because of elevations in the level of liver enzymes, 5 because of adverse events and 1 because of a decision of the patient); these patients remained in the study. Overall 166 patients in the angioplasty group underwent the assigned procedure.

Source of funding: Supported by a grant from Parke-Davis Pharmaceutical Research.

Does the study answer the question?/Further Comments Yes. In low risk patients with stable coronary artery disease, aggressive lipid-lowering therapy is at least as effective as angioplasty and usual care.

Pocock SJ;Henderson RA;Clayton T;Lyman GH;Chamberlain DA;

Quality of life after coronary angioplasty or continued medical treatment for angina: three-year follow-up in the RITA-2 trial. Randomized Intervention Treatment of Angina

Ref ID 5076 **RID:** 607 2000 Mar 15

QUALITY

A. Selection bias (systematic differences between the comparison groups)

A4 Based on your answers t, in your opinion was selection bias present? If so, what is the likely direction of its effect?:

Low risk of bias **Direction =**

B. Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)

B4 Based on your answers to the above, in your opinion was performance bias present? If so, what is the likely direction of its effect?:

Low risk of bias **Direction =**

C. Attrition bias (systematic differences between the comparison groups with respect to loss of participants)

C4 Based on your answers to the above, in your opinion was attrition bias present? If so, what is the likely direction of its effect?:

Low risk of bias **Direction =**

D. Detection bias (bias in how outcomes are ascertained, diagnosed or verified)

D6 Based on your answers to the above, in your opinion was detection bias present? If so, what is the likely direction of its effect?:

Unclear risk of bias **Direction =**

Overall Study Quality -Strengths and Weaknesses:	Strengths:* multicentre (20 centres in UK and Ireland), stratified blocked randomisation. sample size calculation reported. Intention to treat analysis reported. 98% achieved one year follow-up and 67% reached their 3 year follow-up visit. Weakness: allocation concealment not reported.Not reported if it was blind outcome assessment. *This study is a 3 yrs follow-up of the RITA-2 trial.

DETAILS

# of patients:	n=1018 (n=504 in PTCA and n=514 in medical treatment)
Prevalence (Diagnostic):	
Patient Characteristics	See Ref ID 3544 (RITA-2 trial)
Interventions/ Test/ Factor being investigated	PTCA
Comparisons	Medical treatment
Length of Study/ Follow-up	3 years
Outcome measures studied	Quality of life using the SF-36 health survey.
Results	
Effect Size	Quality of life by SF-36 * values (mean;SEM) reported in figures. Reported in text- The PTCA group showed highly significant superiority over the medical group in terms of physical functioning, vitality and general health at both 3 months and 1 year after randomisation. Mental health was also significantly better in the PTCA group at 3 months and 1 year, although the magnitude of this difference was quite small. The slight superiority of the PTCA group in pain, social functioning and physical and emotional role functioning did not achieve such marked levels of statistical significance. None of the 8 SF-36 scores showed a significant treatment difference at 3 years. Physical functioning, vitality and general health were studied to determine their substantial treatment differences and other patient characteristics affecting these quality of life aspects. For physical functioning at one year, 9.7% of PTCA patients and 4.8% of medically treated patients achieved the maximal score of 100 (i.e. no limitation for all 10 items). A further 29.2% of PTCA patients and 20.8% of medically treated patients scored ≥90, which indicates either one item with 'much limitation' or at most, two of the 10 items with 'little limitation'. The distributions of physical functioning are otherwise skewed to the left, with the PTCA and medical groups having similar rates of poor physical functioning, with 15.6% and 17.4% respectively, scoring <50. Vitality at one year showed a more symmetric distribution, with an evident treatment difference in the extremes. That is a score of ≥80 was given by 28.4%and 19.2% of PTCA and medically treated patients, respectively, whereas a rating <50 occurred for 26.1% and 35.9%, respectively. The patient's self-perception of their change in general health over the past year revealed that 33.4% of PTCA patients felt much better as compared with 21.5% of medically treated patients', whereas 14.7% of the medically treated patients felt some what or much worse as compared with only 9.2% of the PTCA patients. The medical therapy group had fewer patients with no anginal symptoms (46.8% medical vs. 65% PTCA) and substantially more patients above any particular angina grade (e.g. 27.6% of medical vs. 17% PTCA with angina grade 2 or worse, p<0.001).

*The SF-36 comprises 36 items that can be combined in to the following eight multi-item summary scores: physical functioning (10 items), vitality (4 items), bodily pain (2 items), mental health (5 items), social functioning (2 items), role limitation due to physical health (4 items) and due to emotional problems (3 items) and general health perception (5 items), plus one item assessing a change in health over the past year. Each summary score is obtained by simple unweighted summation of item scores and is then scaled from 0 to 100, with 0 and 100 indicating 'worst' and 'best' possible health, respectively (higher scores indicate better perceived health). The SF-36 has been validated for use in a British setting.

Source of funding:

The trial was supported by grants from the British Heart Foundation (BHF) and Medical research council

Does the study answer the question?/Further Comments

Yes. The PTCA group had significantly greater improvements in physical functioning, vitality and general health at both 3 months and one year, but not at 3 years. These quality of life scores were strongly related to breathlessness, angina grade and treadmill exercise time both at baseline and at one year. The treatment differences in quality of life are explained by the PTCA groups improvements in breathlessness, angina and exercise time. The attenuation of treatment difference at 3 years is partly attributed to 27% of medically treated patients receiving non randomised interventions in the interim. For both groups, there were also improvements in ratings of physical role functioning, emotional role functioning, social functioning, pain and mental health, but for these the superiority of PTCA over medical treatment was less pronounced. After one year, 33% and 22% of the PTCA and medical groups, respectively, rated their health much better.

Read RC;Murphy ML;Hultgren HN;Takaro T;

Survival of men treated for chronic stable angina pectoris. A cooperative randomized study

Ref ID 2101 **RID:** 498 1978 Jan

QUALITY

A. Selection bias (systematic differences between the comparison groups)

A4 Based on your answers t, in your opinion was selection bias present? If so, what is the likely direction of its effect?:

Low risk of bias **Direction =**

B. Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)

B4 Based on your answers to the above, in your opinion was performance bias present? If so, what is the likely direction of its effect?:

Low risk of bias **Direction =**

C. Attrition bias (systematic differences between the comparison groups with respect to loss of participants)

C4 Based on your answers to the above, in your opinion was attrition bias present? If so, what is the likely direction of its effect?:

Low risk of bias

Direction =

D. Detection bias (bias in how outcomes are ascertained, diagnosed or verified)

D6 Based on your answers to the above, in your opinion was detection bias present? If so, what is the likely direction of its effect?:

Low risk of bias

Direction =

Overall Study Quality -Strengths and Weaknesses:

Strengths: Randomised, baseline comparisons made, 9% lost to follow-up.*. Intention to treat analysis reported.
Limitations: allocation concealment not reported
*Note: Up to the end of patients' accession, 96% adhered to their initial treatment assignment; 91% stayed with this choice. Each 'non adherer' was considered lost to follow-up at the time the treatment was changed.
This is a 4 year follow-up of the VA study.

DETAILS

# of patients:

n=686 (N=332 surgery, n=354 medical therapy)

Prevalence (Diagnostic):

Patient Characteristics

Baseline characteristics:
63% of the 332 in surgery group and 59% of the 354 medically assigned patients reported previous MI. 73% in surgery and 66% in medical had had angina for more than 1 year, 12% in surgery and 13% in medical had diabetes. The ejection fraction was less than 45% in 24% of the surgically treated group and 26% of the medically treated patients. The average of the surgical group was 50.5 years, range 30 to 68, and that of the medical group was 51.1 years, range 27 to 67. Angiograms in 332 patients assigned to surgery, including those with left main disease, revealed single vessel disease in 50 (14%), double vessel disease in 112 (34%) and triple vessel disease in 170 (52%). The distribution in comparable medical cohort (354) was similar: one vessel disease, 52 (14%); two vessel disease, 110 (31%); three vessel disease, 192 (55%). The distribution of patients with a significant main lesion was 46 (14%) in the surgical and 44 (12%) in the medical group.

Inclusion criteria: stable angina for 6 months, medical treatment for 3 months, no MI for 6 months, no evidence of cardiac decompenssation for 3 weeks, abnormal T waves or ST segment changes consistent with myocardial ischemia at rest or after exercise, diastolic blood pressure below 100mmHg, and no other serious disease limiting life expectancy.

Interventions/ Test/ Factor being investigated

surgery

Comparisons

Medical therapy. Varying medical therapy. consisting of nitrates, BB, antihypertensive medication, antiarrythmic drugs, diuretics, digitalis, and dietary regulation.

Length of Study/ Follow-up

4 years

Outcome measures studied

Primary outcome: Overall Survival

Results

Effect Size

Results:
Values reported graphically.
At 4 years, the survival rate in the medical group was 86% and was 83% in the surgical group.
One vessel disease: 1/ 45 death.

In the three vessel disease category in the surgery group, 89% of patients alive at 4 years.
When the outcome of 90 patients with left main disease is examined , the data showed that there was significantly better survival in the 44 operated upon as compared to the 46 in the medical group (p=0.005). Excluding these cases (13%), the survival rate at 4 years is 86% in medical group and 85% in the surgical group.

Source of funding:

supoorted by Veterans Administartion Cooperative Studies Program, Medical Research service, Veterans Administration Central Office, Washington, D.C.

Does the study answer the question?/Further Comments

Yes. Survival in the overall in the surgical group was 86% at 4 years as compared to 83% in the medical group. This difference was eliminated when 90 patients with left main disease, whose longevity was significantly improved (p=0.005) by the operation were excluded.
Authors note: The most important accomplishment of this study is the determination that patients with stable angina, suitable for surgery but not operated upon, live significantly longer than studies cited before in the medical literature would suggest.

Rogers WJ;Bourassa MG;Andrews TC;Bertolet BD;Blumenthal RS;Chaitman BR;Forman SA;Geller NL;Goldberg AD;Habib GB;

Asymptomatic Cardiac Ischemia Pilot (ACIP) study: outcome at 1 year for patients with asymptomatic cardiac ischemia randomized to medical therapy or revascularization. The ACIP Investigators

Ref ID 1751 **RID:** 584 1995 Sep

QUALITY

A. Selection bias (systematic differences between the comparison groups)

A4 Based on your answers t, in your opinion was selection bias present? If so, what is the likely direction of its effect?:

Unclear/unknown risk **Direction =**

B. Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)

B4 Based on your answers to the above, in your opinion was performance bias present? If so, what is the likely direction of its effect?:

Low risk of bias **Direction =**

C. Attrition bias (systematic differences between the comparison groups with respect to loss of participants)

C4 Based on your answers to the above, in your opinion was attrition bias present? If so, what is the likely direction of its effect?:

Low risk of bias

Direction =

D. Detection bias (bias in how outcomes are ascertained, diagnosed or verified)

D6 Based on your answers to the above, in your opinion was detection bias present? If so, what is the likely direction of its effect?:

Low risk of bias

Direction =

Overall Study Quality -Strengths and Weaknesses:

Strengths*: randomised, baseline characteristics reported. Intention to treat analysis reported. At 1 year after entry, follow-up was 100% complete for death and 96% complete for other clinical events.
Weaknesses: allocation concealment not reported.
* This is a 1 year follow-up of the ACIP study.

DETAILS

# of patients:

N=558 (n=183 in angina guided therapy; n=183 in ischemia guided therapy; n=192 in revascularisation).

Prevalence (Diagnostic):

Patient Characteristics

Baseline characteristics:
Characteristic: Angina guided (n=183); Ischemia guided (n=183); Revascularisation (n=192)
Age (yr): 61±8; 62±8; 61±8
Male: 164; 156; 159
White: 157; 153; 168
Angina
Within <6 week of entry: 105; 110; 110
On QV ETT or other stress test: 90; 105; 105
With ischemic episode on QV AECG: 15; 27; 21
Any of these: 125; 131; 135
Diabetes: 21; 35; 34
Previous PTCA: 37; 32; 31
Previous CABG: 9; 12; 10
1 vessel: 41; 45; 50
2 vessels: 66; 64; 81
3 vessels: 76; 74; 61
Ejection fraction: <35%: 0; 4; 4
35% to 49%: 17; 18; 16
50% to 64%: 74; 81; 76
>65%:83; 75; 82
Not available: 9; 5; 14

Inclusion criteria: The target population was clinically stable patients with angiographically documented coronary artery disease (≥ 50% stenosis in ≥ 1 major vessel or branch) suitable for revascularisation. To be eligible, patients also had to have ischemia during exercise or pharmacological stress testing and at least one episode of asymptomatic ischemia during 48 hour ACEG monitoring. Patients were either free of angina or had symptoms that could be well controlled by medical therapy.
Exclusion criteria: Patients with recent MI or unstable angina or who were unable to tolerate at least one of the two prespecified medical treatments were excluded.

Interventions/ Test/ Factor being investigated	1) Phramacologic therapy for angina (angina guided therapy) 2) Pharmacologic therapy to suppress both angina and ECG evdince of ischemia (ischemia guided strategy)
Comparisons	3) Revascularisation with either angioplasty or CABG within 4 weeks of entry according to physician and patienst preference (revascularisation strategy). The choice of procedure, PTCA or CABG, was made by the clinical unit staff and patient based on a coronary angiogram usually performed within 2 months of enrollment.
Length of Study/ Follow-up	1 year.
Outcome measures studied	Primary outcome: Absence of ischemia on an ambulatory ECG recorded 12 weeks after entry. Secondary outcomes: clinical events (death, MI, cardiac arrest, unstable angina, sustained ventricular tachycardia and congestive heart failure) and ambulatory ECG and exercise test findings.
Results	
Effect Size	Results: 1 year Outcome: Angina guided (n=183) vs. Ischemia guided (n=183) vs. Revascularisation (n=192) Stroke: 2 (1.1%) vs. 1 (0.5%) vs. 0 Non protocol Angiolpasty : 16 (8.7%) vs. 13 (7.1%) vs. 10 (5.2%) Non protocol Bypass surgery: 28 (15.3%) vs. 36 (19.7%) vs. 8 (4.2%) MI: 10 (5.5%) vs. 9 (4.9%) vs. 5 (2.6%) Death: 8 (4.4%) vs.3 (1.6%) vs. 0 Hospital admissions: 30% vs. 30% vs. 18% Note: The angina guided strategy consisted of anti ischemia drug treatment sufficient to control angina. The ischemia guided strategy added additional active drug therapy if ischemia was still present during AECG recording. Patients in the angina guided strategy received placebo to maintain blinding. The revascularisation strategy consisted of initial treatment with PTCA or CABG aimed at achieving the most complete revascularisation possible by the method deemed most appropriate by the physician at the clinical site. Pharmacologic therapy consisted of a titrated regimen of atenolol, followed by sustained release nifedipine if needed, or a titrated regimen of diltiazem, followed by sustained release isosorbide dinitrate if needed. During the first 4 weeks, at any time subsequently open label medication was used to suppress angina. During the next 8 weeks, medication was administered in blinded manner, according to whether residual ischemia was found on repeat 48 hour ambulatory ECG recordings at 4 and 8 weeks after randomisation (patients' assigned to angina guided strategy receives placebo; patients assigned to the ischemia guided strategy received active drugs). After the assessment of ischemia by both ambulatory ECG and exercise test at 12 weeks after entry, patients were directed to continue their current medical regimen through 1 year after study entry. Ischemia was again assessed at 6 month and 1 year follow-up visits, but the results were not used to alter medication usage.
Source of funding:	This study was funded by the National Heart, Lung, and Blood Institute, Cardiac diseases Branch, Division of Heart and Vascular disease, National Institutes of
Does the study answer the question?/Further Comments	Yes. Mortality, MI, non protocol revascularisation and hospital admissions was significantly lower in the revascularisation group. After 1 year, revascularisation was superior to both angina guided and ischemia guided medical strategies. However the authors report that these findings require confirmation by a larger scale trial.

Rogers WJ;Coggin CJ;Gersh BJ;Fisher LD;Myers WO;Oberman A;Sheffield LT;

Ten-year follow-up of quality of life in patients randomized to receive medical therapy or coronary artery bypass graft surgery. The Coronary Artery Surgery Study (CASS)

Ref ID 9156 **RID:** 638 1990

QUALITY

A. Selection bias (systematic differences between the comparison groups)

A4 Based on your answers t, in your opinion was selection bias present? If so, what is the likely direction of its effect?:

Low risk of bias **Direction =**

B. Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)

B4 Based on your answers to the above, in your opinion was performance bias present? If so, what is the likely direction of its effect?:

Low risk of bias **Direction =**

C. Attrition bias (systematic differences between the comparison groups with respect to loss of participants)

C4 Based on your answers to the above, in your opinion was attrition bias present? If so, what is the likely direction of its effect?:

Low risk of bias **Direction =**

D. Detection bias (bias in how outcomes are ascertained, diagnosed or verified)

D6 Based on your answers to the above, in your opinion was detection bias present? If so, what is the likely direction of its effect?:

Low risk of bias **Direction =**

Overall Study Quality -Strengths and Weaknesses:

Strengths: randomised (stratified randomisation). Baseline comparisons made. Intention to treat analysis reported. Follow-up was 99.7% complete (778/780) for obtaining data on vital status. For other variables, follow-up was less complete, usually because data were not obtained or were obtained outside the follow-up time period.
Limitations: Allocation concealment not reported.
This is a 10 year follow-up of Quality Life indexes in the CASS trial

DETAILS

# of patients: n=780 (medical (n=390) and surgery (n=390))

Prevalence (Diagnostic):

Patient Characteristics	see Ref ID 2047
Interventions/ Test/ Factor being investigated	Surgery
Comparisons	Medical therapy
Length of Study/ Follow-up	10 years
Outcome measures studied	Primary outcomes: Patients symptomatology, activity level, employment, and smoking habits. Frequency, duration and reasons for repeated hospitalisation.
Results	
Effect Size	Results: Outcome: medical (n=390) vs. surgery (n=390) Mortality: 21.8% vs. 19.2% Asymptomatic: 42% vs. 47% Hospitalisation one or more times occurred in (patients)*: 334 (85.6%) vs. 381 (97.7%); p<0.0001 PTCA: 9 vs. 10 Initial CABG: 144 vs. 360 Repeated CABG: 15 vs. 35 *The cumulative number of hospitalisations was greater for patients assigned to surgery, primarily owing to readmission for the protocol assigned CABG. Note: Compliance with randomised treatment assignment: Of the 390 patients randomly allocated to medical treatment, 144 (37%) subsequently underwent CABG during the next 10 years. Of the 390 patients randomly assigned to CABG, 41 (11%) initially refused, but of these 41, 13 patients subsequently underwent CABG at a mean of 3.6 years after randomisation.
Source of funding:	
Does the study answer the question?/Further Comments	Yes. The was observed similarities of the medically and surgically assigned groups at 10 years reflect return of symptoms in the surgical group, however the authors report that the important explanation for this is the performance of late surgery in a large proportion of the medically assigned patients, rendering them asymptomatic.

Soares PR;Hueb WA;Lemos PA;Lopes N;Martinez EE;Cesar LAM;Oliveira SA;Ramires JAF;

Coronary revascularization (surgical or percutaneous) decreases mortality after the first year in diabetic subjects but not in nondiabetic subjects with multivessel disease: An analysis from the medicine, angioplasty, or surgery study (MASS II)

Ref ID 3779 RID: 706 2006

QUALITY

A. Selection bias (systematic differences between the comparison groups)

A4 Based on your answers t, in your opinion was selection bias present? If so, what is the likely direction of its effect?:

Unclear/unknown risk

Direction = More patients in PCI group had had MI and fewer were current or past smokers; other characteristics similar at baseline;

B. Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)

B4 Based on your answers to the above, in your opinion was performance bias present? If so, what is the likely direction of its effect?:

Low risk of bias

Direction =

C. Attrition bias (systematic differences between the comparison groups with respect to loss of participants)

C4 Based on your answers to the above, in your opinion was attrition bias present? If so, what is the likely direction of its effect?:

Low risk of bias

Direction =

D. Detection bias (bias in how outcomes are ascertained, diagnosed or verified)

D6 Based on your answers to the above, in your opinion was detection bias present? If so, what is the likely direction of its effect?:

low risk of bias

Direction =

Overall Study Quality -Strengths and Weaknesses:

same patients as Hueb 2007 (Ref ID 2913) - this paper subgroups by diabetes or no diabetes

DETAILS

# of patients:

611: Diabetes: CABG 59; PCI 56; Medical Therapy (MT) 75; no diabetes: CABG 144; PCI 149; MT 128

Prevalence (Diagnostic):

Patient Characteristics

Inclusion: Proximal multivessel coronary stenosis >70% and documented ischaemia; suitable for medical therapy or revascularisation.
Exclusion: refractory angina or acute MI requiring emergency revascularisation; ventricular aneurysm requiring surgical repair; left ventricular ejection fraction below 40%; previous coronary revascularisation; single-vessel coronary disease; normal or minimal coronary artery disease; congenital heart disease; valvular heart disease; cardiomyopathy; unable to understand or cooperate with protocol or return for follow up; left main stenosis 50% or more; suspected or known pregnancy; contraindication to PCI or CABG.
Mean age around 60 years
188/611 (31%) female
187/611 (31%) current or past smoker
269/611 (44%) myocardial infarction
365/611 (60%) hypertension
179/611 (29%) diabetes

Interventions/ Test/ Factor being investigated	CABG vs. PCI vs. medical therapy
Comparisons	CABG vs. PCI vs. medical therapy in diabetic versus non-diabetic sub-groups; hazard rates
Length of Study/ Follow-up	5 years (mean 1702 +/- 452 days; median 1840 days)
Outcome measures studied	Primary outcome: incidence of overall mortality

Results

Mortality at 5 years

;	Year 1		Years 2-5		
	No. events	Hazard rate p	No. events	Hazard rate	Mean annualised hazard rate p
Diabetic subjects					0.039
Medical (n=75)	2	2.7	17	26.5	6.6
PCI (n=56)	3	5.5	6	12.0	3.0
CABG (n=59)	4	7.0	5	9.5	2.4
Non-diabetic subjects					0.2
Medical (n=128)	2	1.6	14	11.8	2.9
PCI (n=149)	8	5.5	11	8.1	2.0
CABG (n=144)	7	5.0	16	12.4	3.1

Effect Size	
Source of funding:	not stated
Does the study answer the question?/Further Comments	subgroup analysis of MASS II patients already included (Hueb 2007 ID 2913) so beware double counting> Hazard rate for mortality only; subgroup by diabetes status and by year 1 versus years 2-5 (unclear why; post-hoc analyses) - underpowered to examine this outcome.

Strauss WE;Fortin T;Hartigan P;Folland ED;Parisi AF;

A comparison of quality of life scores in patients with angina pectoris after angioplasty compared with after medical therapy. Outcomes of a randomized clinical trial. Veterans Affairs Study of Angioplasty Compared to Medical Therapy Investigators

Ref ID 1741 **RID:** 664 1995 Oct 1

QUALITY

A. Selection bias (systematic differences between the comparison groups)

A4 Based on your answers t, in your opinion was selection bias present? If so, what is the likely direction of its effect?:

Low risk of bias

Direction =

B. Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)

B4 Based on your answers to the above, in your opinion was performance bias present? If so, what is the likely direction of its effect?:

Low risk of bias

Direction =

C. Attrition bias (systematic differences between the comparison groups with respect to loss of participants)

C4 Based on your answers to the above, in your opinion was attrition bias present? If so, what is the likely direction of its effect?:

Low risk of bias

Direction =

D. Detection bias (bias in how outcomes are ascertained, diagnosed or verified)

D6 Based on your answers to the above, in your opinion was detection bias present? If so, what is the likely direction of its effect?:

Low risk of bias

Direction =

Overall Study Quality -Strengths and Weaknesses:

Strengths: randomisation, detailed baseline comparisons were made in the original study (1900) and also for QOL data, intention to treat analysis used, analysis of those without follow up data (17% PTCA and 11% Med Therapy) with no significant differences between groups with and without follow-up data.
Weaknesses: Small sample size for questionnaire data and particularly when broken down into sub-groups therefore large SDs in mean QOL change score, no means and subscale SDs reported.
*This study reports quality of life questionnaire response from the ACME study at 6 months follow-up

DETAILS

# of patients:

N=212 (n=107 to medical therapy ; n=105 to PTCA)

Prevalence (Diagnostic):

Patient Characteristics

For detailed medical baseline refer to ref id 1900 relevant baselines for current reference:

	Med Therapy	PCTA	
Age	63	62	
Diabetes (%)	19	17	
Angina-free for past 30 days (%)	8	9	
QOL (SD)	96.0 ±18.6	96.7 ±18.6	(p=.78)

At baseline, there were no significant differences in the individual QOL categories, overall QOL score, or physical activity scores (such as physical, anxiety, depression, general health, positive attitude, self confidence and vitality as well as

overall PGWB score) between the patients randomised to either form of treatment.

Inclusion criteria: patients with stable angina, a strikingly positive exercise test (ETT), or MI within the past 3 months and at least 70% stenosis of the proximal two thirds of one major epicardial coronary artery were eligible for inclusion. After written informed consent was obtained, all antianginal medications were discontinued at least 24 hours before a baseline thallium exercise tolerance test. Patients manifesting horizontal or down-sloping ST-segment depression >=1mm in one or more leads that occurred during or immediately after treadmill ETT were eligible for inclusion. Patients with no ST-segment depression who had angina during the test could also be included if there was a reperfusing thallium defect in the region of the involved artery

Interventions/ Test/ Factor being investigated

PTCA

Comparisons

PTCA vs medical therapy

Length of Study/ Follow-up

6 months

Outcome measures studied

Primary endpoint: change from baseline in exercise duration, frequency of angina, use of nitroglycerin The secondary outcome measures used in this study were: Quality of life as measured by a two-part self-administered QOL questionnaire that measured physical functioning and psychological well-being. For the physical component the appropriate sections of the McMaster Health Index Questionnaire (MHIQ) were used. The psychological component was assessed with the Psychological General Well-Being Index (PGWB).

Results

Effect Size

At the 6 month follow-up visit, the mean change in score (follow-up minus baseline) was significantly improved, favouring PTCA for overall psychological status of well-being and for the combined physical function and psychological summed score. In addition, each individual component of the PGWB questionnaire showed a trend in favour of PTCA (p-values for PTCA subscales not explicitly stated):

	Medical therapy	PCTA	P Value
QOL	+1.98±14.7	+7.36 ±15.6	< .02

Groups were then stratified by level of exercise and angiogram improvement by 6 months. Below are results in mean change from baseline from those individuals within the highest improvement category:

	PTCA patients with ETT increase of >2 min in duration (N=38)		Medical patients with ETT increase of >2 min in duration (N=19)	
Mean change score*:				
Overall QOL	7.13	p=.0004	2.57	p=.58
General Health	2.44	p=.0001	1.16	p=.09

* Note. P-values do not refer to PTCA vs Med Therapy, but rather to baseline compare to 6 month change within each group.

	PTCA patients with angiogram improvement >18.8% in lesion severity (N=45)		Medical patients with angiogram improvement >18.8% in lesion severity (N=6)	
Mean change score*:				
Overall QOL	10.6	p=.0001	13.8	p=.04
General Health	2.42	p=.0001	3.67	p=.007

* Note. P-values do not refer to PTCA vs Med Therapy, but rather to baseline compare to 6 month change in each group.

Source of funding:

supported by the Cooperative Studies Program, Research Service, Department of Veteran Affairs, Washington DC

Does the study answer the question?/Further Comments	Yes. At the end of the 6-months evaluation period, patients randomized to PTCA had a significantly greater improvement in overall QOL scores. This improvement in QOL was only noted in PTCA-assigned patients demonstrating an increase in exercise performance and only occurred in patients whose angiograms demonstrated at least 18.8% improvement in lesion severity.

Teo KK;Sedlis SP;Boden WE;O'Rourke RA;Maron DJ;Hartigan PM;Dada M;Gupta V;Spertus JA;Kostuk WJ;Berman DS;Shaw LJ;Chaitman BR;Mancini GBJ;Weintraub WS;

Optimal Medical Therapy With or Without Percutaneous Coronary Intervention in Older Patients With Stable Coronary Disease. A Pre-Specified Subset Analysis of the COURAGE (Clinical Outcomes Utilizing Revascularization and Aggressive druG Evaluation) Trial

Ref ID 3875 **RID:** 531 2009

QUALITY

A. Selection bias (systematic differences between the comparison groups)

A4 Based on your answers t, in your opinion was selection bias present? If so, what is the likely direction of its effect?:

Unclear/unknown risk **Direction =**

B. Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)

B4 Based on your answers to the above, in your opinion was performance bias present? If so, what is the likely direction of its effect?:

Low risk of bias **Direction =**

C. Attrition bias (systematic differences between the comparison groups with respect to loss of participants)

C4 Based on your answers to the above, in your opinion was attrition bias present? If so, what is the likely direction of its effect?:

Low risk of bias **Direction =**

D. Detection bias (bias in how outcomes are ascertained, diagnosed or verified)

D6 Based on your answers to the above, in your opinion was detection bias present? If so, what is the likely direction of its effect?:

Low risk of bias **Direction =**

Overall Study Quality -Strengths and Weaknesses:	Strengths: Randomisation method reported (permuted block design within strata –prior CABG/no prior CABG and by medical centre), sample size calculation reported, Blind outcome assessment (clinical outcome adjudicated by an independent committee whose members were unaware of treatment assignments). 9% of patients were lost to follow-up in the two groups (107 in the PCI group and 97 in the

medical therapy group, p=0.51).Loss to follow-up not reported seperately for subgroup age >65 years. Intention to treat analysis reported.

Weaknesses: Allocation concealment not reported. *
*The study is a post hoc analysis of pre-specified cardiovascular outcomes during a 2.5 to 7 year (median 4.6 year) follow-up among patients aged ≥65 years at baseline.

DETAILS

# of patients:

n=904 (n=444 in optimal medical therapy (OMT) and n=460 in PCI+OMT)

Prevalence (Diagnostic):

Patient Characteristics

Baseline characteristics: aged ≥65 years (n=904)
Characteristics: PCI +OMT vs. OMT
Sex: male: 380 (83) vs. 370 (83)
Race: white: 395 (86) vs. 385 (87)
Age: 72±5 vs. 72±5
Diabetic patient: 151 (33) vs. 159 (36)
Cardiac history
MI: 159 (35) vs. 167 (38)
PCI: 73 (16) vs. 72 (16)
CABG: 70 (15) vs. 67 (15)
CVD: 56 (12) vs. 53 (12)
CHF: 29 (6) vs. 28 (6)
Low EF≤50: 82 (18) vs. 75 (17)
EF: 61.3 ±11 vs. 61.5 ±10
1 vessel disease: 121 (26) vs.120 (27)
2 vessel disease: 165 (37)
3 vessel disease: 159 (36)
Angina duration (months): 5 (2, 24) vs. 6 (2, 24) [interquartile range]

Interventions/ Test/ Factor being investigated

PCI+OMT

Comparisons

OMT

Length of Study/ Follow-up

median 4.6 years

Outcome measures studied

Primary outcomes: all cause mortality or non fatal MI; death; hospitalisation for ACS; the composite of death, MI, or stroke; and the composite of death, MI, stroke, or hospitalisation for ACS. Additional outcomes included the percentage of patients who achieved the target for blood pressure, low density lipoprotein cholesterol, body mass index, smoking cessation, adherence to diet, exercise, and medications, as well as angina free status.

Results

Effect Size

Results:
Outcome: OMT (n=444) vs. PCI (n=460)
Death: 54 (12%) vs. 57 (12%)
MI: 52 (12%) vs. 60 (13%)

The percentage of angina free patients was 73% in the OMT group and 80% in the PCI+OMT arm.

Source of funding:

Does the study answer the question?/Further Comments	Yes. The addition of PCI to OMT did not improve or worsen clinical outcomes in patients ≥65 years of age during a median 4.6 year follow-up. Authors conclusion: The data support adherence to American College of Cardiology/American Heart Association clinical prcatice guidelines that advocate OMT as an appropraite initial management strategy, regardless of age. Funding: Supported by the Cooperative studies program of the U.S. Department of Veterans Affairs Office of Research and Development, in collaboration with the Canadian Institutes of Health Research; and by unrestricted research grants from Merck, Pfizer, Bristol-Myers Squibb, Fujjsawa, Kos Pharmaceuticals, Data scope, Astrazeneca, Key Pharmaceutical, Sanofi-Aventis, First Horizon, and GE Heathcare.

Varnauskas E;

Survival, myocardial infarction, and employment status in a prospective randomized study of coronary bypass surgery

Ref ID 4148 **RID:** 654 1985

QUALITY

A. Selection bias (systematic differences between the comparison groups)

A4 Based on your answers t, in your opinion was selection bias present? If so, what is the likely direction of its effect?:

Unclear/unknown risk **Direction =**

B. Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)

B4 Based on your answers to the above, in your opinion was performance bias present? If so, what is the likely direction of its effect?:

Low risk of bias **Direction =**

C. Attrition bias (systematic differences between the comparison groups with respect to loss of participants)

C4 Based on your answers to the above, in your opinion was attrition bias present? If so, what is the likely direction of its effect?:

Low risk of bias **Direction =**

D. Detection bias (bias in how outcomes are ascertained, diagnosed or verified)

D6 Based on your answers to the above, in your opinion was detection bias present? If so, what is the likely direction of its effect?:

Low risk of bias **Direction =**

Overall Study Quality -Strengths and Weaknesses:

Strengths: randomised. Low attrition bias. Intention to treat analysis used
Weaknesses: reporting of outcome is not always very clear; unclear allocation concealment
This is a 8 and 5 year results of the ECSS.

DETAILS

# of patients:

N=768 (n=373 Medical ; n=394 Surgery)

Prevalence (Diagnostic):

Patient Characteristics

See Ref ID 9157

Interventions/ Test/ Factor being investigated

Surgery

Comparisons

Medical

Length of Study/ Follow-up

5 years and 8 years

Outcome measures studied

Death, Non fatal MI,Quality of life

Results

Effect Size

Results:
Outcome: medical vs. CABG
Death: 69 vs. 41
Sudden cardiac deaths*: 28 vs. 9
Non sudden cardiac deaths: 30 vs. 13

*Sudden death was defined as death occurring within 1 hour after the onset of symptoms.

Survival: Fewer deaths (9/100) among medical patients who eventually underwent surgery than among those who were treated medically (60/273) had a positive effect on the average survival rate for the medical group, which was 83.6% at 5 years and 79.9% at 8 years.
In the surgical group, the relatively high number of deaths in the small subset of patients who were not operated on (8/26) compared with those who were operated on (33/368) had little effect on survival for the entire surgical group, which was 92.4% at 5 years and 88.6% at 8 years.

A significant difference in favour of surgery was observed in total population (P=0.0002 at 5 years and p=0.013 at 8 years), in the sub group of patients with two and three vessel disease, i.e. when the patients with left main artery disease are excluded from the total population (p=0.0011 at 5 years and p=0.0051 at 8 years) and in the sub group of patients with 3 vessel disease (p=0.003 at 5 years and p=0.00015 at 8 years). The difference was not significant in the sub group of patients with 2 vessel disease. In patients with left main artery disease, the survival was 67.9% at 5 years and 63.6% at 8 years for medical patients and 85.7% at 5 years and 81.7% at 8 years for the surgical; the differences between the two treatments are not significant.

Non fatal MI: Incidence of MI in the medical group (11%) was not significantly different from that in the surgical group (15%).
Quality of life:

Functional status and need for drug therapy:
Significant difference in the relief of angina pectoris, improvement of exercise performance, and diminished need for BB and/or nitrate treatment were noted between the two treatments; the results clearly favoured surgery. Although these differences gradually decreased with time, they were still significant at 5 years.

Compliance with randomised treatment:
Of the 374 patients allocated to the medical group, 90 had undergone CABG by 5 years and an additional 10 by 8 years because of unacceptable angina inspite of adequate treatment. Nine of these 100 patients died.

Deviants from surgical treatment:
Of 26 surgical patients who were not operated on, 6 died before the operation could be performed. All 6 were high risk patients, with stenosis in the proximal segment of the LAD and an abnormal resting ECG, and four of the five patients showed more than 2mm ST segment depression during exercise tests. The remaining 20 patients refused surgery. The majority of them had decelerating angina after randomisation; two of them died at 4 years.

Source of funding:

supported by grants from the Department of Health and Social security London, the Swedish National Association against chest diseases (Stockholm), and the

Does the study answer the question?/Further Comments

Yes. A reduction in cardiac deaths was responsible for improved survival with surgery. The incidence of MI in the medical group was not significantly different from that in the surgical group.

Varnauskas E;

Twelve-year follow-up of survival in the randomized European Coronary Surgery Study

Ref ID 1976 **RID:** 650 1988 Aug 11

QUALITY

A. Selection bias (systematic differences between the comparison groups)

A4 Based on your answers t, in your opinion was selection bias present? If so, what is the likely direction of its effect?:

Unclear/unknown risk **Direction =**

B. Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)

B4 Based on your answers to the above, in your opinion was performance bias present? If so, what is the likely direction of its effect?:

Unclear/unknown risk **Direction =**

C. Attrition bias (systematic differences between the comparison groups with respect to loss of participants)

C4 Based on your answers to the above, in your opinion was attrition bias present? If so, what is the likely direction of its effect?:

Low risk of bias

Direction =

D. Detection bias (bias in how outcomes are ascertained, diagnosed or verified)

D6 Based on your answers to the above, in your opinion was detection bias present? If so, what is the likely direction of its effect?:

Unclear

Direction =

Overall Study Quality -Strengths and Weaknesses:

Strengths: randomised, long follow up; Intention to treat analysis used;
Limitation: allocation concealment unclear ; limited the study to relatively high risk patients in whom surgery would be expected to yield greatest survival benefit. Reporting of outcomes not always very clear (many in graphs and not tables). "crossover" of patients between the two groups ie 36% of the medical group patients underwent surgery and 6% of the surgical group patients did not have surgery ; only a fraction of all the patients that could be traced at 10 years were followed for an additionaly 2 years (45 in Med gp and 41 in Surgical gp)

DETAILS

# of patients: N=768 (n=373 Medical ; n=394 Surgery)

Prevalence (Diagnostic):

Patient Characteristics see RMID 9157

Interventions/ Test/ Factor being investigated CABG with either saphenous-vein graft or internal mammary artery vs medical treatment (no details on drugs used)

Comparisons

Length of Study/ Follow-up 10 years and a fraction of them (45 in medical gp and 41 in surgical group) were followed for 12 years.

Outcome measures studied death ; survival (subgroup age, peripheral arterial disease, LAD stenosis, LMD analyses)

Results

Effect Size

Compliance:
136/373 (36%) of the medical gp patients underwent surgery
23/394 (6%)of the surgical gp patients did not have surgery

Deaths

	Medical gp			Surgical gp		
	Medically treated (n=237)	Operated on ; In hospital;	late ; (n=136)	Not operated on (n=23)	Operated on ; in hospital ;	late (n=371)
Cardiac	65	3 ; 8 ;	7 ; 6 ;	33		
Non-cardiac	5	1 ; 2 ;	0 ; 0 ;	13		
Related to surgical procedure	0	1 ; 0 ;	0 ; 6 ;	0		
Cerebrovascular	3	0 ; 0 ;	0 ; 2 ;	4		
Insufficient data	17	0 ; 4 ;	1 ; 1 ;	19		

Total 90 ; 5 ; 14 ; 8 ; 15 ; 69

Survival
Results presented in graphs.
From the text:
cumulative survival rate among patients who had early surgical treatment was significantly higher than that among patients who only had medical treatment throughout observation period (p=0.04)
The significant difference in survival noted at 5 years between the 2 treatment groups (p=0.0001) gradually decreased, but it remained significant at 10 years (p=0.02) and 12 years (p=0.04)
Subgroup analysis covering 10 years follow up data (as sample for additional 2 years too small)

- Age
Population was subdivided arbitrarily into 3 subgroups of similar size
Age<47 p>0.20
Age 47-53 p>0.2
Age >53 p= 0.007

- Peripheral Arterial Disease
Among patients with peripheral arterial disease, the cumulative survival rates were

	Medical group (n=30)	Surgical group(n=28)	P
5 years	66 (+ - 17%)	89 (+ - 11%)	0.04
10 years	46 (+ - 18.2%)	65 (+ - 18.6%)	0.08

- Lesion in the proximal segment of the left anterior descending coronary artery
Results presented as graphs
A lesion in the proximal segment of the left anterior descending coronary artery was a predictor of both a poor prognosis and a significantly improved outcome with early surgical treatment, as compared with medical therapy
Multi vessel disease:
LAD stenosis absent (n=104 in surgical patients, n=102 in medical group): p>0.2
LAD stenosis present (n=262 in surgical gp and n=240 in medical gp): p=0.007

Left main disease: (n=28 in surgical gp and n=31 in medical gp) p>0.2

Source of funding: not reported

Does the study answer the question?/Further Comments

Yes. A significant improvement in survival after coronary artery surgery may be detected for 12 years in selected patients with stable angina and multivessel disease, although this effect appears to decrease gradually after 5 years.
The benefit of surgical treatment tended to be greater, but not significantly so, as assessed by interaction analysis, in the subgroups of patients who were older or who had peripheral arterial disease, and proximal obstruction in the left anterior descending artery.

Varnauskas E;Olsson SB;Carlstrom E;

Long-term results of prospective randomised study of coronary artery bypass surgery in stable angina pectoris

Ref ID 3940 **RID:** 683 1982

QUALITY

A. Selection bias (systematic differences between the comparison groups)

A4 Based on your answers t, in your opinion was selection bias present? If so, what is the likely direction of its effect?:

Unclear/unknown risk

Direction =

B. Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)

B4 Based on your answers to the above, in your opinion was performance bias present? If so, what is the likely direction of its effect?:

Unclear/unknown risk

Direction =

C. Attrition bias (systematic differences between the comparison groups with respect to loss of participants)

C4 Based on your answers to the above, in your opinion was attrition bias present? If so, what is the likely direction of its effect?:

Low risk of bias

Direction =

D. Detection bias (bias in how outcomes are ascertained, diagnosed or verified)

D6 Based on your answers to the above, in your opinion was detection bias present? If so, what is the likely direction of its effect?:

Unclear

Direction =

Overall Study Quality -Strengths and Weaknesses:

Strengths: randomised, long follow up. Intention to treat analysis used ;Low risk of attrition bias(Medical group: 3/373 patients lost; Surgical group: 2/394 patients lost)
Limitation: unclear allocation concealment ; limited the study to relatively high risk patients in whom surgery would be expected to yield greatest survival benefit. Reporting of outcomes not always very clear (many in graphs and not tables). "crossover" of patients between the two groups ie 27% of patients assigned to medical therapy ended up undergoing surgery and 7% of patients assigned to surgical group did not have surgery

DETAILS

# of patients: N=768 (n=373 Medical ; n=394 Surgery)

Prevalence (Diagnostic):

Patient Characteristics see RMID9157

Interventions/ Test/ Factor being investigated CABG with either saphenous-vein graft or internal mammary artery vs medical treatment (no details on drugs used)

Comparisons surgery (CABG) vs medical therapy

Length of Study/ Follow-up

5 years

Outcome measures studied

death, survival, angina severity

Results

Effect Size

Compliance:
Medical group: 100/373 (27%) patients had surgery
Surgical group: 26/394 (7%) patients did not have surgery (6 died before operation was done, 19 refused surgery and 1 had liver disease)

Deaths

	Medical gp		Surgical gp	
	Medically treated (n=273)	Operated on(n=100); In hospital; late	Not operated on (n=26)	Operated on(n=368); in hospital ; late
Cardiac	52	3 ; 2 ; 7 ; 6 ; 7		
Non-cardiac	1	0 ; 2 ; 0 ; 0 ; 5		
Related to surgical procedure	0	1 ; 0 ; 0 ; 5 ; 0		
Cerebrovascular	1	0 ; 0 ; 0 ; 2 ; 3		
Insufficient data	6	0 ; 1 ; 1 ; 1 ; 4		
Total	60	4 ; 5 ; 8 ; 14 ; 19		

Survival
5-year Results presented as graphs. Values obtained from text

	Surgical group	Medical group	P value
Total survival	92.4%	83.6%	p=0.00025
LMD subset (n=28 in Surgical gp and n=31 in Medical gp)	85.7%	67.9%	p=0.11
3 vessel-disease (n=219 in S gp ; n=188 in M gp)	94%	82.4%	p=0.0003
2 vessel disease (n=147 in S gp ; n=154 in M gp)	91.2%	88.2%	p>0.2
LAD present (n=262 in S gp ; n=240 in M gp)	92.7%	82%	p=0.0004
No Peripheral arterial disease* (n=347 in S gp ; n=317 in M gp)	92.8%	84.8%	p=0.0015
Peripheral arterial disease present* (n=28 in S gp; n=30 in M gp)	89.2%	66.2%	p=0.0361

* information missing for 26 patients in the Medical gp and 19 patients in the Surgical group

Angina
5-year Results presented as graphs. Values obtained from text

Follow up period (yrs)	0-1 ; 0-2 ; 0-3 ; 0-4 ; 0-5	
Angina symptoms improve	83% ; 79% ; 78% ; 77% ; 75% in S gp	
	45%; 48% ; 51% ; 53% ; 60% in M gp	p<0.01
Angina free patients	58%; 55% ; 50% ; 48% ; 46% in S gp	
	14% ; 16% ; 21% ; 22% ; 28% in M gp *	p<0.001

* improvement in the medical gp largely due to operations

Source of funding:

not reported

Does the study answer the question?/Further Comments

On the evidence of this study, coronary bypass grafting should be seriously considered as the treatment of choice in certain patient categories even when angina responds adequately to medical management. The greatest benefit of surgery is obtained in patients at high risk. Surgery is unlikely to improve 5-yr survival in patients who are free from peripheral arterial disease. In terms of anginal attacks, the surgical group did significantly better than the medical group throughout the 5 years of follow up, but the difference between the 2 treatments

tended to decrease

Weintraub WS;Spertus JA;Kolm P;Maron DJ;Zhang Z;Jurkovitz C;Zhang W;Hartigan PM;Lewis C;Veledar E;Bowen J;Dunbar SB;Deaton C;Kaufman S;O'Rourke RA;Goeree R;Barnett PG;Teo KK;Boden WE;Mancini GB;

Effect of PCI on quality of life in patients with stable coronary disease

Ref ID 9248 **RID:** 871 2008 Aug 14

QUALITY

A. Selection bias (systematic differences between the comparison groups)

A4 Based on your answers t, in your opinion was selection bias present? If so, what is the likely direction of its effect?:

Low risk of bias **Direction =**

B. Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)

B4 Based on your answers to the above, in your opinion was performance bias present? If so, what is the likely direction of its effect?:

Low risk of bias **Direction =**

C. Attrition bias (systematic differences between the comparison groups with respect to loss of participants)

C4 Based on your answers to the above, in your opinion was attrition bias present? If so, what is the likely direction of its effect?:

Low risk of bias **Direction =**

D. Detection bias (bias in how outcomes are ascertained, diagnosed or verified)

D6 Based on your answers to the above, in your opinion was detection bias present? If so, what is the likely direction of its effect?:

Unclear risk of bias **Direction =**

Overall Study Quality -Strengths and Weaknesses: See Ref ID 483

DETAILS

# of patients: N=2287 (n=1149 PCI and n=1138 in OMT)

Prevalence (Diagnostic):

Patient Characteristics	See Ref ID 483
Interventions/ Test/ Factor being investigated	PCI plus optimal medical therapy
Comparisons	Optimal medical therapy alone. All patients received aspirin, and those who were undergoing PCI also received clopidogrel in accordance with treatment guidelines. Ant ischemic therapy included long acting metoprolol, amlodipine, and isosorbide mononitrate, alone or in combination, together with simvastatin and either lisinopril or losartan for secondary prevention.
Length of Study/ Follow-up	Patients were followed for a minimum of 30 months.
Outcome measures studied	Health status. Health status related to angina was assessed directly from patients at baseline; at 1,3,6 and 12 months; and at annual evaluations there after. Each assessment was performed with the use of the Seattle Angina Questionnaire, a 19 item questionnaire that quantifies physical limitations due to angina, any recent change in the severity of angina, the frequency of angina, satisfaction with treatment, and quality of life. Scores range from 0 to 100; higher scores indicate better health status. Measurement of general health status: General health status was measured with the use of the RAND-36 health survey, which includes the following domains: physical functioning, role limitation due to physical problems, role limitation due to emotional problems, vitality, emotional well being social functioning, pain, and general health. Scores for each domain range from 0 to 100, with higher scores reflecting better health status. The RAND-36 health survey contains the same items as the Medical Outcomes Study 36-item Short Form General Health Survey (SF-36).

Results

Effect Size	Results: Scores on the Seattle Angina questionnaire at 36 months Domain: PCI plus OMT vs. OMT; p value; [missing data – PCI ,OMT] Physical limitation Baseline:66±25 vs. 66±25;p=0.58;[18,18] 3months:76±24 vs. 72±23;p=0.004; [24,24] 6 months:77±23 vs. 72±24; p<0.001;[21,25 12 months:75±24 vs. 73±24;p=0.21;[24,25] 24 months: 74±24 vs. 72±24;p=0.16; [26,26] 36 months: 74±24 vs. 74±24; p=0.68; [33, 32] Angina stability Baseline: 54±33 vs. 53±32; p=0.56; [17, 17] 3 months:77±28 vs. 73±27;p=0.002;[23,23] 6 months: 76±28 vs. 73±28;p=0.02;[20,25] 12 months: 74±27 vs. 70±28; p=0.02; [22,24] 24 months: 73±27 vs. 69±27;p=0.003;[26,27] 36 months: 72±28 vs. 70±28; p= 0.39; [33, 32] Angina frequency Baseline: 68±26 vs. 69±26;p=0.20;[16,15] 3 months: 85±22 vs. 80±23; p<0.001; [22,22] 6 months: 87±20 vs. 83±22;p<0.001; [19,23] 12 months: 87±19 vs. 84±21;p=0.003; [20.23] 24 months: 89±18 vs. 86±19;p=0.002;[24,25] 36 months: 89±18 vs. 88±18; p=0.37; [32, 31] Treatment satisfaction Baseline:88±15 vs. 86±16;p=0.008; [16,16] 3 months: 92±12 vs. 88±15;p<0.001; [24,22] 6 months: 92±13 vs. 90±14; p<0.001; [22, 22] 12 months: 92±12 vs. 90±14; p=0.002; [20,22] 24 months: 92±13 vs. 92±13; p=0.35; [24,26]

36 months: 92±12 vs. 92±11; p=0.78; [31, 31]
Quality of life
Baseline: 51±25 vs. 51±25; p=0.80; [16, 16]
3 months:73±22 vs. 68±23;p<0.001; [22, 22]
6 months: 75±22 vs. 70±23;p<0.001;[19,24]
12 months: 76±21 vs. 73±22;p=0.008;[20,22]
24 months: 77±22 vs. 76±22;p=0.10;[24,26]
36 months: 79±20 vs. 77±20; p=0.32; [31, 31]

General Health status:

There were no significant differences at baseline between the groups for any RAND-36 domain. There was improvement in all domains in both groups between randomisation and follow-up at 1 to 3 months (p<0.001 for all comparisons).There was also an incremental advantage of PCI over medical therapy at 3 months for the scores in five domains: physical functioning (69±27vs. 65±26,p<0.001), role limitation-physical (60±42 vs. 52±43,p<0.001), vitality (56±23 vs. 53±23,p=0.008), pain (72±25 vs. 68±26,p=0.006), and general health (61±21 vs. 58±21,p<0.001).The benefit across domains was less consistent than seen in the results for the Seattle Angina Questionnaire, with an advantage of PCI that was noted in most but not all domains and that had a shorter duration. At 6 months, the PCI group was more likely than the medical therapy group to have a clinically significant improvement in physical functioning (50% vs. 43%)and role limitation-physical (48% vs. 43%), but no advantage was observed at 12 months. There were no significant subgroup interactions in the RAND-36 results.

Source of funding:

Department of Veterans Affairs Cooperative Studies Program, with additional funding from the Canadian Institutes of Health Research

Does the study answer the question?/Further Comments

Yes. Among patients with stable angina, both those treated with PCI and those treated with optimal medical therapy alone had marked improvements in health status during follow-up. The PCI had small, but significant, incremental benefits that disappeared by 36 months.

Yusuf S;Zucker D;Peduzzi P;Fisher LD;Takaro T;Kennedy JW;Davis K;Killip T;Passamani E;Norris R;

Effect of coronary artery bypass graft surgery on survival: overview of 10-year results from randomised trials by the Coronary Artery Bypass Graft Surgery Trialists Collaboration

Ref ID 1802 **RID:** 687 1994 Aug 27

QUALITY

A. Selection bias (systematic differences between the comparison groups)

A4 Based on your answers t, in your opinion was selection bias present? If so, what is the likely direction of its effect?:

Direction =

B. Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)

B4 Based on your answers to the above, in your opinion was performance bias present? If so, what is the likely direction of its effect?:

Direction =

C. Attrition bias (systematic differences between the comparison groups with respect to loss of participants)

C4 Based on your answers to the above, in your opinion was attrition bias present? If so, what is the likely direction of its effect?:

Direction =

D. Detection bias (bias in how outcomes are ascertained, diagnosed or verified)

D6 Based on your answers to the above, in your opinion was detection bias present? If so, what is the likely direction of its effect?:

Direction =

Overall Study Quality -Strengths and Weaknesses:

This is an IPD (Individual patient data) meta analysis. Review addresses an appropriate and clearly focused question. The review included only RCT's which was relevant to the review question. There was adequate description of the methodolgy used in the meta analysis. The mortality analysis was an ITT (irrespective of crossover between treatments or failure of CABG patients to receive surgery).

The paper does not report the search strategy used. The IPD meta analysis did not look at the longest follow-up of the VA trial comparing medical treatment to surgery in stable angina patients (22 years for VA study). Quality assessment of individual studies not reported*. This IPD meta analyses did not include all studies relevant to the question.** Sub group analyses conducted for selected sub groups. If a study had no event in a given subgroup, it was omitted from the analysis for that sub group.
* we have seperately assessed the qualityof individual studies in the evidence review.
**Additional studies have been included in the study level meta analyses conducted by us.
Note:
One study (Texas) from this meta analyses was not included in our evidence review as the study did not meet our inclusion criteria (study poplualtion was recurrent MI).

DETAILS

# of patients:

1324 assigned to CABG and 1325 assigned to medical treatment.

Prevalence (Diagnostic):

Patient Characteristics

Baseline characteristics: % of patients
Age distribution (yr):
<40: 8.5%
41-50: 38.2%
51-60: 48%
>60: 7.3%
Ejection fraction (n=2474)
<40: 7.2%
40-49: 12.5%
50-59: 28%
>60: 52.3%
Male: 96.8%
Severity of angina:
None: 11.2%
Class I or II: 53.8%
Class III or IV: 35%
Diabetes: 9.6%
Drugs at baseline:
BB (n=2308): 47.4%
Anti platelet (n=1195): 3.2%
Digitalis (n=2319): 12.9%
Diuretics (n=1940): 12.6%
No. of vessels diseased
Left main artery: 6.6%
One vessel: 10.2%
Two vessels: 32.4%
Three vessels: 50.6%
Locations of disease:
Proximal LAD: 59.4%
LAD diagonal: 60.4%
Circumflex: 73.8%
Right coronary: 81.6%

Methods:
Trials in which patients with stable coronary heart disease (stable angina not severe enough to necessitate surgery on grounds of symptoms alone, or MI) were randomly assigned CABG surgery or medical treatment. 7 trials were identified that met the criteria. Principal investigators from each of these trials and a group of independent expert cardiac surgeons, cardiologists, and statisticians were invited to take part in the collaborative effort.
The primary analysis was the comparison of CABG and medical therapy in terms of mortality. The mortality analysis was an intention to treat analysis.

Follow-up 10 years. The 10 year cut-off was chosen because follow-up was nearly complete up to then but incomplete thereafter. Similar analyses were done for 5-7 years. As with the analyses at individual time points, results were obtained first for each study individually and then combined across studies by weighted averaging, with weighting according to the inverse of the variance of the estimated difference.

Interventions/ Test/ Factor being investigated

Medical treatment

Comparisons

surgery. 1240 (93.7%) of the 1324 patients assigned to CABG underwent surgery. There were 40 deaths (3.2%) within 30 days among these patients. Overall 37.4% of patients assigned to medical treatment crossed over to surgery.

% of medical group patients who underwent surgery

Allocated treatment:	5 yr	7 yr	10 yr
Overall:	25	33	41
VA:	25	34	44
European:	28	38	43

CASS:	25	33	40
Vessel disease			
Left main artery:	42	57	65
Three vessel:	29	39	48
One/two vessel	19	25	32
LV function			
Normal:	25	34	43
Abnormal:	23	28	35
Severity of angina:			
Class 0, I and II:	24	32	39
Class III and IV:	26	36	45

Length of Study/ Follow-up

5,7 and 10 years

Outcome measures studied

Primary aim : mortality. Secondary aim: Assess the interaction between the extent of coronary artery disease and the degree of LV dysfunction and the effect of CABG surgery.

Results

Effect Size

5 yrs mortality
Trial: CABG vs. Medical
VA: 58/332 vs. 79/354 ;OR 0.74 (0.50 -1.08)
European: 30/394 vs. 63/373; OR 0.40 (0.26 -0.64)
CASS: 20/390 vs. 32/390; OR 0.60 (0.34 -1.08)
Texas: 10/56 vs. 13/60; OR 0.79 (0.31-1.97)
Oregon: 4/51 vs. 8/ 49; OR 0.44 (0.12-1.56)
New Zealand: 5/51 vs. 7/49; OR 0.65 (0.19 -2.20)
New Zealand: 8/50 vs. 8/50; OR 1.00 (0.34-2.91)
Total: 135 (10.2%) vs. 210 (15.8%); OR 0.61 (0.48-0.77); p<0.001

7 yr mortality
Trial: CABG vs. Medical
VA: 76 /332 vs.106 /354;OR O.69 (0.49 -0.98)
European: 51/394 vs. 76/373; OR 0.58 (0.39 -0.65)
CASS: 43/390 vs. 53/390; OR 0.79 (0.51-1.21)
Texas: 15/56 vs. 18/60; OR 0.85 (0.38-1.92)
Oregon: 7/51 vs. 11/ 49; OR 0.55 (0.19-1.56)
New Zealand: 7/51 vs. 13/49; OR 0.43 (0.15-1.18)
New Zealand: 10/50 vs. 11/50; OR 0.90 (0.36-2.35)
Total: 209 (15.8%) vs. 288 (21.7%); OR 0.68 (0.56 -0.83); P<0.001

10 yrs mortality
Trial: CABG vs. Medical
VA: 118/332 vs. 141/354;OR 0.83 (0.61- 1.14)
European: 91/394 vs.109 /373; OR 0.72 (0.52-0.99)
CASS: 72/390 vs. 83/390; OR 0.84 (0.59-1.19)
Texas: 23 /56 vs. 25/60; OR 0.97 (0.46-2.04)
Oregon: 14/51 vs. 14/ 49; OR 0.94 (0.39-2.26)
New Zealand: 15/51 vs. 16/49; OR 0.94 (0.38-2.31)
New Zealand: 17/50 vs. 16/50; OR 1.15 (0.50-2.65)
Total: 350 (26.4%) vs. 404 (30.5%); OR 0.83 (0.70 – 0.98); P=0.03

Sub group effects at 5 years

Subgroup: overall deaths	medical mortality rate(%)	OR; p (CABG vs. medical)
Vessel disease:		
One vessel: 21/271	9.9%	0.54 (0.22-1.33); p=0.18
Two vessel: 92/859	11.7%	0.84 (0.54-1.32); p=0.45
Three vessels: 189/1341	17.6%	0.58 (0.42-0.80); p<0.001
Left main artery: 39/150	36.5%	0.32 (0.15-0.70); p=0.004
P for interaction- p=0.19		
LV function		
Normal: 228/2095	13.3%	0.61 (0.46-0.81); p<0.001
Abnormal: 115/549	25.2%	0.59 (0.39 -0.91); p=0.02
P for interaction- p=0.90		
Severity of angina		

Class 0, I, II:	178/1716	12.5%	0.63 (0.46-0.87); p=0.005
Class III, IV:	167/924	22.4%	0.57 (0.40-0.81); p =0.001
P for interaction- p=0.69			

Source of funding:

Does the study answer the question?/Further Comments

Yes.The CABG group had significantly lower mortality than the medical treatment group at 5 years, 7 years and 10 years. The risk reduction was greater in patients with left main artery disease than in those with disease in 3 vessels or one or 2 vessels. The reduction in risk of death was similar for patients with normal or abnormal LV function at 5 years and showed no significant difference between sub groups at 10 years. The benefits of surgery were similar among all severity of angina classes.

Study Type	Cohort

Hueb W;Lopes NH;Gersh BJ;Soares P;Machado LAC;Jatene FB;Oliveira SA;Ramires JAF;

Five-year follow-up of the Medicine, Angioplasty, or Surgery Study (MASS II): A randomized controlled clinical trial of 3 therapeutic strategies for multivessel coronary artery disease

Ref ID 2913 **RID:** 691 2007

QUALITY

A. Selection bias (systematic differences between the comparison groups)

A4 Based on your answers t, in your opinion was selection bias present? If so, what is the likely direction of its effect?:

Unclear/unknown risk **Direction =** More patients in PCI group had had MI and fewer were current or past smokers; other characteristics similar at baseline;

B. Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)

B4 Based on your answers to the above, in your opinion was performance bias present? If so, what is the likely direction of its effect?:

Low risk of bias **Direction =**

C. Attrition bias (systematic differences between the comparison groups with respect to loss of participants)

C4 Based on your answers to the above, in your opinion was attrition bias present? If so, what is the likely direction of its effect?:

Low risk of bias **Direction =**

D. Detection bias (bias in how outcomes are ascertained, diagnosed or verified)

D6 Based on your answers to the above, in your opinion was detection bias present? If so, what is the likely direction of its effect?:

low risk of bias **Direction =**

Overall Study Quality -Strengths and Weaknesses: Large randomised controlled trial; no loss to follow up. Randomisation and allocation concealment unclear but referenced to another paper.

DETAILS

# of patients: 611 total: 203 medical therapy (MT), 205 PCI, 203 CABG

Prevalence (Diagnostic):

Patient Characteristics	Inclusion: Proximal multivessel coronary stenosis >70% and documented ischaemia; suitable for medical therapy or revascularisation. Exclusion: refractory angina or acute MI requiring emergency revascularisation; ventricular aneurysm requiring surgical repair; left ventricular ejection fraction below 40%; previous coronary revascularisation; single-vessel coronary disease; normal or minimal coronary artery disease; congenital heart disease; valvular heart disease; cardiomyopathy; unable to understand or cooperate with protocol or return for follow up; left main stenosis 50% or more; suspected or known pregnancy; contraindication to PCI or CABG. Mean age around 60 years 188/611 (31%) female 187/611 (31%) current or past smoker 269/611 (44%) myocardial infarction 365/611 (60%) hypertension 179/611 (29%) diabetes
Interventions/ Test/ Factor being investigated	PCI vs.CABG vs. MT
Comparisons	1 way ANOVA compared between the three groups and multiple comparison tests or multivariate analysis for pairwise comparisons between PCI, CABG and MT.
Length of Study/ Follow-up	5 years (minimum)
Outcome measures studied	Primary outcome: incidence of overall mortality, MI or refractory angina requiring revascularisation/angioplasty. Secondary outcomes: angina status, stroke/cerebrovascular accident
Results	Outcomes at 5 years CABG PCI Medical therapy p Death 12.8% 15.5% 16.2% 0.824 Cardiac death 7.9% 11.6% 12.3% 0.631 Additional interventions 7 (3.5%) 66 (32.2%) 49 (24.2%) p<0.0001 Relative risk of additional interventions: CABG compared with MT RR 0.13 (95% CI 0.05 to 0.32) PCI compared with MT RR 0.90 (95% CI 0.58 to 1.40) no difference Acute MI 8.3% 11.2% 15.3% 0.785 Cerebrovascular accident 5.9% 3.4% 3.5% 0.310 Event-free survival 30 (14.63%) 113 (55.12%) 89 (43.41%) 0.0026 Relative risk for event-free survival: CABG compared with PCI RR 0.24 (95% CI 0.16 to 0.38) CABG compared with MT RR 0.53 (95% CI 0.36 to 0.77) PCI compared with MT RR 0.93 (95% CI 0.67 to 1.30) no difference Angina-free 126 (74.2%) 119 (77.3%) 92 (54.8%) CABG compared with PCI: p=0.165 CABG compared with MT: p<0.001 PCI compared with MT: p<0.001
Effect Size	
Source of funding:	Zerbini Foundation, Sao Paulo, Brazil
Does the study answer the question?/Further Comments	Large randomised controlled trial (MASS II). Compared to those underoing PCI or maintained on medical therapy, patients underoing CABG had the highest event-free survival and the lowest need for additional intervention; the MT group had the lowest chance of being free of angina

Evidence Table

Question: In adults with stable angina, what is the clinical/cost effectiveness of revascularisation techniques to alleviate angina symptoms and to improve long term outcomes?

Study Type	Meta-analysis

Hlatky MA;Boothroyd DB;Bravata DM;Boersma E;Booth J;Brooks MM;Carrie D;Clayton TC;Danchin N;Flather M;Hamm CW;Hueb WA;Kahler J;Kelsey SF;King SB;Kosinski AS;Lopes N;McDonald KM;Rodriguez A;Serruys P;Sigwart U;Stables RH;Owens DK;Pocock SJ;

Coronary artery bypass surgery compared with percutaneous coronary interventions for multivessel disease: a collaborative analysis of individual patient data from ten randomised trials

Ref ID 2878 **RID:** 703 2009

QUALITY

A. Selection bias (systematic differences between the comparison groups)

A4 Based on your answers t, in your opinion was selection bias present? If so, what is the likely direction of its effect?:

Direction =

B. Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)

B4 Based on your answers to the above, in your opinion was performance bias present? If so, what is the likely direction of its effect?:

Direction =

C. Attrition bias (systematic differences between the comparison groups with respect to loss of participants)

C4 Based on your answers to the above, in your opinion was attrition bias present? If so, what is the likely direction of its effect?:

Direction =

D. Detection bias (bias in how outcomes are ascertained, diagnosed or verified)

D6 Based on your answers to the above, in your opinion was detection bias present? If so, what is the likely direction of its effect?:

Direction =

Overall Study Quality -Strengths and Weaknesses:

This is an IPD (Individual patient data) meta-analysis. Review addresses an appropriate and clearly focused question. The review included only RCT's which was relevant to the review question. There was adequate description of the methodology used in the meta-analysis. The papers report the search strategy used in detail. The authors report that all the included trials were reviewed and approved by ethics committees. All analyses followed the Intention to treat principle.

This IPD meta analysis included 10 trials.
Note: The IPD included 4 trials which was not included in the study level meta-analysis
1) BARI -<30% with stable angina, 2) ERACI-II - 92% unstable

angina and
3) Toulouse (Carrie.D) - Study reports- Few patients presented with stable angina, whereas the majority complained of unstable angina or recent MI 4)MASS II22% stable angina patients

DETAILS

# of patients:

n=7812 (n= 3889 in CABG and n=3923 in PCI)

Prevalence (Diagnostic):

Patient Characteristics

Baseline characteristics:
The ten participating trials provided data on 7812 patients. The median age of the study population was 61 years, with 389 patients (5%) aged 75 years or older (only 19 patients were aged 80 years or older). Median follow-up time in surviving patients was 5.9 years and varied among trials from 3 years to 13 years.

Variable: overall; ARTS ; BARI ; CABRI; EAST; ERACI-II; GABI; MASS II; RITA-1; SOS; Toulose
Age >65 yrs: 933 (34%); 453 (38%); 709 (39%); 320 (31%); 155 (40%); 162 (36%); 86 (27%); 142 (35%); 166 (16%); 395 (40%); 100 (66%)
female: 1831 (23%); 283 (23%);489 (27%); 234 (22%); 103 (26%); 93 (21%); 67 (21%); 125 (31%); 196 (19%); 206 (21%); 35 (23%)
Diabetes :1233 (16%) ; 208 (17%); 353 (19%); 124 (12%); 90 (23%); 78 (17%); 41 (13%); 115 (28%); 62 (6%); 142 (14%); 20 (13%)
Unstable symptoms: 2653 (41%); 451 (37%); 1250 (68%); 166 (16%); NA; 412 (92%); 41 (13%); 0%; NA; 202 (20%); 131 (86%)
Abnormal LV function: 1166 (17%); 189 (17%);341 (19%); 138 (15%); 63 (16%); 88 (20%); 25 (13%); 13 (3%); 142 (26%); 153 (20%);14 (9%)
3 vessel :2853 (37%); 338 (29%); 754 (41%); 449 (43%); 156 (40%); 219 (49%); 119 (38%); 230 (56%); 125 (12%); 419 (42%); 44 (29%)
Proximal LAD : 3391 (51%); NA; 668 (37%); 638 (61%); 283 (72%); 230 (51%); 92 (28%); 389 (95%); 567 (56%); 457 (46%);67 (44%)
Follow-up (yrs): 5.9; 5.1; 10.4; 3.0; 8.2; 5.0; 13.0; 5.1; 10.0; 6.0; 4.9
Stents use in PCI: 1432 (37%); 580 (98%); 9 (1%); 0%; 0%; 221 (100%); 0% ; 157 (82%); 0%; 465 (97%); 0%
IMA use in CABG : 2573 (83%); 539 (93%); 729 (82%); NA; NA; 198 (96%); 62 (39%); 188 (95%); 364 (74%);451 (93%); 42 (55%)

Patients with missing data were omitted from the calculation of percentages for baseline characteristics.

Inclusion criteria: Clinical trials that randomly assigned patients with multivessel coronary artery disease to either CABG or PCI and that reported at least 3 years of follow-up were eligible for inclusion. The authors excluded trials that compared either method alone with medical therapy, those that compared two forms of PCI, and those that compared two forms CABG.

Interventions/ Test/ Factor being investigated

CABG .8 trials provided data on IMA use.

Comparisons

PCI . Balloon angioplasty in 6 trials and bare metal stents in 4 trials.

Length of Study/ Follow-up

Median follow-up 5.9 years

Outcome measures studied

The primary outcome measure of this study was all cause mortality over all available follow-up, and the principal research question was whether survival after random assignment to CABG or PCI was modified by patient's baseline clinical characteristics.

Results

Effect Size

Results:
Data on stroke within 90 days of randomisation were available from 7 trials. (ARTS, ERACI II, GABI, MASS II, RITA-1, SoS, Toulouse). 26 (1%) of 2268 patients assigned to CABG had a stroke compared with 12 (0.5%) of 2269 patients assigned to PCI (p=0.02).

5 year event rate % (95% CI):
Outcome: CABG vs. PCI; Hazard ratio (95% CI), p value
Death: 8.4% (7.4 -9.2) vs. 10% (9.0-10.9); 0.91 (0.82-1.02), p=0.12
Death or MI: 15.4% (14.2-16.6) vs. 16.7% (15.4-17.9); 0.97 (0.88-1.06), p=0.47
Death or repeat revascularisation: 9.9% (8.9-10.9) vs. 24.5% (23-26); 0.41 (0.37-0.45), p<0.0001
Death, MI or repeat revascularisation: 20.1% (18.7-21.4) vs. 36.4% (34.8-38); 0.52 (0.49-0.57), p<0.0001

Angina at 1 year of follow-up was significantly less frequent (p<0.0001) in the CABG group (439 [14%] of 3228 patients) than in the PCI group (856 [26%] of 3240 patients; difference 13%, 95% CI 11-15).

Sub group analyses for total mortality:
Sub group: CABG vs. PCI; 5 year mortality % (CABG vs. PCI); Hazard ratio (95% CI)
Age <55 years: 107/1063 vs. 88/1122; 5.5 vs. 5%; 1.25 (0.94-1.66)
Age 55-64 yrs: 201/1477 vs. 220/1456; 8% vs. 9.4%; 0.90 (0.75-1.09)
Age >65 yrs: 267/1347 vs. 319/1341; 0.82 (0.70-0.97)
P for interaction =0.002

Women: 162/909 vs. 164/922; 9.6% vs. 12%; 1.02 (0.82-1.27)
Men: 413/2980 vs. 464/3001; 8% vs. 9.4%; 0.88 (0.77-1.00)
P for interaction=0.25

No diabetes: 432/3263 vs. 448/3298; 7.6% vs. 8.1%; 0.98(0.86-1.12)
Diabetes: 143/615 vs. 179/618; 12.3% vs. 20%; 0.70 (0.56-0.87)
P for interaction=0.014

Stable symptoms: 205/1840 vs. 256/1900; 8.2% vs. 10.2%; 0.83 (0.69-0.99)
Unstable symptoms: 262/1347 vs. 266/1306; 9.6% vs. 11.1%; 0.95 (0.80-1.12)
P for interaction=0.30

Normal LV function: 375/2789 vs. 398/2791 ; 7.6% vs. 9.1%; 0.92(0.80-1.06)
Abnormal LV function: 126/551 vs. 151/615; 12.4% vs. 14.4%; 0.93 (0.73-1.18)
P for interaction=0.87

Less than 3 vessel disease: 325/2386 vs. 371/2523; 7.7% vs. 8.8%; 0.91 (0.78-1.06)
3 vessel disease: 248/1477 vs. 253/1376; 9.5% vs. 12.1%; 0.91 (0.77-1.09)
P for interaction=0.98

No proximal LAD: 278/1567 vs. 310/1636; 8.2% vs. 10.2%; 0.92 (0.79-1.09)
Proximal LAD: 249/1707 vs. 268/1684; 8.8% vs. 10.5%; 0.90 (0.75-1.07)
P for interaction =0.77

Balloon angioplasty trails: 436/2356 vs. 481/2405; 8.5% vs. 10.9%; 0.91 (0.80-1.03)
Bare-metal stent trials: 139/1533 vs. 147/1518; 8.2% vs. 8.6%; 0.94 (0.74-1.18)
P for interaction =0.19

Source of funding:

Work supported under a contract with the Agency for Healthcare Research and Quality, Rockville, MD USA; some of the contributing trials were initially conducted

Does the study answer the question?/Further Comments

Yes. PCI was done with balloon angioplasty in 6 trials and with bare metal stents in 4 trials. Over a median follow-up of 5.9 years, 575 (15%) of 3889 patients assigned to CABG died compared with 628 (16%) of 3923 patients assigned to PCI (HR 0.91, 95% CI 0.82-1.02,p=0.12). In patients with diabetes (CABG, n=615; PCI, n=618), mortality was substantially lower in the CABG group than in the PCI group (HR 0.70, 0.56-0.87); however, mortality was similar between groups in patients without diabetes (HR 0.98, 0.86-1.12; p=0.014 for interaction). Patient

age modified the effect of treatment on mortality, with hazard ratios of 1.25 (0.94-1.66) in patients younger than 55 years, 0.90 (0.75-1.09) in patients aged 55-64 years, and 0.82 (0.70-0.97) in patients 65 years and older (p=0.002) for interaction). Treatment effect was not modified by the number of diseased vessels or other baseline characteristics. Angina at 1 year was significantly less frequent in the CABG group than in the PCI group.

Study Type	Randomised Controlled Trial

First-year results of CABRI (Coronary Angioplasty versus Bypass Revascularisation Investigation). CABRI Trial Participants

Ref ID 1732 **RID:** 688 1995 Nov 4

QUALITY

A. Selection bias (systematic differences between the comparison groups)

A4 Based on your answers t, in your opinion was selection bias present? If so, what is the likely direction of its effect?:

Low risk of bias **Direction =**

B. Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)

B4 Based on your answers to the above, in your opinion was performance bias present? If so, what is the likely direction of its effect?:

Low risk of bias **Direction =**

C. Attrition bias (systematic differences between the comparison groups with respect to loss of participants)

C4 Based on your answers to the above, in your opinion was attrition bias present? If so, what is the likely direction of its effect?:

Low risk of bias **Direction =**

D. Detection bias (bias in how outcomes are ascertained, diagnosed or verified)

D6 Based on your answers to the above, in your opinion was detection bias present? If so, what is the likely direction of its effect?:

Low risk of bias **Direction =**

Overall Study Quality -Strengths and Weaknesses:

Strengths : Multicentre, randomised (computerised random number generation), allocation concealment reported, baseline comparisons made, nos. Lost to follow-up reported (4/1054) (0.3%), Intention to treat analysis reported.
Weakness: No blinding.*
This study is a first year follow-up of the CABRI trial

DETAILS

# of patients: N=1054 (n=513 in CABG and n=541 in PTCA)

Prevalence (Diagnostic):

Patient Characteristics

Baseline characteristics:
Variable: CABG (n=513) ; n=541
Age (yrs)
Male: 59.2 ; 59.3
Female: 63.7; 62.7
Male: 399 (78%); 421 (78%)
Angina (class)
None: 4% ;6%
Class 1:6% ;5%
Class 2 : 24% ;29%
Class 3: 36% ;34%
Class4 :13% ;11%
Unstable: 15% ;14%
Medications:
BB: 65% ;60%
Ccb:65%; 67%
Nitrates: 69%;65%
Aspirin: 96%; 97%
Diabetes:12 %; 12%
Past MI:42% ;41%
1 vessel disease: 1% ; 2%
2 vessel disease: 56% ;58%
3 vessel disease: 435 ; 40%

Inclusion criteria:
Patients had to be under 76 years old and to present with typical angina pectoris or unstable angina.
Patients with single vessel disease were excluded as were those with left ,main coronary disease or severe triple vessel.Patients with overt cardiac failure or who had had an acute MI within the previous 10 days, a recent cerebrovascular event, or previous CABG or PTCA were excluded. So were those with severe concomitant cardiac illness such as valvular heart disease, aortic aneurysm, or other conditions affecting short term survival.

Interventions/ Test/ Factor being investigated

PTCA

Comparisons

CABG

Length of Study/ Follow-up

1 year

Outcome measures studied

Primary outcomes to be compared were mortality and symptom status (based on angina class) at 1 year. Secondary outcomes were MI, requirement for medication, and subsequent revascularisation procedures after the initial revascularisation.

Results

Effect Size

Results: (1 year)
Outcome: CABG (n=513) vs. PTCA (n=541)
Mortality : 14 vs. 21 (p=0.297)
Angina CCS class
None : 350 (75%) vs. 328 (67%)
Class 1: 65 (14%) vs. 84 (17%)
Class 2: 36 (8%) vs. 47 (10%)
Class 3: 8 (2%) vs. 22 (4%)
Class 4: 1 ()%) vs. 2 ()%)
Unstable: 7 (1%) vs. 4 (1%)
Atypical: 13 (3%) vs. 20 (4%)

Medication:
BB: 185 (40%) vs.224 (46%)
CCB: 145 (31%) vs. 255 (53%)

Nitrate: 89 (19%) vs. 155 (32%)
No drugs: 216 (47%) vs. 144 (30%)
1 drug: 193 (42%) vs. 202 (42%)
2 drugs: 86 (19%) vs. 153 (32%)
3 drugs: 18 (4%) vs. 42 (9%)

75/502 in PTCA (13.9%) and 52/485 (10.1%) in CABG had angina of CCS class >1. The presence of clinically significant angina at 1 year was significantly associated with PTCA treatment strategy (RR 1.54 (1.09 -2.16)).
Patients in the PTCA group had a risk of re-intervention 5 times greater than patients in the CABG group (RR 5.23 (3.90-7.03), P<0.001).
No significant difference for risk of non fatal MI during the first year: RR =5.23 (3.90-7.03), P<0.001).
During the first year follow-up, the PTCA group took significantly more anti angina drugs (nitrates, CCB, BB) than did the CABG group (RR 1.30 (1.18 -1.43), P<0.001).

Source of funding: Educational and Research grants from CR Bard (USCI) Inc, the World Health Organisation and the European society of Cardiology

Does the study answer the question?/Further Comments Yes. After 1 year 2.7% of those randomised to CABG and 3.9% of those randomised to PTCA had died. The PTCA groups RR of death was 1.42 (95% CI 0.73-2.76). Patients randomised to PTCA required significantly more re-interventions and took significantly more medication at 1 year compared to CABG. PTCA group were also more likely to have clinically significant angina .

Abizaid A;Costa MA;Centemero M;Abizaid AS;Legrand VM;Limet RV;Schuler G;Mohr FW;Lindeboom W;Sousa AG;Sousa JE;van HB;Hugenholtz PG;Unger F;Serruys PW;

Clinical and economic impact of diabetes mellitus on percutaneous and surgical treatment of multivessel coronary disease patients: insights from the Arterial Revascularization Therapy Study (ARTS) trial

Ref ID 9151 **RID:** 621 2001 Jul 31

QUALITY

A. Selection bias (systematic differences between the comparison groups)

A4 Based on your answers t, in your opinion was selection bias present? If so, what is the likely direction of its effect?:

Low risk of bias **Direction =**

B. Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)

B4 Based on your answers to the above, in your opinion was performance bias present? If so, what is the likely direction of its effect?:

Low risk of bias **Direction =**

C. Attrition bias (systematic differences between the comparison groups with respect to loss of participants)

C4 Based on your answers to the above, in your opinion was attrition bias present? If so, what is the likely direction of its effect?:

Unclear/unknown risk

Direction =

D. Detection bias (bias in how outcomes are ascertained, diagnosed or verified)

D6 Based on your answers to the above, in your opinion was detection bias present? If so, what is the likely direction of its effect?:

Low risk of bias

Direction =

Overall Study Quality -Strengths and Weaknesses:

Strengths*: randomised, allocation concealment reported. Baseline comparisons made. Clinical events adjudicated by an independent committee.
Weakness : Loss to follow-up not reported.
**this study is a sub-analysis of the ARTS trial comparing CABG vs. stenting for the treatment of diabetic patients with multivessel disease.

DETAILS

# of patients: N=1205 [(CABG n=605; diabetic, 96) and stent implantation n=600; diabetes n=112)]. Total diabetes patients in both groups n=208

Prevalence (Diagnostic):

Patient Characteristics

Interventions/ Test/ Factor being investigated Stent Implantation

Comparisons CABG

Length of Study/ Follow-up 1 year

Outcome measures studied Primary and secondary outcomes not stated. Outcomes assessed: death, MI, and any repeat revascularisation, as well as the combined major cardiac (Death, MI, and repeated revascularisation) and cerebrovascular (stroke, transient ischemic attacks, and reversible ischemic neurological deficits) events (MACCE).

Results

Effect Size

Results: (1 year)
Outcome: Diabetes, Stent (n=112) vs. Diabetes, CABG (n=96)
Death, n (%): 7 (6.3)* vs. 3 (3.1); p=0.294
Cerebrovascular events, n (%): 2 (1.8) vs. 6(6.3); p=0.096
MI, n (%): 7 (6.3) vs. 3 (3.1); p=0.294
Repeat revascularisation:
CABG, n (%): 9 (8.0) vs. 0; p <0.001
PTCA, n (%): 16 (14.3) vs. 3 (3.1); p<0.001
Event free, n (%): 71 (63.4) vs. 81 (84.4); p<0.001

*The cause of death in the diabetic patients assigned to stented angioplasty was as follows: procedure-related complication (1 patient), stent thrombosis (2 patients), sudden death (2 patients), sudden death (2 patients), MI complicated by heart failure (1 patient), and non cardiac death due to renal cancer (1 patient). In the CABG group, the causes of death were periprocedural MI (2 patients) and

	sudden death (1 patient).
Source of funding:	Cordis Corporation, a Johnson &Johnson Company, Mimai Lakes, Fla.
Does the study answer the question?/Further Comments	Yes. At 1year, diabetic patients treated with stenting had significantly lower event free survival rate (63.4%) because of a higher incidence of repeat revascularisation compared to diabetic patients treated with CABG (84.4%, P<0.001).

Aoki J;Ong AT;Arampatzis CA;Vijaykumar M;Rodriguez Granillo GA;Disco CM;Serruys PW;

Comparison of three-year outcomes after coronary stenting versus coronary artery bypass grafting in patients with multivessel coronary disease, including involvement of the left anterior descending coronary artery proximally (a subanalysis of the arterial

Ref ID 9141 **RID:** 623 2004 Sep 1

QUALITY

A. Selection bias (systematic differences between the comparison groups)

A4 Based on your answers t, in your opinion was selection bias present? If so, what is the likely direction of its effect?:

Low risk of bias **Direction =**

B. Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)

B4 Based on your answers to the above, in your opinion was performance bias present? If so, what is the likely direction of its effect?:

Low risk of bias **Direction =**

C. Attrition bias (systematic differences between the comparison groups with respect to loss of participants)

C4 Based on your answers to the above, in your opinion was attrition bias present? If so, what is the likely direction of its effect?:

Low risk of bias **Direction =**

D. Detection bias (bias in how outcomes are ascertained, diagnosed or verified)

D6 Based on your answers to the above, in your opinion was detection bias present? If so, what is the likely direction of its effect?:

Low risk of bias **Direction =**

Overall Study Quality -Strengths and Weaknesses:	Strengths*: Multi centre, randomised, allocation concealment reported, sample size calculation reported, baseline comparisons made. Nos. lost to follow-up reported (1.2%; 3/243 in stenting and 3.1%; 8/253 in CABG). Intention to treat analysis reported. Clinical events adjudicated by an independent committee. Weakness: None * This study is a sub-analysis of the ARTS trial comparing 3 year outcomes after stenting vs. CABG in patients with multivessel disease involving the proximal left anterior descending artery.

DETAILS

# of patients:	n=1205 (ARTS trial) [Patients with segment-proximal LAD disease n=449 (n=246 in stenting and n=253 in CABG)]
Prevalence (Diagnostic):	
Patient Characteristics	Baseline characteristics: Characteristics: Stenting (n=246); Surgery (n=253) Men: 77.2%; 80.2% Age (yrs); 60 ±10; 62±10 Previous MI: 43.1%; 39.5% Diabetes Mellitus: 12.6%; 15.4% Systemic hypertension: 42.7%; 42.3% Unstable angina: 40.7%; 35.2% 3 vessel coronary disease: 29.3%; 41.5%
Interventions/ Test/ Factor being investigated	PCI with stenting
Comparisons	CABG
Length of Study/ Follow-up	3 years
Outcome measures studied	The primary endpoint was defined as the absence of any of the following major adverse cardiac or cerebrovascular events (MACCEs) ≤ 3 years after randomisation: death, stroke, transient ischemic attacks, reversible ischemic neurologic deficits, documented non fatal MIs and repeated revascularisation by Percutaneous intervention or surgery. Deaths from all causes were reported.
Results	
Effect Size	Results: 3years Variable: Stenting (n=246) vs. n= (253) Death: 4.5% vs. 4.3%; RR 1.03 (0.45-2.33) CVA: 2.0% vs. 2.8%; RR 0.73 (0.23-2.34) MI: 6.9% vs. 6.3%; RR 1.10 (0.54-2.21) Repeat revascularisation: 22.0% vs. 4.8%; RR 4.63 (2.41-8.90) CABG: 4.9% vs. 0.8%; RR 6.17 (1.37-27.9) Repeat PTCA: 17.1% vs. 4%; RR 4.32 (2.11-8.82) Event free survival: 72% vs. 85.4%
Source of funding:	Cordis Corporation
Does the study answer the question?/Further Comments	Yes. At 3 years, there was no difference in the combined incidence of death, stroke, and myocardial infarction in either stent or CABG group, but the need for repeat revascularisation was more frequent in the stenting group than in the CABG group.

Banning AP;Westaby S;Morice MC;Kappetein AP;Mohr FW;Berti S;Glauber M;Kellett MA;Kramer RS;Leadley K;Dawkins KD;Serruys PW;

Diabetic and Nondiabetic Patients With Left Main and/or 3-Vessel Coronary Artery Disease Comparison of Outcomes With Cardiac Surgery and Paclitaxel-Eluting Stents1

Ref ID 9251 **RID:** 873 2010 Mar 16

QUALITY

A. Selection bias (systematic differences between the comparison groups)

A4 Based on your answers t, in your opinion was selection bias present? If so, what is the likely direction of its effect?:

Low risk of bias **Direction =**

B. Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)

B4 Based on your answers to the above, in your opinion was performance bias present? If so, what is the likely direction of its effect?:

Low risk of bias **Direction =**

C. Attrition bias (systematic differences between the comparison groups with respect to loss of participants)

C4 Based on your answers to the above, in your opinion was attrition bias present? If so, what is the likely direction of its effect?:

Low risk of bias **Direction =**

D. Detection bias (bias in how outcomes are ascertained, diagnosed or verified)

D6 Based on your answers to the above, in your opinion was detection bias present? If so, what is the likely direction of its effect?:

Low risk of bias **Direction =**

Overall Study Quality -Strengths and Weaknesses:

Strengths- Randomised, ITT used, one year MACCE was evaluated in 849 (94.6%) CABG patients (645 non diabetic and 204 medically treated diabetes) and 891 (98.7%) PES patients (664 non diabetic and 227 with medically treated diabetes). Allocation concealment reported. Baseline comparisons made.
This is a sub group analysis of the SYNTAX trial.

DETAILS

# of patients:

N=1800 (n=452 (221 CABG, 231 PES) diabetic patients and n=1348 (non diabetic patients).

Prevalence (Diagnostic):

Patient Characteristics	Baseline characteristics: Patients with denovo left main and/or 3 vessel disease. Variable: Patients with no diabetes (n=1348) vs. Patients with diabetes (n=452) Age (yrs): 65.0±9.9 vs. 65.4±9.2; p=0.41 Male: 79.9 vs. 71.0;p<0.001 Unstable angina:28.0 (378/1348) vs. 29.6 (134/452) ;p=0.51 No. Of lesions: 4.3±1.8 (1340) vs. 4.6±1.8 (449);p=0.003 Left main, any: 35.9 (480/1338) vs. 29 (130/449); p=0.007 Left main only: 3.9 (52/1338) vs. 2.2 (10/449); p=0.10 Left main+1 vessel: 5.6 (75/1338) vs. 2.2 (10/449);p=0.10 Left main +2 vessels: 12 (160/1338) vs. 11.1 (50/449); p=0.64 Left main+3 vessels: 14.4 (193/1338) vs. 11.6 (52/449); p=0.13 3 vessel only: 64.1 (858/1338) vs. 71 (319/449); p=0.007 Overall compared with non diabetic patients, diabetic patients had increased incidence of co morbid risk factors and increased lesion complexity. Medication use: For patients treated with PES, glycoprotein IIa/IIIA INHIIORS (abciximab,eptifibatide, or tirofiban) were used in 34.3% (79 of 230) and 35.4% (236 of 666) of diabetic and non diabetic patients, respectively. Statin use at baseline was balanced between CABG and PES patients in both diabetic patients (71.5% vs. 71%, p=0.91) and non diabetic patients (76.6% vs. 75.3%,p=0.57). However, at discharge, statin use was significantly lower in e CABG group for both diabetic patients (73.8% vs. 83.%, p=0.02) and non diabetic patients (74.7% vs. 88%, p<0.001). Thienopyridine anti platelet use at 1 year post procedure was 19% and 71.8% in diabetic patients and 13.8% and 70.8% in non diabetic patients, the CABG and PES groups, respectively.
Interventions/ Test/ Factor being investigated	PCI with TAXUS Express Paclitaxel eluting stents (PES)
Comparisons	CABG
Length of Study/ Follow-up	1 year
Outcome measures studied	Primary outcome: Major adverse cardiac and cerebrovascular events (MACCE) included a composite of all cause death, cerebrovascular accident, or repeat revascularisation (any subsequent PCI or CABG procedure in any coronary vessel).
Results	
Effect Size	Results: In No diabetic patients (n=1348) Outcome: CABG (676) vs. PES (n=672); Death: 17/645 vs. 20/664; RR 1.14 (0.60-2.16) Cardiac death: 10/645 vs. 17/664; RR 1.65 (0.76-3.58) CVA: 14/645 VS. 3/664; RR 0.21 (0.06-0.72) MI: 19/645 vs. 32/664; RR 1.64 (0.94-2.86) Repeat revascularisation: 37/645 vs. 74/664; RR 1.94 (1.33-2.84) In Medically treated diabetes: (n=452) Outcome: CABG (n=221) vs. PES (n=231) Death: 13/204 vs. 19/227; RR 1.31 (0.67-2.59); p for interaction=0.75 Cardiac death: 8/204 vs. 16/227; RR 1.80 (0.79-4.11); p for interaction=0.86 CVA: 5/204 vs. 2/227; RR 0.36 (0.07-1.83); p for interaction=0.60 MI: 9/204 vs. 11/227; RR 1.10 (0.46-2.60); p for interaction=0.45 Repeat revascularisation: 13/204 vs. 46/227; RR 3.18 (1.77-5.71); p for interaction=0.13

Source of funding:

Funded by Boston Scientific Corporation, Natick, Massachussets

Does the study answer the question?/Further Comments	Yes.The presence of diabetes was associated with increased mortality after either revasctularisation treatment. sub group analyses suggests that the 1 year major adverse cardiac and cerebrovascular event rate was higher among diabetic patients with left main and/or 3 vessel disease treated with PES compared with CABG, driven by an increase in repeat revascularisation. However, death/stroke/MI was comparable between the 2 treatment options for diabetic and non diabetic patients. Authors note: Although further study is needed, these exploratory results may extend the evidence for PES use in selected patients with less complex left main and/or 3 vessel lesions.

Booth J;Clayton T;Pepper J;Nugara F;Flather M;Sigwart U;Stables RH;SoS I;

Randomized, controlled trial of coronary artery bypass surgery versus percutaneous coronary intervention in patients with multivessel coronary artery disease: six-year follow-up from the Stent or Surgery Trial (SoS)

Ref ID 267 **RID:** 592 2008 Jul 22

QUALITY

A. Selection bias (systematic differences between the comparison groups)

A4 Based on your answers t, in your opinion was selection bias present? If so, what is the likely direction of its effect?:

Low risk of bias **Direction =**

B. Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)

B4 Based on your answers to the above, in your opinion was performance bias present? If so, what is the likely direction of its effect?:

Low risk of bias **Direction =**

C. Attrition bias (systematic differences between the comparison groups with respect to loss of participants)

C4 Based on your answers to the above, in your opinion was attrition bias present? If so, what is the likely direction of its effect?:

Low risk of bias **Direction =**

D. Detection bias (bias in how outcomes are ascertained, diagnosed or verified)

D6 Based on your answers to the above, in your opinion was detection bias present? If so, what is the likely direction of its effect?:

Low risk of bias **Direction =**

Overall Study Quality -Strengths and Weaknesses:

Strengths*- Multi centre, randomisation method reported, allocation concealment reported, sample size calculation reported, baseline comparisons made, Numbers lost to follow reported (5 years- (1.8%) 9/479 in PCI and (3%)15/500 in CABG), Intention to treat analysis reported. Blind outcome assessment (A clinical events committee, consisting of study interventionists and surgeons, adjudicated all outcome measures. The members of the clinical events committee did not adjudicate patients treated at their own centres and were blinded to the randomisation allocation and of the identities of patients and centres).

Weakness- Patients aware of treatment allocation.

* This study reports 2 and 6 year follow-up of the SoS trial.

DETAILS

# of patients:

n=988 (n=488 in PCI and n=500 in CABG)

Prevalence (Diagnostic):

Patient Characteristics

Baseline characteristics:
Characteristics: PCI (n=488); CABG (n=500)
Men: 390 (80%); 392 (78%)
Age: 61; 62
Previous MI: 214 (44%); 234 (47%)
Type 1 diabetes: 19 (4%); 9 (2%)
Type 2 non-insulin dependent diabetes: 40 (10%); 65 (13%)
Hypertension: 212 (43%); 235 (47%)
CCS class IV: 94 (19%); 108 (22%)
CCS class III: 116 (24%); 133 (27%)
Two vessel disease: 303 (62%); 262 (52%)
Three vessel disease: 183 (38%); 236 (47%)
Diseased vessel territory
Left main stem: 4(1%); 3 (1%)
Left anterior descending (proximal): 235 (48%); 222 (44%)
Left anterior descending (other): 214(44%); 241 (48%)
Circumflex: 342 (70%); 374 (75%)
Right coronary artery: 361 (74%); 395 (79%)
One occluded vessel: 77 (16%); 70 (14%)
Two occluded vessels: 4(1%); 12 (2%)

Interventions/ Test/ Factor being investigated

PCI

Comparisons

CABG

Length of Study/ Follow-up

2 years and 5 years

Outcome measures studied

The primary outcome of the trial was the rate of repeat revascularisation after the index procedure. Secondary outcomes included death or non fatal Q-wave MI; all cause mortality, symptoms of angina, medication requirements.

Results

Effect Size

Results: At 2 years (median follow-up)
Outcome: PCI (n=488) vs. Surgery (n=500); Hazard ratio (95% CI); p value
Repeat revascularisation: 101 (20.7%) vs. 30 (6%); HR 3.85 (2.56 to 5.79); p<0.001
Death or MI: 46 (9.4%) vs. 49 (9.8%); HR 0.95 (0.63 to 1.42); p=0.80
Mortality: 22 (4.5%) vs. 8 (1.6%); HR 2.91 (1.29 to 6.53); p=0.01

At 2 years: Diabetes subgroup
Outcome: PCI (n=68) vs. CABG (n=74); Hazard ratio (95% CI)
Repeat revascularisation: 17 vs. 4; HR 5.25 (1.77 to 15.60)
Death or MI: 7 vs.9; HR 0.73 (0.27 to 1.97)
Mortality: 3 vs. 1; HR 3.11 (0.32 to 29.90)

At Median follow-up 6 years (maximum 8 years):
Outcome: PCI (n=479) vs. CABG (n=485); Hazard ratio (95% CI); p value
Death: 53 (10.9%) vs. 34 (6.8%); HR 1.66 (1.08 to 2.55); p=0.022
Cardiovascular death: 22 vs. 17
Non cardio vascular death*: 25 vs. 11
Unknown: 6 vs. 6
*Cancer was reported as the predominant cause of non cardiovascular death, affecting 20 patients in the PCI group compared with 8 in the CABG group. The types of cancer are wide ranging and where specified, include lung, gastric, oesophageal, ovarian, and lymphoma tumours. In the classification of the causes of death, the initial 30 of 87 deaths were adjudicated by a clinical events committee, whereas subsequent events were investigator reported. This may limit the reliability of an assessment of differences in cardiovascular and non cardiovascular.

Median follow-up 6 years: Mortality by subgroups-
Patients with diabetes*:
Outcome: PCI (n=68) vs. CABG (n=74); Hazard ratio (95% CI)
Deaths: 12 vs. 4; HR 3.52 (1.14 to 10.95)
* Among non diabetic patients, 9.8% of patients (41 of 420) died in the PCI group compared with 7% (30 of 426) in the CABG group. The statistical test for interaction gave little evidence that the treatment effect on mortality differed between diabetic and non diabetic patients (p=0.15).

No. of diseased vessels**:
2 vessels: PCI (n=305) vs. CABG (n=16); Hazard ratio (95% CI)
Death: 31 vs. 16; HR 1.72 (0.94 to 3.15)
3 vessels: PCI (n=183) vs. CABG (n=236); Hazard ratio (95% CI)
Death: 22 vs. 18; HR 1.64 (0.88 to 3.06)
** No sig. difference in mortality between 2 and 3 diseased vessels (p=0.91)

Source of funding:

The work was supported by funding from a consortium of stent manufacturers: Bard (now Medtronic), Guidant ACS, and Schneider (now Boston Scientific)

Does the study answer the question?/Further Comments

Yes. At a median follow-up of 6 years, there was significantly higher mortality in PCI compared to CABG. At 2 years follow-up repeat revascularisation was significantly higher in PCI for the entire group and also in the subgroup of patients with diabetes compared to CABG.

Buszman P;Wiernek S;Szymanski R;Bialkowska B;Buszman P;Fil W;Stables R;Bochenek A;Martin J;Tendera M;

Percutaneous versus surgical revascularization for multivessel coronary artery disease: a single center 10 year follow-up of SOS trial patients

Ref ID 9122 RID: 576 2009 Sep 1

QUALITY

A. Selection bias (systematic differences between the comparison groups)

A4 Based on your answers t, in your opinion was selection bias present? If so, what is the likely direction of its effect?:

Low risk of bias

Direction =

B. Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)

B4 Based on your answers to the above, in your opinion was performance bias present? If so, what is the likely direction of its effect?:

Low risk of bias

Direction =

C. Attrition bias (systematic differences between the comparison groups with respect to loss of participants)

C4 Based on your answers to the above, in your opinion was attrition bias present? If so, what is the likely direction of its effect?:

High risk of bias

Direction =

D. Detection bias (bias in how outcomes are ascertained, diagnosed or verified)

D6 Based on your answers to the above, in your opinion was detection bias present? If so, what is the likely direction of its effect?:

Low risk of bias.

Direction =

Overall Study Quality -Strengths and Weaknesses:

Strengths*- randomisation method reported, allocation concealment reported, baseline comparisons made, Numbers lost to follow reported (10 years- (36%)18/50 in PCI and (28%)14/50 in CABG), Intention to treat analysis reported. Blind outcome assessment (Adverse events were adjudicated by a Polish events committee during the main SoS study follow-up period. Subsequently, they were adjudicated by the committee chairman using the same guidelines. For repeat revascularisation, each post baseline procedure was considered, even if it was not the original lesion treated at baseline.).

Weakness - High attrition, patients aware of treatment allocation.

*This study is a single centre (Poland) 10 year follow-up of the SoS trial.

DETAILS

# of patients: N=100 (PCI (n=50); CABG (n=50)

Prevalence (Diagnostic):

Patient Characteristics

Baseline characteristics: (Of patients in one centre in the SoS trial)
Variables: PCI (n=50); CABG (n=50)
Male (%): 80; 78
Age (yrs): 54.7; 52.7
Previous MI (%): 38; 36

	Diabetes Mellitus (%): 14; 18 NYHA (%) NYHA I: 54; 50 NYHA II: 42; 42 NYHA III: 4; 6 NYHA IV: 0; 2 CCS (%) CCS 0:0; 0 CCS I: 8; 14 CCS II: 20; 32 CCS III: 66; 50 CCS IV: 6; 4 Unstable angina (%): 18; 20 2 vessel disease: 60; 58 3 vessel disease: 40; 42
Interventions/ Test/ Factor being investigated	PCI
Comparisons	CABG
Length of Study/ Follow-up	9.6±0.85 years
Outcome measures studied	Primary endpoint of the present study is the LVEF. Other endpoints include MACCE, severity of angina, survival and number of repeat revascularisation. MACCE were defined as death, stroke, and repeat revascularisation. All deaths were categorised to cardiac or non cardiac related.
Results	
Effect Size	Results: At 10 years Outcome: PCI (n=50) vs. CABG (n=50) Improvement in Severity of angina presented in CCS scale (% of patients)*: 88.9% vs. 84.38%; p=ns Death: 10 (20%) vs. 9 (18%); p=ns Repeat revascularisation: 21 (42%) vs. 9 (18%); p<0.05 MACCE**: 28 (56%) vs. 36 (72%); p<0.05 *Severity of angina was assessed in accordance with the Canadian Cardiovascular Society classification. **Analysing MACCE without repeat revascularisation, no statistical difference was observed between the two groups. Subgroup of patients with Diabetes: Outcome: PCI (n=7) vs. CABG (n=9) Death: 2 vs. 1 MI: 2 vs. 0 Stroke: 0 vs. 1 Repeat revascularisation: 3 vs.4 Total MACCE: 7 vs.6
Source of funding:	The SoS trial was supported by funding from a consortium of stent manufacturers: Bard (now Medtronic), Guidant ACS, and Schneider (now Boston Scientific)
Does the study answer the question?/Further Comments	Yes. There was no significant difference between PCI and CABG for death, angina severity. Increased repeat revascularisation occurred in the PCI compared to CABG. There was no difference between CABG and PCI diabetic cohorts for death, MI, stroke, repeat revascularisation and total MACCE.

Buszman PE;Kiesz SR;Bochenek A;Peszek PE;Szkrobka I;Debinski M;Bialkowska B;Dudek D;Gruszka A;Zurakowski A;Milewski K;Wilczynski M;Rzeszutko L;Buszman P;Szymszal J;Martin JL;Tendera M;

Acute and late outcomes of unprotected left main stenting in comparison with surgical revascularization

Ref ID 9132 **RID:** 626 2008 Feb 5

QUALITY

A. Selection bias (systematic differences between the comparison groups)

A4 Based on your answers t, in your opinion was selection bias present? If so, what is the likely direction of its effect?:

Unclear/unknown risk **Direction =**

B. Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)

B4 Based on your answers to the above, in your opinion was performance bias present? If so, what is the likely direction of its effect?:

Low risk of bias **Direction =**

C. Attrition bias (systematic differences between the comparison groups with respect to loss of participants)

C4 Based on your answers to the above, in your opinion was attrition bias present? If so, what is the likely direction of its effect?:

High risk of bias **Direction =**

D. Detection bias (bias in how outcomes are ascertained, diagnosed or verified)

D6 Based on your answers to the above, in your opinion was detection bias present? If so, what is the likely direction of its effect?:

Low risk of bias **Direction =**

Overall Study Quality -Strengths and Weaknesses:

Strengths*: Randomised, baseline comparisons made, blind outcome assessment for some outcomes (all clinical outcomes were analysed by the Clinical Event Committee. Echocardiographic and stress test recordings were read centrally by a group of independent investigators unaware of treatment assignment). Intention to treat analysis reported.
Weakness: allocation concealment not reported, nos. lost to follow-up not reported, small sample size.
*This study reports 1 year follow-up results of the LE MANS (study of unprotected Left main stenting versus bypass surgery) study.

DETAILS

# of patients: n=105 (n=52 in PCI and n=53 in CABG)

Prevalence (Diagnostic):

Patient Characteristics

Baseline characteristics:
Variables: PCI (n=52); CABG (n=53)
Age (yrs): 60.6; 61.3
Male (%): 60; 73
CCS class: 3.1±1.0; 2.8±1.0
Diabetes Mellitus: 19; 17
Hypertension (%): 75; 70
Previous MI:
STEMI (%): 25 ; 21
NSTEMI (%): 11; 11
Distal LM disease (%): 56; 60
No. of diseased vessels: 1.7±0.93; 2.08±0.83
1 vessel disease (%): 13; 6
2 vessel disease (%): 13; 6
3 vessel disease (%): 60 ;75
Complete revascularisation (%): 79; 89
Hospitalisation (days): 6.8±3.7 ;12.04±9.6

Inclusion criteria: Patients were enrolled with >50% narrowing of Unprotected left main coronary artery (ULMCA) , with or without multivessel coronary artery disease suitable for equal revascularisation both with PCI and CABG. All patients had to be symptomatic with documented myocardial ischemia.
Exclusion criteria included acute MI, total occlusion of left main, co morbid conditions, or coronary anatomic considerations that increased the surgical risk to a Euroscore of 8 or more, stroke or transient ischemic attack within 3 months, renal dysfunction, or contraindication to antiplatelet therapy.

Interventions/ Test/ Factor being investigated

PCI: Drug eluting stents (DES) were used for the left main with a reference diameter of <3.8 mm, and Bare metal stents (BMS) were implanted if the left main reference diameter was 3.8 mm or greater.

Comparisons

CABG: All but 1 operation were performed through a median sternotomy, with standard cardiopulmonary bypass and moderate systemic hypothermia

Length of Study/ Follow-up

1, 3, 6, and 12 months after the procedure.

Outcome measures studied

Primary endpoint: The change in LVEF assessed by 2 dimensional echocardiography 12 months after the index intervention.
Secondary endpoint: Secondary endpoints included 30 day and 1 year major adverse events (MAE) and major adverse cardiac and cerebrovascular events (MACCE), length of hospitalisation, exercise tolerance measured with electrocardiographic treadmill stress test along with angina severity according to the Canadian Cardiovascular Society classification after 1 year, total survival and freedom from MACCE, and target vessel failure (TVF) and revascularisation (TVR).

The MAE were defined as all-cause mortality, acute MI (defined as an increase in creatinine phosphokinase (CPK)-MB to higher than 3 times the upper limit of normal after PCI and 5 times after CABG), repeat revascularisation, acute heart failure (e.g. pulmonary oedema, cardiogenic shock), or low output syndrome requiring intravenous inotropic agents and/or intra-aortic balloon pump support, post-procedural complications leading to reintervention, stroke, arrhythmia (ventricular fibrillation, ventricular tachycardia, or atrial fibrillation), major bleeding requiring additional blood transfusion, and/or acute/sub acute in-stent thrombosis were considered MACCE. Target vessel failure was defined as any MACCE related to insufficient flow through the LMCA, and TVR as any repeat intervention (PCI or CABG) caused by narrowing of the LMCA. The incidence of stent thrombosis was evaluated in accordance with the Academic Research Consortium Definitions of Stent Thrombosis.

Results

Effect Size	Results: 1 year Outcome: CABG (n=53) vs. PCI (n=52) Death: 4 vs. 1 Non fatal MI: 3 vs. 1 Repeat revascularisation: 5 vs. 15 (p<0.01) Any MACCE: 13 vs. 16 Any MAE: 24 vs. 20 Rate of angina (based on CCS classification)*: 1.0 ±0.9 vs. 1.3±0.9 (p=0.11) Actuarial 1 year survival: 92.5% vs. 98.1% (p=0.37) MACCE free 1 year survival: 75.5% vs. 71.2%; p=0.29 Treadmill stress tests: 6.4±2.6 vs. 7.2±3.3 (p=0.53) *A significant reduction of angina severity (CCS classification) after 1 month was observed in both groups (p<0.001). Between the index procedure and 30 days later, there were no deaths in the PCI group and 2 deaths in the CABG group (p=0.16). PCI was associated with significantly shorter hospitalisation (6.8±3.7 days vs. 12.0±9.6 days; p=0.0007). Patients after PCI performed better in the treadmill stress test in the first month after the procedure.
Source of funding:	This study was sponsored by the Polish Ministry of Science and Informatics.
Does the study answer the question?/Further Comments	Yes. After 12 months, patients after PCI and CABG performed equally well on the treadmill stress tests. Both groups demonstrated similar improvement in angina and total and MACCE-free survival was comparable in the PCI and CABG groups, but there was a trend towards lower risk of death in the PCI group. Compared to CABG, PCI was associated with significantly shorter hospitalisation.

Cisowski M;Drzewiecki J;Drzewiecka-Gerber A;Jaklik A;Kruczak W;Szczeklik M;Bochenek A;

Primary stenting versus MIDCAB: preliminary report-comparision of two methods of revascularization in single left anterior descending coronary artery stenosis

Ref ID 9147 **RID:** 594 2002 Oct

QUALITY

A. Selection bias (systematic differences between the comparison groups)

A4 Based on your answers t, in your opinion was selection bias present? If so, what is the likely direction of its effect?:

Unclear/unknown risk **Direction =**

B. Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)

B4 Based on your answers to the above, in your opinion was performance bias present? If so, what is the likely direction of its effect?:

Low risk of bias **Direction =**

C. Attrition bias (systematic differences between the comparison groups with respect to loss of participants)

C4 Based on your answers to the above, in your opinion was attrition bias present? If so, what is the likely direction of its effect?:

High risk of bias

Direction =

D. Detection bias (bias in how outcomes are ascertained, diagnosed or verified)

D6 Based on your answers to the above, in your opinion was detection bias present? If so, what is the likely direction of its effect?:

Low risk of bias

Direction =

Overall Study Quality -Strengths and Weaknesses:

Strengths – Randomised, comparable at baseline, blind outcome assessment.
Weaknesses – randomisation and allocation concealment methods not reported, high attrition
At 1 yr follow-up: 44% in PCI; 52% in E-ACAB)

DETAILS

# of patients:

N=100 (PCI with direct primary stenting (n=50), E-ACAB (endoscopic atraumatic coronary artery bypass grafting [LITA-to-LAD]) (n=50))

Prevalence (Diagnostic):

Patient Characteristics

Baseline characteristics:
Age(y) 53.3 ±10.2 ; 54.1±9.1
Sex (male/female) 42/8 ; 41/9
Stable angina pectoris
CCS1 5(10%) ; 3(6%)
CCS2 21(42%) ; 20(40%)
CCS3 18(36%) ; 23(46%)
CCS4 6(12%) ; 4(8%)
Unstable angina pectoris 5(10%) ; 4(8%)
Risk factors
Smoking 26(52%) ; 24(48%)
Insulin-dependent diabetes 4(8%) ; 3(6%)
Family history 20(40%) ; 22(44%)
Hypertension 26(52%) ; 28(56%)
Hypercholesterolemia 39(78%) ; 38(76%)
Obesity (BMI>30) 13(26%) ; 10(20%)

Inclusion criteria:
Confirmed angina pectoris, CCS class II or higher, stenosis >=70% in promixal parts of LAD, artery diameter >=3mm, lesion length >=20mm, no significant lesions in other arteries, EF(ejection fraction) >=40%
Exclusion criteria:
Recent MI, recent non-Q MI with EF <40%, LAD occlusion (C-type lesion), significant calcification of stenotic lesion, history of previous PCI or cardiac surgery, any concomitant valvular disease, insulin-dependent diabetes mellitus, pleural adhesions

Interventions/ Test/ Factor being investigated

PCI with direct primary stenting

Comparisons

minimally invasive LITA-to-LAD bypass grafting (E-ACAB)

Length of Study/ Follow-up

Follow-up at 1, 6, 12 and 24 months

Outcome measures studied

Death, myocardial infarction, reoccurrence of angina pectoris (ie a major adverse coronary event [MACE] that required hospital treatment and repeat revascularisation of the target vessel). The primary and secondary outcomes were not reported.

Results

Effect Size

Results:
6 months follow up
Outcome: PCI (n=50) vs. E-ACAB (n=50) (%)
Death: 0 ; 0
Myocardial infarction: 0 ; 0
MACE: 11(22%) ; 0; p<0.001
Free of angina symptoms: 36(72%) ; 49(98%) ; p<0.01
CCS1 2(4%) ; 1(2%)
CCS2: 5(10%) ; 0
CCS3: 6(12%) ; 0 ; p<0.05
CCS4: 1(2%) ; 0
Reintervention: 6 (12%) vs. 1 (2%); p<0.05

One year follow up
Outcome: PCI (n=28) vs. E-ACAB (n=24) (%)
Death: 1(3.6%) ; 0
Myocardial infarction: 0 ; 0
MACE: 1(3.6%) ; 0
Free of angina symptoms: 21(75%) ; 24(100%) ; p<0.01 (Fisher)
CCS1 2(7.1%) ; 0
CCS2: 3(10.7%) ; 0
CCS3: 2(7.1%) ; 0
CCS4: 1(3.6%) ; 0

Source of funding:

The funding for this study was not reported

Does the study answer the question?/Further Comments

Yes. The study showed that revascularisation of isolated proximal LAD stenosis using E-ACAB resulted in low patient morbidity and mortality rates as well as good intermediate-term results. Both angiographic analysis and clinical outcome confirmed that repeated revascularisation was required significantly more often after PCI than after endoscopic atraumatic coronary artery bypass grafting, and was followed by more recurrence of angina pectoris.

Drenth DJ;Veeger NJ;Grandjean JG;Mariani MA;van Boven AJ;Boonstra PW;

Isolated high-grade lesion of the proximal LAD: a stent or off-pump LIMA?

Ref ID 988 RID: 596 2004 Apr

QUALITY

A. Selection bias (systematic differences between the comparison groups)

A4 Based on your answers t, in your opinion was selection bias present? If so, what is the likely direction of its effect?:

Unclear/unknown risk

Direction =

B. Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)

B4 Based on your answers to the above, in your opinion was performance bias present? If so, what is the likely direction of its effect?:

Low risk of bias

Direction =

C. Attrition bias (systematic differences between the comparison groups with respect to loss of participants)

C4 Based on your answers to the above, in your opinion was attrition bias present? If so, what is the likely direction of its effect?:

Low risk of bias

Direction =

D. Detection bias (bias in how outcomes are ascertained, diagnosed or verified)

D6 Based on your answers to the above, in your opinion was detection bias present? If so, what is the likely direction of its effect?:

Low risk of bias

Direction =

Overall Study Quality -Strengths and Weaknesses:

Strengths: Single centre, prospective, randomised study. Baseline comparisons made.Nos. lost to follow-up reported (3/51(5.8%) in MICAB and 0/51(0%) for PTCA +stenting). Intention to treat analysis reported. Clinical events adjudicated by an event monitoring committee of an experienced cardiologist and cardiac surgeon.
Weakness: Allocation concealment not reported. No formal sample size calculation used. *
*This study is a 4 year follow-up of the study by Derk.J.Drenth 2002 (Ref ID 2597)

DETAILS

# of patients:

n=102 (n=51 in MICAB group and n=51 in PTCA group).

Prevalence (Diagnostic):

Patient Characteristics

Baseline characteristics:
Characteristic: MICAB vs. PTCA +stenting
Age (yrs): 60±1.6; 61±1.3
Female: 22%; 25%
Diabetes: 8%; 18%
Hypertension: 16%; 33%
Previous MI: 24%; 18%
Duration of angina pectoris (months): 16; 16
CCS classification:
Class II- 31% ;27%
Class III- 24% ; 46%

	Class IV- 45% ; 27% Triple therapy No BB/CCB/L.A. Nitrate: 6% ; 6% One of BB/CCB/LA nitrates: 33% ;31% At least 2 of BB/CCB/LA nitrates: 61% ; 63% Percentage stenosis: 75±1.5 ; 75±1.7 Inclusion criteria: Patients with chronic stable angina pectoris of CCS class 2 or greater caused by an isolated typeB2 or C lesion of the proximal LAD were selected. Patients had to be eligible for both MICAB and PTCA with primary stenting by unanimous forum decision of cardiologists and cardiac surgeons. Exclusion criteria: Patients with overt congestive heart failure, previous PTCA or ACBG procedures, previous MI or creatine kinase MB(CK-MB) increase of twice the normal range in the last 2 weeks, congenital heart disease, history of cerebrovascular accident, or need for a concomitant operation were excluded.
Interventions/ Test/ Factor being investigated	PTCA with stenting. In the PTCA group, stent implantation was performed after predilatation.
Comparisons	MICAB (Minimally invasive coronary artery bypass grafting). Off pump coronary artery bypass grafting.
Length of Study/ Follow-up	4 years (90% mid-range 3.0 -5.1 years).
Outcome measures studied	Primary endpoint:4 year freedom from MACCEs. MACCEs were death, MI, stroke and need for repeat target vessel revascularisation (TVR). Secondary endpoints were angina pectoris class (according to the CCS) and need for anti anginal medication at 4 year follow-up.
Results	
Effect Size	MICAB- N=51[3 patients assigned to MICAB underwent PCI] Results: Outcome: PCI (n=51) vs. Surgery (n=51) Cardiac death*: 0 vs. 2; p=0.50 Non cardiac death: 0 vs. 1;p=1.00 MI: 5 vs. 1; p= 0.20 Repeat target vessel revascularisation (TVR): 8 vs. 2; p=0.09 Non-TVR: 1 vs. 1; p=1.00 CCS classification: (p=0.03) Class 0 (%): 67 vs.85 Class 2 or more (%): 33 vs. 15 Triple therapy: (p=0.002) No BB/CCB/L.A nitrates: 24 vs. 29 One of BB/CCB/L.A. Nitrates: 41 vs. 65 At least 2 of BB/CCB/L.A Nitrates: 35 vs. 6 *One patient died 3 days after surgery due to ongoing inferoposterior MI. autopsy revealed a patent anastomosis but a 40% stenosis in the right coronary artery that was judged insignificant prior to the operation. Another patient died 1 week after discharge from hospital due to an unknown cause after an uncomplicated operation and convalescent period. The third patient died due to a pancreatic tumour 3.5 years after the initial operation.
Source of funding:	Cordis Europe, Waterloo, Belgium.

Does the study answer the question?/Further Comments

Yes. All cause mortality did not differ significantly between both treatment groups, although 3 patients died after surgery. Although the patients under investigation had isolated LAD disease at the start of the study, progression of their disease resulted in an additional non-TVR once in both treatment groups. TVR was clinically driven and not angiographically driven. More patients were free from angina 4 years after surgery 85% versus 67% (p=0.03). The need for antinaginal medication was also lower after surgery (p=0.002).

Drenth DJ;Veeger NJ;Middel B;Zijlstra F;Boonstra PW;

Comparison of late (four years) functional health status between percutaneous transluminal angioplasty intervention and off-pump left internal mammary artery bypass grafting for isolated high-grade narrowing of the proximal left anterior descending corona

Ref ID 4620 **RID:** 511 2004

QUALITY

A. Selection bias (systematic differences between the comparison groups)

A4 Based on your answers t, in your opinion was selection bias present? If so, what is the likely direction of its effect?:

Unclear/unknown risk **Direction =**

B. Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)

B4 Based on your answers to the above, in your opinion was performance bias present? If so, what is the likely direction of its effect?:

Low risk of bias **Direction =**

C. Attrition bias (systematic differences between the comparison groups with respect to loss of participants)

C4 Based on your answers to the above, in your opinion was attrition bias present? If so, what is the likely direction of its effect?:

Low risk of bias **Direction =**

D. Detection bias (bias in how outcomes are ascertained, diagnosed or verified)

D6 Based on your answers to the above, in your opinion was detection bias present? If so, what is the likely direction of its effect?:

Low risk of bias **Direction =**

Overall Study Quality -Strengths and Weaknesses:

Strengths: Single centre, prospective, randomised study. Baseline comparisons made. Nos. lost to follow-up reported (3/51(5.8%) in MICAB and 0/51(0%) for PTCA +stenting). Intention to treat analysis reported. Clinical events adjudicated by an event monitoring committee of an experienced cardiologist and cardiac surgeon.

Weakness: Allocation concealment not reported. No formal sample size calculation used. *
*This study is a 4 year follow-up of the study by Derk.J.Drenth 2002 (Ref ID 2597)

DETAILS

# of patients:

n=102 (n=51 in MICAB and n=51 in PTCA +stenting)

Prevalence (Diagnostic):

Patient Characteristics

Baseline characteristics:
Characteristic: MICAB vs. PTCA +stenting
Age (yrs): 60±1.6; 61±1.3
Female: 22%; 25%
Diabetes: 8%; 18%
Hypertension: 16%; 33%
Previous MI: 24%; 18%
Duration of angina pectoris (months): 16; 16
CCS classification:
Class II- 31% ;27%
Class III- 24% ; 46%
Class IV- 45% ; 27%
Triple therapy
No BB/CCB/L.A. Nitrate: 6% ; 6%
One of BB/CCB/LA nitrates: 33% ;31%
At least 2 of BB/CCB/LA nitrates: 61% ; 63%
Percentage stenosis: 75±1.5 ; 75±1.7

Interventions/ Test/ Factor being investigated

PTCA (Percutaneous Transluminal coronary angioplasty) with stenting technique.

Comparisons

MICAB (Minimally invasive coronary artery bypass grafting). MICAB was performed through a small left anterior thoracotomy without cardiopulmonary bypass.

Length of Study/ Follow-up

Mean follow-up time was 4 years (range 3-5)

Outcome measures studied

Major adverse cardiac and cerebrovascular events (MACCEs), such as cardiac death, MI, stroke and need for repeat target vessel revascularisation. Secondary endpoints were angina pectoris class and need for antianginal medication at 4 year follow-up. Assessments of Functional Health Status (FHS) were performed with mailed questionnaires complimentary to the clinical outcome at 4 year follow-up.

Results

Effect Size

Comparison of FHS with Short form-36 (SF-36)* and Minnesota Living with heart failure questionnaire (MLHFQ) ** between angioplasty and surgery..
Variable: PTCA +stenting (n=51) vs. MICAB (n=48)
Short form-36 questionairre
Physical functioning: 77 vs. 81 ;p=0.48
Social functioning: 87 vs. 87 ;p=0.89
Role-physical: 76 vs. 78;p=0.81
Role-emotional: 87 vs. 85;p=0.98
Mental health:: 82 vs. 81; p=0.86
Vitality:70 vs. 70;p=0.96
Bodily pain:90 vs.88; p=0.97
General health perception: 69 vs. 70;p=0.78
Minnesota Living with heart failure questionnaire
Physical dimension: 5.9 vs. 3.8; p=0.56

*SF-36 comprises 36 items covering the above 8 domains. These items were scored on a 0 to 100 range. Next, the items in the same domain were averaged together to create domain scores. For each domain, a high score indicates a more favourable health status (i.e., better physical functioning, less emotional problems, less pain and so forth).For the physical domain of the MLHFQ, 8 items were scored from 0 to 5. These 8 items were added to a domain score of 0 to 40, with a low score indicating a more favourable FHS.

Source of funding: Cordis Europe, Waterloo, Belgium.

Does the study answer the question?/Further Comments Yes. Functional Health Status did not differ between angioplasty and surgery

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Drenth DJ;Veeger NJ;Winter JB;Grandjean JG;Mariani MA;Boven van AJ;Boonstra PW;

A prospective randomized trial comparing stenting with off-pump coronary surgery for high-grade stenosis in the proximal left anterior descending coronary artery: three-year follow-up

Ref ID 1165 **RID:** 510 2002 Dec 4

QUALITY

A. Selection bias (systematic differences between the comparison groups)

A4 Based on your answers t, in your opinion was selection bias present? If so, what is the likely direction of its effect?:

Unclear/unknown risk **Direction =**

B. Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)

B4 Based on your answers to the above, in your opinion was performance bias present? If so, what is the likely direction of its effect?:

Low risk of bias **Direction =**

C. Attrition bias (systematic differences between the comparison groups with respect to loss of participants)

C4 Based on your answers to the above, in your opinion was attrition bias present? If so, what is the likely direction of its effect?:

Low risk of bias **Direction =**

D. Detection bias (bias in how outcomes are ascertained, diagnosed or verified)

D6 Based on your answers to the above, in your opinion was detection bias present? If so, what is the likely direction of its effect?:

Low risk of bias.

Direction =

Overall Study Quality -Strengths and Weaknesses:

Strengths: Single centre, prospective, randomised study. Baseline comparisons made. Nos. lost to follow-up reported (3/51(5.8%) in surgery and 0/51(0%) for PTCA +stenting). Intention to treat analysis reported. Clinical events adjudicated by an event monitoring committee of an experienced cardiologist and cardiac surgeon.
Weakness: Allocation concealment not reported. No formal sample size calculation used. . *
*This study is a 3 year follow-up of the study by Derk.J.Drenth 2002 (Ref ID 2597)

DETAILS

# of patients:

n=102 (n=51 in surgery and n=51 in PTCA+stenting)

Prevalence (Diagnostic):

Patient Characteristics

Baseline characteristics:
Characteristic: MICAB vs. PTCA +stenting
Age (yrs): 60±1.6; 61±1.3
Female: 22%; 25%
Diabetes: 8%; 18%
Hypertension: 16%; 33%
Previous MI: 24%; 18%
Duration of angina pectoris (months): 16; 16
CCS classification:
Class II- 31% ;27%
Class III- 24% ; 46%
Class IV- 45% ; 27%
Triple therapy
No BB/CCB/L.A. Nitrate: 6% ; 6%
One of BB/CCB/LA nitrates: 33% ;31%
At least 2 of BB/CCB/LA nitrates: 61% ; 63%
Percentage stenosis: 75±1.5 ; 75±1.7

Baseline demographic and clinical characteristics of both groups did not significantly differ between both treatments.

Inclusion criteria:
Patients with chronic stable angina pectoris of CCS class 2 or greater caused by an isolated typeB2 or C lesion of the proximal LAD were selected. Patients had to be eligible for both MICAB and PTCA with primary stenting by unanimous forum decision of cardiologists and cardiac surgeons.

Exclusion criteria:
Patients with overt congestive heart failure, previous PTCA or ACBG procedures, previous MI or creatine kinase MB(CK-MB) increase of twice the normal range in the last 2 weeks, congenital heart disease, history of cerebrovascular accident, or need for a concomitant operation were excluded.

Interventions/ Test/ Factor being investigated

PTCA with stenting

Comparisons

MICAB (Minimally invasive coronary artery bypass grafting) . Off pump coronary artery bypass surgery was performed through a small left anterolateral thoracotomy on the beating heart without cardiopulmonary bypass using a mechanical coronary stabiliser.

Length of Study/ Follow-up

Mean follow-up was 2.9 years (90% mid-range, 1.9 to 3.9 years)

Outcome measures studied

Primary endpoint was 3 year freedom from major cardiac and cerebrovascular events (MACCEs). The MACCE were death, MI, stroke, and need for repeat target vessel revascularisation (TVR). The TVR was performed only in patients with angiographic restenosis of more than 50% in combination with objective signs of myocardial ischemia. Secondary endpoints were angina pectoris class, use of antinaginal medication, other clinical events and MACCE without revascularisation.

Results

Effect Size

Results:

Outcome: PCI (n=51) vs. Surgery (n=51)
Death*: 0 vs. 2 ;p=0.50
MI: 5 vs. 1; p=0.21
TVR: 8 vs. 2; p=0.09
CCS classification (%): (p=0.02)
Class 0: 65 vs. 88
Class 1: 2 vs. 4
Class 2: 21 vs. 4
Class 3: 12 vs. 4
Class 4: 0 vs. 0
Triple therapy: (p=0.01)
No BB/CCB/L.A.nitrates: 28% vs. 31%
One of BB/CCB/L.A. nitrates: 39% vs. 48%
Atleast 2 of BB/CCB/L.A. Nitrates: 33% vs. 21%
*After surgery 2 patients died. One patient died three days postoperatively due to an ongoing inferoposterior myocardial infarction by unknown causes. Autopsy showed a patent anastomosis of the left internal mammarian artery to the LAD, but revealed a proximal luminal diameter of 40% in the right coronary artery already known from the pre-operative angiography but not identified as significantly stenotic. One week after discharge, the other patient died at home for unknown reasons after an uncomplicated operation and hospitalisation period.

Source of funding:

Cordis Europe, Waterloo, Belgium sponsored the study in part.

Does the study answer the question?/Further Comments

Yes. Authors conclusion- Incidence of MACCE was 23.5% after PCI and 9.8% after surgery (p=0.07). After surgery a significantly lower anginal class (p=0.02) and need for antianginal medication (p=0.01) was found compared to PCI. Target vessel revascularisation was 15.7% after PCI and 4.1% after surgery (p=0.09).

Drenth DJ;Winter JB;Veeger NJGM;Monnink SHJ;Van B;Grandjean JG;Mariani MA;Boonstra PW;

Minimally invasive coronary artery bypass grafting versus percutaneous transluminal coronary angioplasty with stenting in isolated high-grade stenosis of the proximal left anterior descending coronary artery: Six months' angiographic and clinical follow-u

Ref ID 2597 **RID:** 491 2002

QUALITY

A. Selection bias (systematic differences between the comparison groups)

A4 Based on your answers t, in your opinion was selection bias present? If so, what is the likely direction of its effect?:

Unclear/unknown risk

Direction =

B. Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)

B4 Based on your answers to the above, in your opinion was performance bias present? If so, what is the likely direction of its effect?:

Low risk of bias

Direction =

C. Attrition bias (systematic differences between the comparison groups with respect to loss of participants)

C4 Based on your answers to the above, in your opinion was attrition bias present? If so, what is the likely direction of its effect?:

Low risk of bias

Direction =

D. Detection bias (bias in how outcomes are ascertained, diagnosed or verified)

D6 Based on your answers to the above, in your opinion was detection bias present? If so, what is the likely direction of its effect?:

Low risk of bias

Direction =

Overall Study Quality -Strengths and Weaknesses:

Strengths: Single centre, prospective, randomised study.Baseline comparisons made. Nos. lost to follow-up reported (2/51* (3.92%) in MICAB and 0/51 (0%) for PTCA +stenting). Intention to treat analysis reported. Blind outcome assessment (Clinical events adjudicated by an event monitoring committee of an experienced cardiologist and cardiac surgeon.)
Weakness: Allocation concealment not reported. No formal sample size calculation used.
*Six months follow-up was completed for 100 patients, and after surgical intervention, 2 patients died.

DETAILS

# of patients:

n=102 (n=51 in MICAB and n=51 in PTCA+stenting)

Prevalence (Diagnostic):

Patient Characteristics

Baseline characteristics:
Characteristic: MICAB vs. PTCA +stenting
Age (yrs): 60±1.6; 61±1.3
Female: 22%; 25%
Diabetes: 8%; 18%
Hypertension: 16%; 33%
Previous MI: 24%; 18%
Duration of angina pectoris (months): 16; 16
CCS classification:
Class II- 31% ;27%

	Class III- 24% ; 46% Class IV- 45% ; 27% Triple therapy No BB/CCB/L.A. Nitrate: 6% ; 6% One of BB/CCB/LA nitrates: 33% ;31% At least 2 of BB/CCB/LA nitrates: 61% ; 63% Percentage stenosis: 75±1.5 ; 75±1.7 Inclusion criteria: Patients with chronic stable angina pectoris of CCS class 2 or greater caused by an isolated type B2 or C lesion of the proximal LAD were selected. Patients had to be eligible for both MICAB and PTCA with primary stenting by unanimous forum decision of cardiologists and cardiac surgeons. Exclusion criteria: Patients with overt congestive heart failure, previous PTCA or CABG procedures, previous MI or creatine kinase MB (CK-MB) increase of twice the normal range in the last 2 weeks, congenital heart disease, history of cerebrovascular accident, or need for a concomitant operation were excluded.
Interventions/ Test/ Factor being investigated	PTCA (Percutaneous Transluminal coronary angioplasty) with stenting technique.
Comparisons	MICAB (Minimally invasive coronary artery bypass grafting). MICAB was performed through a small left anterior thoracotomy without cardiopulmonary bypass.
Length of Study/ Follow-up	6 months.
Outcome measures studied	Primary endpoint: Quantitative angiographic outcome at 6 months. Secondary endpoint: Major adverse cardiac or cerebrovascular events (MACCEs), angina pectoris status, use of medication, need for repeat target vessel revascularisation and hospitalisation time. MACCEs were cardiac death, MI, and cerebrovascular accident.
Results	
Effect Size	Results: (6 months) Outcome: MICAB (n=51) vs. PTCA +stenting (n=51) Death: 2 vs. 0; p=0.50 Non fatal MI:1 vs. 5 ;p=0.21 Cerebrovascular accident: 0 vs. 1;p=1.00 Hospitalisation for unstable angina pectoris: 1 vs. 2 ;p=1.00 Repeat revascularisation: 2 vs. 4; p=0.68 Return of angina pectoris:3 vs. 5 ; p=0.72 Patients clinical characteristics at 6 months: CCS classification: MICAB vs. PTCA +stenting (p=0.25) Class 0 : 92% vs. 80% Class 1: 2% vs. 10% Class 2: 6% vs. 8% Class 3: 0% vs. 2% Class 4: 0% vs. 0% Positive exercise test: 12% vs. 20%;p=0.41 Peak exercise test (w): 148 ±6.8 vs. 150 ±5.9 ;p=0.83 Triple therapy:(p=0.11) No BB/CCB/LA nitrates: 31% vs. 18% One of BB/CCB/LA nitrates: 43% vs. 37% At least 2 of BB/CCB/LA nitrates: 26% vs. 45%
Source of funding:	This study was supported in part by Cordis Europe, Waterloo, Belgium.

Does the study answer the question?/Further Comments

Yes. At 6 months clinical outcomes did not differ significantly between MICAB and PTCA among patients with isolated high grade stenosis (American Cardiology/American Heart Association classification type B2 or C) of the proximal left anterior descending coronary artery. CCS status, exercise testing with a bicycle stress test, and maximal workload capacity did not differ between the 2 groups. Use of antianginal drugs did not significantly differ although a slight trend of less need for antianginal drugs was found after MICAB.

Eefting F;Nathoe H;van DD;Jansen E;Lahpor J;Stella P;Suyker W;Diephuis J;Suryapranata H;Ernst S;Borst C;Buskens E;Grobbee D;de JP;

Randomized comparison between stenting and off-pump bypass surgery in patients referred for angioplasty

Ref ID 1030 **RID:** 567 2003 Dec 9

QUALITY

A. Selection bias (systematic differences between the comparison groups)

A4 Based on your answers t, in your opinion was selection bias present? If so, what is the likely direction of its effect?:

Low risk of bias **Direction =**

B. Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)

B4 Based on your answers to the above, in your opinion was performance bias present? If so, what is the likely direction of its effect?:

Low risk of bias **Direction =** An independent committee which was blind to the treatment received by each patient, evaluated all events.

C. Attrition bias (systematic differences between the comparison groups with respect to loss of participants)

C4 Based on your answers to the above, in your opinion was attrition bias present? If so, what is the likely direction of its effect?:

Low risk of bias **Direction =**

D. Detection bias (bias in how outcomes are ascertained, diagnosed or verified)

D6 Based on your answers to the above, in your opinion was detection bias present? If so, what is the likely direction of its effect?:

low risk **Direction =**

Overall Study Quality -Strengths and Weaknesses:

Method of Randomistion and allocation concealment reported.No loss to follow up. Analysis was conducted on an intent-to-treat basis. An independent committee blinded to the treatment allocation evaluated all events.Risk of bias was low

DETAILS

# of patients: n=280 (n=138 to stent group and n=142 to off-pump group)

Prevalence (Diagnostic):

Patient Characteristics

	Stent (n=138)	Off-Pump (n=142)	P
Age, y	60.3 (9.1)	58.9 (10.0)	0.13
Male, %	70	72	0.78
Stable angina CCS I or II, %	16	27	0.05
Stable angina CCS III or IV, %	53	39	0.02
Unstable angina, Braunwald (I–IIB), %	30	34	0.64
Previous conditions			
Stroke, %	1	2	0.77
MI, %	25	23	0.78
Coronary angioplasty, %	4	5	0.82
Peripheral arterial disease, %	7	7	0.95
Risk factors			
Hypertension, %	33	31	
0.67			
Hypercholesterolemia, %	59	60	0.94
Diabetes, %	9	14	0.23
Family history %	60	62	0.75
Currently smoking, %	25	19	0.20
Quetelet index _30 kg/m2, %	17	15	
0.55			
Creatinine, mg/dL	1.00	1.04	0.09
No. of diseased vessels, %			
One	68	74	0.28
Two	30	24	0.22
Three	1	2	0.68
Coronary artery with >50% stenosis, %			
Left anterior descending	88	90	0.51
Left circumflex	17	18	0.72
Right coronary	27	20	0.16
No. of treated segments	1.48	1.50	0.39
Lesion type, %			
A	15	25	0.06
B1	44	36	0.16
B2	21	22	0.95
C 21 17 0.87			
Normal ventricular function, %	91	89	
0.16			

Interventions/ Test/ Factor being investigated Stenting. "Stenting was performed by use of standard techniques." No further information provided.

Comparisons Stenting versus off-pump bypass surgery (Off pump surgery was performed by use of the "Octopus" tissue stabilizer.)

Length of Study/ Follow-up 1 year post randomisation

Outcome measures studied The primary end point was freedom from all-cause death, stroke, acute MI, and repeat revascularization at 12 months. Secondary end points were survival free of stroke and acute MI, freedom from angina and medication, quality of life, and cost-effectiveness.

Results

Effect Size

7 patients assigned to stenting did not undergo the assigned treatment; 5 underwent balloon angioplasty and 2 on-pump surgery. 6 patients randomised to off-pump surgery did not undergo the assigned treatment; 2 underwent on-pump surgery and 4 angioplasty.

Clinical events

	Stent	Off-Pump	Relative risk (95% CI
	(n_138)	(n_142)	
Events at 1 y			
Mortality	0 (0.0)	4 (2.8)	
Cardiovascular	0 (0.0)	2 (1.4)	
Other	0 (0.0)	2 (1.4)	
Stroke	0 (0.0)	0 (0.0)	
MI	6 (4.4)	7 (4.9)	1.24 (0.39–3.95)
Repeated revascularization	21 (15.2)	6 (4.2)	4.80 (1.41–16.34)
CABG	6 (4.4)	1 (0.7)	
PTCA	15 (10.9)	5 (3.5)	3.43 (0.96–12.20)
Any event occurred	27 (19.6)	17 (12.0)	1.72 (0.87–3.37)
Event-free survival	118(85.5)	130(91.5)	0.93(0.86-1.02)

MI by Q-wave and non Q-wave
An acute MI occurred in 6 patients in the stent group (Q-wave, 4; non–Q-wave, 2) and in 7 in the off-pump group (Q-wave, 5; non–Q-wave, 2).

Secondary outcomes

Quality of life, symptoms and use of medication at 1 year

Quality-of-life domains*	Stent	Off-pump	p value
Physical functioning	81.0	83.7	0.25
Role physical	69.3	69.8	0.71
Role emotional	77.1	82.4	0.26
Pain	82.4	82.4	0.89
Vitality	62.4	66.5	0.12
Social	80.5	81.9	0.31
General health perception	61.6	66.9	0.03
General mental health	75.2	77.8	0.39
Free of angina, n (%)	108 (78.3)	120 (87.0)	0.06
Free of antianginal medication, n (%)	57 (41.3)	79 (57.2)	0.01

*Quality-of-life assessment by the Short Form-36 generic instrument: scores range from 0 (worst) to 100 (best imaginable health status). n denotes number of patients, with percentage in parenthesis.

At 1 month, quality of life (EQ-5D) was significantly higher after stenting than after off-pump surgery but was
comparable at 1 year.

Source of funding:

The Netherlands National Health Insurance Council.

Does the study answer the question?/Further Comments

Yes. There was no difference in event-free survival after stenting and off-pump surgery at 1 year. At one year quality of life was similar between the two groups.

Goy JJ;Eeckhout E;Burnand B;Vogt P;Stauffer JC;Hurni M;Stumpe F;Ruchat P;Sadeghi H;Kappenberger L;

Coronary angioplasty versus left internal mammary artery grafting for isolated proximal left anterior descending artery stenosis

Ref ID 9161 **RID:** 686 1994 Jun 11

QUALITY

A. Selection bias (systematic differences between the comparison groups)

A4 Based on your answers t, in your opinion was selection bias present? If so, what is the likely direction of its effect?:

Unclear/unknown risk

Direction = Although both patients and clinicians could not be blinded to type of treatment it is not clear whether the investigator

B. Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)

B4 Based on your answers to the above, in your opinion was performance bias present? If so, what is the likely direction of its effect?:

Low risk of bias

Direction =

C. Attrition bias (systematic differences between the comparison groups with respect to loss of participants)

C4 Based on your answers to the above, in your opinion was attrition bias present? If so, what is the likely direction of its effect?:

Low risk of bias

Direction =

D. Detection bias (bias in how outcomes are ascertained, diagnosed or verified)

D6 Based on your answers to the above, in your opinion was detection bias present? If so, what is the likely direction of its effect?:

Low risk.

Direction =

Overall Study Quality -Strengths and Weaknesses:

No loss to follow-up. An intent-to-treat analysis was conducted. The risk of bias is low due to well described methods of randomisation. However, it is unclear whether the investigator was independent and blind to treatment allocation.

DETAILS

# of patients: n=134 (n=66 in CABG group and n=68 in PTCA group)

Prevalence (Diagnostic):

Patient Characteristics

Patients had left anterior descending artery stenosis and normal left ventricular function.

	CABG N=66	PTCA n=68
Age (yr) *	54(52-57)	57(54-60)
Sex (M/F)	80/20	80/20
Angina functional class		
I	0	1
II	14	7
III	45	49
IV	33	31
Unstable	8	12
Drugs		
B-blockers	61	71
Calcium antagonists	76	84
Nitrates	89	91
Molsidomine	6	4
Risk factors		
Current smoker	52	59
Diabetes	12	12
Family history of CAD	48	50
Hypertension	41	46
Hyperlipidaemia	52	50
Percentage stenosis*		
Before procedure	79(78-80)	77(76-78)
After procedure	ND	25(23-27)
Lesion type		
A	46	59
B	30	29
C	24	12

ND: Not done. * Mean (95% CI)

Interventions/ Test/ Factor being investigated

Percutaneous transluminal coronary angioplasty (PTCA). Standard techniqures with over-the-wire or monorail balloon catheters.

Comparisons

PTCA versus CABG.

Length of Study/ Follow-up

Median follow-up of 24 months, interquartile range 12 to 36 months.

Outcome measures studied

The primary endpoint was a composite of procedure-related cardiac death, myocardial infarction, and the need for repeat revascularisation. Secondary outcome measures were angina functional class, improvement in exercise tolerance, clinical need for repeat angiography and the postprocedureal antianginal drug regimen.

Results

Effect Size

	CABG N=66	PTCA n=68	p
Cardiac death	1	0	0.49
Myocardial infarction			
Q-wave	1	2	
Non Q-wave	1	6	
Total	2	8	0.09
Revascularisation			
CABG	0	9	
PTCA	2	8	
Total	2	17	<0.01
Any composite primary Endpoint *	5	25	<0.01

*Relative risk: 4.4(3.0-6.3)

Secondary outcomes

CCS angina functional class and exercise testing
Assessment of both these outcomes in both treatment groups revealed no differences before treatment or during follow-up.

Drug treatment at 2 years follow-up

Drug	CABG N=66	PTCA N=68
None	3	1
Aspirin	54	14
Aspirin+one antianginal	36	51
Aspirin+two antianginals	7	29
Aspirin+three antianginals	0	5

At 2 years follow-up patients in the PTCA group were taking significantly more anitanginal drugs than those treated by CABG ($p<0.01$, chi square test).

Source of funding: Foundation de Cardiologie, Lausanne, Switzerland.

Does the study answer the question?/Further Comments Yes. The study was well conducted and sample size was derived from a power calculation (95% power) which was based on previous reports of the effects of CABG. The study concludes that both CABG and PTCA improve the clinical status of symptomatic patients with single-vessel coronary artery disease. However, there were significantly more repeat interventions in the PTCA group than in the CABG group.

Goy JJ;Kaufmann U;Goy-Eggenberger D;Garachemani A;Hurni M;Carrel T;Gaspardone A;Burnand B;Meier B;Versaci F;Tomai F;Bertel O;Pieper M;de BM;Eeckhout E;

A prospective randomized trial comparing stenting to internal mammary artery grafting for proximal, isolated de novo left anterior coronary artery stenosis: the SIMA trial. Stenting vs Internal Mammary Artery

Ref ID 9149 **RID:** 512 2000 Nov

QUALITY

A. Selection bias (systematic differences between the comparison groups)

A4 Based on your answers t, in your opinion was selection bias present? If so, what is the likely direction of its effect?:

Unclear/unknown risk **Direction =**

B. Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)

B4 Based on your answers to the above, in your opinion was performance bias present? If so, what is the likely direction of its effect?:

Low risk of bias **Direction =**

C. Attrition bias (systematic differences between the comparison groups with respect to loss of participants)

C4 Based on your answers to the above, in your opinion was attrition bias present? If so, what is the likely direction of its effect?:

Low risk of bias

Direction =

D. Detection bias (bias in how outcomes are ascertained, diagnosed or verified)

D6 Based on your answers to the above, in your opinion was detection bias present? If so, what is the likely direction of its effect?:

Low risk of bias

Direction =

Overall Study Quality -Strengths and Weaknesses:

Strengths: randomised (method of randomisation not reported), formal sample size calculation, baseline comparisons made, intention to treat analysis reported, nos. lost to follow-up reported (1/60 (1.6%) in CABG and 1/63 (1.5%) in Stent. After randomisation when the medical records were reviewed, 1 patient in each group was excluded by the safety committee because of a protocol variation).
Weakness: allocation concealment not reported, no blinding.

DETAILS

# of patients:

N=123 (CABG (n=60); Stent (n=63))

Prevalence (Diagnostic):

Patient Characteristics

Baseline characteristics:
Characteristics: CABG (n=59); Stent (n=62)
No (%) M/F: 49 (83)/10 (17) ; 47 (76)/15 (24)
Mean age (yrs): 60 ; 59
No (%) with previous MI: 1(2); 1(2)
Angina functional class, No (%) of patients
I-II:30 (51%) ; 32 (52%)
II-IV, unstable: 29 (49%) ;30 (48%)
Drugs, No. (%) of patients
BB: 32 (55%); 35 (56%)
CCB: 19 (33%) ; 21 (33%)
Nitrates: 42 (72%); 39 (63%)
ACE inhibitors: 0(0); 1(2%)
Diabetes Mellitus: 8 (13%); 7(11%)

Inclusion criteria: Patients with symptomatic or silent cardiac ischemia and isolated proximal LAD coronary artery stenosis and left ventricular ejection fraction greater than 45% were candidates to enter the Stenting vs. Internal Mammary artery (SIMA) trial.

Exclusion criteria: Patients with unstable angina refractory to medical treatment were not included. Previous Q-wave anterior myocardial infarction, defined as creatine kinase (CK) level more than 3 times the normal value before the intervention, and occurrence of a new Q wave were also exclusion criteria.

Interventions/ Test/ Factor being investigated

PTCA (Stent implantation) was peformed by a right or left femoral approach.

Comparisons

CABG (surgical revascularisation with internal mamary artery)

Length of Study/ Follow-up	Mean ±SD follow-up was 2.4±0.9 years.(Between 9-15 months for quality of life and at 1 year for Angina functional class)
Outcome measures studied	Primary composite end point was cardiac death, MI, and repeated revascularisation. Secondary endpoints were angina functional class, exercise tolerance, quality of life assessment, and post procedural drug regimen.
Results	
Effect Size	No patients in the stent group crossed over to CABG, but 5 patients in the CABG group refused surgery, despite having given prior consent and were treated with stent implantation within 3 days after diagnostic angiography Results: Outcome: CABG (n=59) vs. Stent (n=62) Cardiac death: 1 (2%) VS. 1 (2%) Non cardiac death: 1(2%) vs. 0(0) MI Q-wave: 1 (2%) vs. 0(0) Non Q wave: 1 (2%) vs. 3 (5%) Additional revascularisation CABG: 0(0) vs. 4 (6%) Repeated PTCA: 0(0) vs. 8(13%) CABG +repeated PTCA: 0(0) vs. 3 (5%) Total: 0(0) vs. 15 (24%) Composite primary end point: 4 (7%) vs. 19 (31%); p<0.001 At 1 year follow-up: Outcome: CABG (n=59) vs. stent (n=62) Angina functional class 0 or class 1: 56 (95%) vs. 56 (91%); p=0.90 Class III or IV: 3 vs. 6; p=0.08 Between 9-15 months: Quality of life (SF-36 questionnaire): Stent (n=62)vs. CABG (n=59) Physical functioning: 90 vs. 88* Role physical: 96 vs. 91 Bodily pain: 91 vs. 77 General health: 80 vs. 81 Vitality: 71 vs. 74 Social functioning: 91 vs. 90 Role emotional: 80 vs. 96 Mental health: 82 vs. 81 Seattle questionnaire: Stent (n=62) vs. CABG (n=59) Physical limitation: 86 vs. 91 Angina stability: 88 vs. 98 Angina frequency: 90 vs. 98 Treatment satisfaction: 87 vs. 89 Disease perception: 79 vs. 76 The quality of life questionnaires did not show significant differences between the groups. Only perception of the disease was more marked (but not significantly) after surgery. *values are number of patients (as reported in the paper)
Source of funding:	This study was supported by a grant from the Swiss Foundation of Cardiology, Bern, Switzerland, and Johnson & Johnson, Warren, N.J.
Does the study answer the question?/Further Comments	Yes. The primary composite endpoint of cardiac death, MI, and repeated revascularisation occurred significantly less in the CABG compared to Stent, there was significantly higher incidence of additional revascularisation in the stent group compared to CABG. Cardiac death and MI were rare and the rates did not differ significantly. The CCS angina functional class of the treatment groups revealed no differences before treatment or during follow-up. The quality of life questionnaires did not show significant differences between the groups.

Goy JJ;Kaufmann U;Hurni M;Cook S;Versaci F;Ruchat P;Bertel O;Pieper M;Meier B;Chiarello L;Eeckhout E;

10-year follow-up of a prospective randomized trial comparing bare-metal stenting with internal mammary artery grafting for proximal, isolated de novo left anterior coronary artery stenosis the SIMA (Stenting versus Internal Mammary Artery grafting) trial

Ref ID 9169 **RID:** 711 2008 Sep 2

QUALITY

A. Selection bias (systematic differences between the comparison groups)

A4 Based on your answers t, in your opinion was selection bias present? If so, what is the likely direction of its effect?:

Unclear/unknown risk **Direction =**

B. Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)

B4 Based on your answers to the above, in your opinion was performance bias present? If so, what is the likely direction of its effect?:

Low risk of bias **Direction =**

C. Attrition bias (systematic differences between the comparison groups with respect to loss of participants)

C4 Based on your answers to the above, in your opinion was attrition bias present? If so, what is the likely direction of its effect?:

Low risk of bias **Direction =**

D. Detection bias (bias in how outcomes are ascertained, diagnosed or verified)

D6 Based on your answers to the above, in your opinion was detection bias present? If so, what is the likely direction of its effect?:

Low risk of bias **Direction =**

Overall Study Quality -Strengths and Weaknesses:

Strengths*: randomised (method of randomisation not reported), formal sample size calculation, baseline comparisons made, intention to treat analysis reported, nos. lost to follow-up reported (2% lost to follow-up).
Weakness: allocation concealment not reported, no blinding of outcome assessors.
*This study is a 10 year follow-up of the SIMA trial

DETAILS

# of patients: N=123 (CABG (n=60); Stent (n=63))

Prevalence (Diagnostic):

Patient Characteristics	Baseline characteristics: Characteristics: CABG (n=59); Stent (n=62) No (%) M/F: 49 (83)/10 (17); 47 (76)/15 (24) Mean age (yrs): 60; 59 No (%) with previous MI: 1(2); 1(2) Angina functional class, No (%) of patients I-II: 30 (51%); 32 (52%) II-IV, unstable: 29 (49%); 30 (48%) Drugs, No. (%) of patients BB: 32 (55%); 35 (56%) CCB: 19 (33%); 21 (33%) Nitrates: 42 (72%); 39 (63%) ACE inhibitors: 0(0); 1(2%) Diabetes Mellitus: 8 (13%); 7(11%)
Interventions/ Test/ Factor being investigated	PTCA (first generation bare metal stents)
Comparisons	CABG
Length of Study/ Follow-up	10 years
Outcome measures studied	The primary composite endpoint was all causes of death, MI, and the need for additional revascularisation. A secondary endpoint was angina functional class.

Results

Effect Size	Results: At 10 years Outcome: Stent (n=62) vs. CABG (n=59) Death: 5 vs. 4; p=0.4 Cardiac death: 2 vs. 1 Non cardiac death: 3 vs. 3 Q-wave MI: 0 vs. 1 Non Q-wave MI: 3 vs. 2 Target lesion revascularisation (TLR): 13 vs. 0; p <0.0001 Target vessel revascularisation (TVR): 2 vs. 0 Non-LAD PTCA: 3 vs. 3 Total additional revascularisation: 18 vs. 3 Any event: 26 (42%) vs. 10 (17%); p<0.0001 Angina functional class showed no significant differences between the 2 groups (data not reported). At 10 years, most of the patients in both groups were asymptomatic (93%) or suffered mild angina (7%). A majority of patients received anti platelet therapy (94% PCI and 96% CABG). Rates of lipid lowering therapy increased gradually from 24% at 2 years to 89% (88% PCI and 91% CABG). BB, ACE inhibitors, and CCB's were given to more than 50% of the patients without differences between the 2 groups. Treatment varied significantly during follow-up. `
Source of funding:	This study was supported by a grant from the Swiss Foundation of Cardiology, Bern, Switzerland, and Johnson & Johnson, Warren, N.J.
Does the study answer the question?/Further Comments	Yes. At 10 years, mortality and myocardial infraction rates were not statistically different between the PTCA and CABG. Significantly more patients in PTCA required additional revascularisation. No patients randomised to CABG required a second revascularisation of the LAD. No significant difference between the groups for angina functional class.

Hamm CW;Reimers J;Ischinger T;Rupprecht HJ;Berger J;Bleifeld W;

A randomized study of coronary angioplasty compared with bypass surgery in patients with symptomatic multivessel coronary disease. German Angioplasty Bypass Surgery Investigation (GABI)

Ref ID 1800 **RID:** 538 1994 Oct 20

QUALITY

A. Selection bias (systematic differences between the comparison groups)

A4 Based on your answers t, in your opinion was selection bias present? If so, what is the likely direction of its effect?:

Unclear/unknown risk **Direction =**

B. Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)

B4 Based on your answers to the above, in your opinion was performance bias present? If so, what is the likely direction of its effect?:

Low risk of bias **Direction =**

C. Attrition bias (systematic differences between the comparison groups with respect to loss of participants)

C4 Based on your answers to the above, in your opinion was attrition bias present? If so, what is the likely direction of its effect?:

Low risk of bias **Direction =**

D. Detection bias (bias in how outcomes are ascertained, diagnosed or verified)

D6 Based on your answers to the above, in your opinion was detection bias present? If so, what is the likely direction of its effect?:

Low risk of bias **Direction =**

Overall Study Quality -Strengths and Weaknesses:

Strengths: Multicentre, randomised, baseline comparisons made, formal sample size calculation reported, nos. lost to follow-up reported (38/177 (21.4%) for bypass surgery and 27/182 (14.8%) for angioplasty, Intention to treat analysis reported.
Weakness: No blinding, allocation concealment not reported.

DETAILS

# of patients: N=359 (CABG (n=177); PTCA (n=182))

Prevalence (Diagnostic):

Patient Characteristics	Baseline characteristics: Variable: CABG (n=177); PTCA (n=182) Female (%): 20 ; 21 Double vessel disease:78 ; 85 Triple vessel disease: 22 ; 15 Previous MI: 47; 46 Unstable angina: 15; 13 Previous stroke: 2 ; 5 Peripheral vascular disease: 8 ;8 Diabetes: 15; 10 Hypertension: 39; 42 Inclusion criteria: Patients under 75 years with symptomatic multivessel coronary disease (CCS class ≥II and stenosis ≥ 70 percent in diameter) were considered for enrolment. Revascularisation of at least two major coronary arteries supplying different myocardial regions (the left anterior descending, left circumflex, and right coronary arteries) had to be clinically necessary and technically feasible according to the judgement of the local cardiologists and surgeons, based on clinical and angiographic criteria. Patients with totally occluded vessels (TIMI grade 0) and lesions of the left main coronary artery (stenosis >30% in diameter) were excluded.
Interventions/ Test/ Factor being investigated	PTCA
Comparisons	CABG
Length of Study/ Follow-up	6 months and 1 year
Outcome measures studied	Primary endpoint was freedom from angina pectoris (CCS class <II) one year after the intervention. Secondary endpoints included the incidence of major cardiovascular events (death or MI) ,procedure related complications and the rate of further investigations.
Results	
Effect Size	Results: At 1 year Outcome: CABG (n=139) vs. PTCA (n=155) Free of angina: 74% vs. 71% Mean difference in the Proportions of patients in the two groups who were free of angina: 3.0 ±10.4 percent (95% CI -7.4 to 13.4 percent) Class II or IV angina present: 7% vs. 8% (p=0.82) % of patients not using any anti anginal medication: 22% vs. 12% (p=0.041) Death *: 9 vs. 4 Acute MI : 13 VS. 7 Further interventions CABG: 2 vs. 41 PTCA: 7 vs. 50 *In the interval between randomisation and intervention 5 patients died (4 in the CABG group and 1 in the PTCA group).
Source of funding:	Supported by a grant from the Bundesministerium fur Forschung und Technologie, Bonn, Germany
Does the study answer the question?/Further Comments	Yes. PTCA and CABG as initial treatments resulted in equivalent improvement in angina after one year. However, in order to achieve similar clinical outcomes, the patients treated with PTCA were likely to require further interventions and antianginal drugs, whereas the patients treated with CABG were more likely to sustain an acute MI at the time of the procedure.

Hampton JR;Henderson RA;Julian DG;Parker J;Pocock SJ;Sowton E;Wallwork J;Chamberlain DA;Dark JF;Joy D;Seed P;Youard B;

Coronary angioplasty versus coronary artery bypass surgery: The Randomised Intervention Treatment of Angina (RITA) trial

Ref ID 2818 **RID:** 684 1993

QUALITY

A. Selection bias (systematic differences between the comparison groups)

A4 Based on your answers t, in your opinion was selection bias present? If so, what is the likely direction of its effect?:

Low risk of bias **Direction =**

B. Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)

B4 Based on your answers to the above, in your opinion was performance bias present? If so, what is the likely direction of its effect?:

Low risk of bias **Direction =** Patients and clinicians were not blind to treatment due to the nature of the study. However, the primary

C. Attrition bias (systematic differences between the comparison groups with respect to loss of participants)

C4 Based on your answers to the above, in your opinion was attrition bias present? If so, what is the likely direction of its effect?:

Low risk of bias **Direction =**

D. Detection bias (bias in how outcomes are ascertained, diagnosed or verified)

D6 Based on your answers to the above, in your opinion was detection bias present? If so, what is the likely direction of its effect?:

Low risk **Direction =**

Overall Study Quality -Strengths and Weaknesses:

This is a well conducted RCT. Methods of randomisation and concealment well described. It was not appropriate to blind patients or clinicians but primary endpoint was assessed by independent, blinded investigators. An intention to treat analysis was conducted and no patients were lost to follow up for survival*.
*Study reports that 11 patients withdrew from further visits and were in follow-up by telephone only.

DETAILS

# of patients: n=1011 (n=501 in the CABG arm and n=510 in the PTCA arm)

Prevalence (Diagnostic):

Patient Characteristics

5 patients received PCI instead of the intended CABG and 7 patients were treated by CABG rather than randomised PCI.

	CABG N=501	PTCA N=510
Treatment vessels		
One	222	234
Two	218	213
Three	61	63
Age (yr):		
<40	13	14
40-49	88	91
50-59	207	225
60-69	169	156
70-79	21	23
Women:	107	88
Angina:		
None	33	36
Grade 1	33	44
Grade 2	128	140
Grade 3	155	159
Grade 4	149	130
At rest	275	282
Causing hospital admission:	187	189
Median time since onset (lower and upper quartiles):	8(4,24)	9(5,24)
Previous MI:	210	217
Not working due to coronary disease:	191	193
Current medication:		
Beta-blocker	369	383
Calcium antagonist	363	365
Long-acting nitrate	314	334
Aspirin	353	370
Antianginal drugs:		
None	14	13
One	116	95
Two	174	216
Three	194	185

Interventions/ Test/ Factor being investigated

Percutaneous transluminal coronary angioplasty (PTCA). (PTCA was conventional balloon angioplasty.)

Comparisons

PTCA versus coronary artery bypass surgery (CABG).

Length of Study/ Follow-up

2.5 years since randomisation.

Outcome measures studied

Primary outcome: 5-year incidence of death and definite non-fatal myocardial infarction. Secondary outcomes include other secondary events (angina, stroke, cardiac failure and arrhythmia) subsequent interventions, angina incidence, anti-anginal medication, employment status and exercise tolerance.

Results

Effect Size

Deaths, myocardial infarctions and new interventions during a median 2.5 years follow-up since randomisation.

Event	CABG N=501	PTCA N=510
Death		
All causes	18	16
Pre-hospital discharge	6	4
Other cardiac death	4	4
Non-cardiac death	8	8

Non-fatal MI		
Definite	20	33
Silent	6	1
Patients with primary endpoint (death or MI)	43	50
Subsequent interventions		
CABG	4	96
PTCA	16	93
Coronary arteriography	39	159

There is no evidence of a difference between CABG and PTCA groups for the primary endpoint (relative risk for CABG:PTCA is 0.88 with 95% CI 0.59 to 1.29; lonrank p=0.47).

Secondary outcomes

Secondary events after 6 months.

Event	CABG	PTCA
Unstable angina	5	15
Stroke	3	6
Cardiac failure	8	6
Arrhythmia	3	5

Anti-anginal medication 2 years since randomisation

	CABG	PTCA
N	301	316
None	198	124
One	76	106
Two	22	67
Three	5	19

Physical activity
AT 2 years 66% of patients in the CABG group were physically active (moderately or vigorously active) and 63% of patients in the PTCA group.

Employment status
At 2 years, 23% of men in the CABG group, aged <63 at randomisation, were not working due to coronary disease. The corresponding number In the PTCA group was 25%.

Exercise testing
At 2 years there is a slightly greater mean increase in exercise time after CABG compared with After PTCA, but the difference is not significant. (exact difference not reported, but shown in a figure).

Source of funding:

British Heart Foundation, British Cardiac Society and Department of health. Additional financial support has been provided by Advanced Cardiovascular

Does the study answer the question?/Further Comments

Yes. Although the primary endpoint in this study is the combined 5-year incidence of death and definite non-fatal myocardial infarction, this interim 2.5 year analysis is useful. These interim findings indicate that recovery after CABG, the more invasive procedure , takes longer than after PCTA. However, CABG leads to less risk of angina and fewer additional diagnostic and therapeutic interventions in the first 2 years than PTCA. So far, ther is no significant difference in risk of death or myocardial infarction, and follow-up continues to at least 5 years.

Henderson RA;Pocock SJ;Sharp SJ;Nanchahal K;Sculpher MJ;Buxton MJ;Hampton JR;

Long-term results of RITA-1 trial: clinical and cost comparisons of coronary angioplasty and coronary-artery bypass grafting. Randomised Intervention Treatment of Angina

Ref ID 263 RID: 700 1998 Oct 31

QUALITY

A. Selection bias (systematic differences between the comparison groups)

A4 Based on your answers t, in your opinion was selection bias present? If so, what is the likely direction of its effect?:

Low risk of bias

Direction =

B. Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)

B4 Based on your answers to the above, in your opinion was performance bias present? If so, what is the likely direction of its effect?:

Low risk of bias

Direction =

C. Attrition bias (systematic differences between the comparison groups with respect to loss of participants)

C4 Based on your answers to the above, in your opinion was attrition bias present? If so, what is the likely direction of its effect?:

Low risk of bias

Direction =

D. Detection bias (bias in how outcomes are ascertained, diagnosed or verified)

D6 Based on your answers to the above, in your opinion was detection bias present? If so, what is the likely direction of its effect?:

Low risk of bias

Direction =

Overall Study Quality -Strengths and Weaknesses:

Strengths*: randomised, allocation concealment reported, loss to follow-up reported (3.3%) 17/510 in PTCA and (2.1%) 11/501 in CABG), Intention to treat analysis reported. Clinical events adjudicated by an independent committee. It was not appropriate to blind patients or clinicians.

Weakness: None.
*this study is the 6.5 year follow-up of the RITA trial.

DETAILS

# of patients: n=1011 (PCI (n=510) vs. CABG (n=501)

Prevalence (Diagnostic):

Patient Characteristics Refer to the evidence table : Ref ID 2818 (Hampton JR, Henderson RA, Julian DG et al. Coronary angioplasty versus coronary artery bypass surgery: The Randomised Intervention Treatment of Angina (RITA) trial).

Interventions/ Test/ Factor being investigated PTCA

Comparisons	CABG
Length of Study/ Follow-up	The median duration of follow-up was 6.5 years (range 5.0 to 8.7).
Outcome measures studied	The Primary end point was the combined 5 year rate of death and definite non fatal MI.
Results	
Effect Size	Results: Outcome: PCI (n=510) vs. CABG (n=501) Death: 39 vs. 45; p=0.51 Cardiac death: 18 vs. 21 Non fatal MI: 55 (10.8%) vs. 37 (7.4%) ; p=0.08 Reintervention CABG: 134 (26%) vs. 4 (3%) PTCA: 138 (27%) vs. 47 (9%) Changes in angina grade between 1 year and 5 year follow-up visits: Variable: PTCA (n=461) vs. CABG (n=446) Improved: 79 vs. 39 Unchanged (no angina): 233 vs. 295 Unchanged (some angina): 38 vs. 22 Worsened: 111 vs. 90 Subgroup: Single vessel disease Outcome: PCI (n=233) vs. CABG (n=222) Death: 17 vs. 21 Non fatal MI: 31 vs. 17 Patients with subsequent intervention CABG: 49 (51) vs. 6 (6) PTCA: 62 (88) vs. 23 (33) Multivessel disease: Outcome: PCI (n=277) vs. CABG (n=279) Death: 22 vs. 24 Non fatal MI: 24 vs. 20 Patients with subsequent intervention CABG: 85 (89) vs. 8(10) PTCA: 76 (92) vs. 24 (30)
Source of funding:	The RITA-1 trial is supported by a grant from the UK Department of Health, with previous grants from the British Heart Foundation and the British Cardiac Society
Does the study answer the question?/Further Comments	Yes. There was no significant difference between PTCA and CABG for death and non fatal MI. There was significantly higher repeat revascularisation in PTCA compared to CABG. There was no difference between patients with single vessel and multi vessel disease in the risk of death or MI.

Kaehler J;Koester R;Billmann W;Schroeder C;Rupprecht HJ;Ischinger T;Jahns R;Vogt A;Lampen M;Hoffmann R;Riessen R;Berger J;Meinertz T;Hamm CW;

13-year follow-up of the German angioplasty bypass surgery investigation

Ref ID 710 **RID:** 561 2005 Oct

QUALITY

A. Selection bias (systematic differences between the comparison groups)

A4 Based on your answers t, in your opinion was selection bias present? If so, what is the likely direction of its effect?:

Unclear/unknown risk

Direction =

B. Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)

B4 Based on your answers to the above, in your opinion was performance bias present? If so, what is the likely direction of its effect?:

Low risk of bias

Direction =

C. Attrition bias (systematic differences between the comparison groups with respect to loss of participants)

C4 Based on your answers to the above, in your opinion was attrition bias present? If so, what is the likely direction of its effect?:

Low risk of bias

Direction =

D. Detection bias (bias in how outcomes are ascertained, diagnosed or verified)

D6 Based on your answers to the above, in your opinion was detection bias present? If so, what is the likely direction of its effect?:

Low risk of bias

Direction =

Overall Study Quality -Strengths and Weaknesses:

Strengths: Multicentre, randomised, baseline comparisons made, formal sample size calculation reported, nos. lost to follow-up reported (17/177 (9.6%) for bypass surgery and 18/182 (9.8%) for angioplasty, Intention to treat analysis reported. Blind outcome assessment (A data review committee unaware of treatment assignment, reviewed all available information regarding deaths, MIs, and other relevant medical information before statistical analysis).
Weakness: allocation concealment not reported.*
Author reported limitation: Study not poweredto detect a difference in survival. More patients of the surgical group died on the on the waiting list or withdrew their consent and therefore did not have the planned procedure.
*This study is a 13 year follow-up of the GABI (Hamm C.W 1993, Ref ID 1800)

DETAILS

# of patients: n=324 (n=160 in CABG and n=164 in PTCA)

Prevalence (Diagnostic):

Patient Characteristics	Baseline characteristics of 324 patients who were followed up for this study: Variable: CABG (n=160) ; PTCA (n=164) Female: 32 ; 34 Two vessel disease: 125 ; 139 Three vessel disease: 35 ; 25 Previous MI: 75; 75 Unstable angina: 24; 21 Diabetes: 24; 16 Hypertension: 62; 69 Age: 65±9 ;65±11 Inclusion criteria: Patients under 75 years with symptomatic multivessel coronary disease (CCS class ≥II and stenosis ≥ 70 percent in diameter) were considered for enrolment. Revascularisation of at least two major coronary arteries supplying different myocardial regions (the left anterior descending, left circumflex, and right coronary arteries) had to be clinically necessary and technically feasible according to the judgement of the local cardiologists and surgeons, based on clinical and angiographic criteria. Patients with totally occluded vessels (TIMI grade 0) and lesions of the left main coronary artery (stenosis >30% in diameter) were excluded.
Interventions/ Test/ Factor being investigated	PTCA
Comparisons	CABG
Length of Study/ Follow-up	13 years (12.3 -15.1 years)
Outcome measures studied	Primary endpoint was freedom from angina pectoris (CCS class <II) . Secondary endpoints included the incidence of major cardiovascular events (death or MI) ,procedure related complications and the rate of further investigations.
Results	
Effect Size	Results: Outcome: CABG (n=160) vs. PTCA (n=164) Mortality all causes: 35 vs. 41 ; p=0.64 Mortality due to MI: 9 VS. 7; p=0.60 Mortality due to HF: 6 vs. 10; p=0.48 Sudden cardiac death: 5 vs. 1; p=0.24 Mortality due to Non cardiac, cardiovascular: 3 vs. 4; p=0.96 Mortality due to Non cardiac, non cardiovascular: 10 vs. 15; p=0.44 Unknown: 2 vs. 4; p=0.46 Re-interventions: 94 vs. 136 Degree of angina and use of anti anginal medication are reported as being similar in both groups. Data reported in graphical figures, hence cannot be analysed.
Source of funding:	GABI follow-up was sponsored by Jomed, Rangendingen, Germany
Does the study answer the question?/Further Comments	Yes. Both PTCA and CABG are associated with a comparable long-term survival and symptomatic efficacy. Authors note: GABI trial was established before the use of statins became widespread, and the treatment with these drugs could affect long term outcome differently with patients undergoing CABG or PTCA.

Kapur A;Hall RJ;Malik IS;Qureshi AC;Butts J;de BM;Baumbach A;Angelini G;de BA;Oldroyd KG;Flather M;Roughton M;Nihoyannopoulos P;Bagger JP;Morgan K;Beatt KJ;

Randomized comparison of percutaneous coronary intervention with coronary artery bypass grafting in diabetic patients. 1-year results of the CARDia (Coronary Artery Revascularization in Diabetes) trial

Ref ID 9240 **RID:** 858 2010 Feb 2

QUALITY

A. Selection bias (systematic differences between the comparison groups)

A4 Based on your answers t, in your opinion was selection bias present? If so, what is the likely direction of its effect?:

Low risk of bias **Direction =**

B. Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)

B4 Based on your answers to the above, in your opinion was performance bias present? If so, what is the likely direction of its effect?:

Low risk of bias **Direction =**

C. Attrition bias (systematic differences between the comparison groups with respect to loss of participants)

C4 Based on your answers to the above, in your opinion was attrition bias present? If so, what is the likely direction of its effect?:

Low risk of bias **Direction =**

D. Detection bias (bias in how outcomes are ascertained, diagnosed or verified)

D6 Based on your answers to the above, in your opinion was detection bias present? If so, what is the likely direction of its effect?:

Low risk of bias **Direction =**

Overall Study Quality -Strengths and Weaknesses:

Strengths: Randomsation undertaken either by a local secure computer-based system or telephone contact with the coordinating centre stratifying for urgency of intervention, sex, and number of diseased vessels. Allocation concealment reported. Sample size calculation reported. Blind outcome assessors. ITT used.
Weakness: None

DETAILS

# of patients: N=510 (n=254 CABG and n=256 PCI)

Prevalence (Diagnostic):

Patient Characteristics

Baseline characteristics:
Variable: CABG (n=254) vs. PCI (n=256)
Age (yrs): 63.6 vs. 64.3
Male,: 197 vs. 181
Ethnicity
White: 181 vs. 171
Asian: 52 vs.66
Black: 6 vs. 6
Other: 11 vs. 12
Diabetes status
Type 1: 17 vs. 8
Non insulin treated: 155 vs. 168
Insulin treated: 99 vs. 88
Years with diabetes (mean): 10.4 vs. 10.1
Diseased vessels
3 vessel disease: 149 vs.166
2 vessel disease: 88 vs. 72
Bifurcation: 5 vs. 2
Proximal LAD: 12 vs. 16
LV function
Normal or good: 106 vs. 98
Mild impairment: 37 vs. 43
Moderate impairment: 23 vs. 34
Severe impairment: 2 vs. 2
Ejection fraction %: 60 vs. 59.1%

Inclusion criteria: Patients were considered eligible if they had diabetes and either multivessel coronary disease or complex single vessel disease (ostial or proximal left anterior descending artery) and were recommended to have coronary revascularisation on clinical grounds.

Exclusion criteria: Inability to consent, age older than 80 years, previous revascularisation, left main stem disease, cardiogenic shock, recent ST segment elevation MI (within 6 weeks), known ejection fraction <20%, and contraindications to antiplatelet therapy.

Interventions/ Test/ Factor being investigated

PCI. PCI strategy included the unrestricted use of stents and routine administration of abciximab. The trial started using BMS, but when they become available patients received DES.

Comparisons

CABG. contemporary techniques such as arterial revascularisation and off-pump procedures were encouraged in patients randomised to CABG.

Length of Study/ Follow-up

median 365 days (1 year)

Outcome measures studied

Primary outcome: composite of all cause mortality, MI, and stroke, and the main secondary outcome included the addition of repeat revascularisation to the primary outcome events.

Results

Effect Size

Results:
Major endpoints at 1 year:
Outcome: CABG (n=248) vs. PCI (n=254); Hazard ratio (95% CI)
Death: 8 vs. 8; 0.98 (0.37 to 2.61) ,p=0.97
Non fatal MI: 14 vs. 25; 1.77 (0.92 to 3.40),p=0.088
Peri procedural MI: 11 vs. 12; 1.08 (0.47 to 2.44), p=0.819
Late MI: 3 vs. 14; 4.64 (1.33 to 16.16), p=0.016
Non fatal stroke: 7 vs. 1; 0.14 (0.02 to 1.14), p=0.06
Further revascularisation: 5 vs. 30 ; 6.18 (2.40 to 15.94), p<0.001

Outcomes in sub groups: At 1 year
Death, MI, stroke: CABG vs. PCI; Hazard ration (95% CI), interaction p value
2 vessel disease: 102 vs. 90; 0.9 (0.36 to 2.28), p=0.419
3 vessel disease: 146 vs. 164; 1.42 (0.76 to 2.67)

BMS group: 70 vs. 82; 2.99 (0.97 to 9.16); p=0.076
DES group: 178 vs. 172; 0.93 (0.51 to 1.71)
Female: 56 vs. 74; 2.13 (0.68 to 6.68), p=0.289
Male: 192 vs. 180; 1.07 (0.59 to 1.93)
Age <65 yrs: 123 vs. 119; 1.04 (0.49 to 2.17), p=0.497
Age >65 yrs: 125 vs. 135 ; 1.48 (0.72 to 3.05)

CCS class: CABG vs. PCI (at 1 year)
Class 0: 192 vs. 159 (p=0.001) –global p value for all classes of angina
Class1: 16 vs. 37
Class 2: 8 vs. 21
Class 3: 1 vs. 2
Class 4: 0 vs. 3
Class 4a: 0 vs. 1

Note: In the CABG group, 230 of 254 patients (91%) actually underwent CABG, with 1 patient ding before the operation and 14 crossing over to PCI. In the PCI group 253 of 256 patients (99%) actually underwent PCI, and 1 patient crossed over to CABG.

Source of funding: Unrestricted research grants from Eli Lilly, Cordis Johnson&Johnson, Bristol-Myers Squibb, Sanofi-Aventis, and the Hammersmith hospitals special trustees

Does the study answer the question?/Further Comments Yes. The 1 year results did not show that PCI is non inferior to CABG. Authors note: The trial did show that multivessel PCI is feasible in patients with diabetes, but long term follow-up and data from other trials will be needed to provide a more precise comparison of the efficacy of these 2 revascularisation strategies.

King IIIS;Kosinski AS;Guyton RA;Lembo NJ;Weintraub WS;

Eight-year mortality in the Emory Angioplasty versus Surgery Trial (EAST)

Ref ID 3079 **RID:** 632 2000

QUALITY

A. Selection bias (systematic differences between the comparison groups)

A4 Based on your answers t, in your opinion was selection bias present? If so, what is the likely direction of its effect?:

Low risk of bias **Direction =**

B. Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)

B4 Based on your answers to the above, in your opinion was performance bias present? If so, what is the likely direction of its effect?:

Low risk of bias **Direction =** Clinical investigators were independent and blind to patients' treatment.

C. Attrition bias (systematic differences between the comparison groups with respect to loss of participants)

C4 Based on your answers to the above, in your opinion was attrition bias present? If so, what is the likely direction of its effect?:

Low risk of bias

Direction =

D. Detection bias (bias in how outcomes are ascertained, diagnosed or verified)

D6 Based on your answers to the above, in your opinion was detection bias present? If so, what is the likely direction of its effect?:

low risk

Direction =

Overall Study Quality -Strengths and Weaknesses:

Randomisation methods were not well described although an independent centre collected all data. Clinical investigators were independent and blind to treatment. Analyses was on an intent-to-treat basis and no patients were lost to follow up.

DETAILS

# of patients:

n=392 (n=194 in the CABG group and n=198 in the PTCA group)

Prevalence (Diagnostic):

Patient Characteristics

	CABG N=194	PTCA n=198
Age (yr)	61.4(10.0)	61.8(10.1)
Male sex	141(72.7)	148(74.7)
White race	183(94.3)	184(92.9)
No. of diseased vessels		
Two	117(60.3)	119(60.1)
Three	77(39.7)	79(39.9)
Proximal LAD stenosis		
>=50%	143(73.7)	140(70.7)
No. of lesions per patients	3.4(1.4)	3.4(1.2)
Prior myocardial infarction	79(40.7)	81(40.9)
Congestive heart failure	8(4.1)	5(2.5)
Angina		
No angina	8(4.2)	8(4.2)
CCS class I	9(4.8)	11(5.8)
CCS class II	17(9.0)	24(12.6)
CCS class III	33(17.5)	35(18.4)
CCS class IV	122(64.6)	112(58.9)
Diabetes mellitus	41(21.2)	49(24.7)
Hypertension	100(51.5)	106(53.5)

Interventions/ Test/ Factor being investigated

Percutaneous transluminal coronary angioplasty (PCTA). (PTCA was performed by standard methods.)

Comparisons

PCTA versus CABG.(CABG was performed in a standard fashion.)

Length of Study/ Follow-up

Eight to 10.5 years after randomisation.

Outcome measures studied

The primary focus of the extended follow-up is all-cause mortality and requirement for repeat revascularization procedures. Death was also classified as to cause, and these were divided into cardiac and noncardiac.

Results

Effect Size

Primary outcome
At eight years the surgery survival is 82.7% and the angioplasty survival is 79.3%, and this does not reach statistical significance (p= 0.40).

Subgroup analysis

Vessel disease
Because of the concern that patients with more diffuse disease might have better outcomes with surgery, the
patients were randomized according to the presence of three-vessel disease (40% of the patients) or two-vessel
disease (60% of the patients). At three years neither the three-vessel disease patients nor the two-vessel disease
patients showed better survival by treatment assignment (three-vessel: surgery 93.5%, angioplasty 91.1%; two-vessel: surgery 94.0%, angioplasty 94.1%). By eight years there was slight, but not significant, separation of the curves in favor of surgery for three-vessel disease (three-vessel surgery 81.6%, angioplasty 75.5%, p 5 0.35) but not for two-vessel disease (two-vessel surgery 83.4%, angioplasty 81.8%, p =0.75).

Left anterior descending stenosis
Patients with proximal left anterior descending stenosis had little difference in survival at three years, and the curves
diverged slightly, but not significantly, for this cohort over the remaining follow-up (eight-year surgical survival 85.6%, angioplasty 79.6%, p= 0.16).

Diabetes
There were 59 treateddiabetic patients in EAST (30 surgery, 29 angioplasty). At three years the survival was similar (surgery 90%, angioplasty 93.1%), and this was also similar to the patients without treated diabetes. In the extended follow-up this has changed. After five years the curves began to diverge, and by eight years, even though they did not reach statistical significance, they favored surgery in this group (surgical survival 75.5%, angioplasty 60.1%, p = 0.23). Likewise, the angioplasty patients with diabetes had a worse survival than the nondiabetic patients by eight years (nondiabetic 82.6%, diabetic 60.1%, p = 0.02). Similar to the BARI five-year follow-up of patients without treated diabetes, this follow-up of EAST showed no survival advantage for either treatment assignment for the 333 nondiabetic patients at eight years (surgery 84%, angioplasty 82.6%, p= 0.71).

Comparisons were made for all other baseline variables including left ventricular function, age, gender, anginal
status, hypertension, cigarette smoking and baseline choles-terol values, and no survival differences by treatment assignment were seen.

Revascularisation
The surgery patients had very few surgical procedures in follow-up, and after three years the percent of
angioplasty patients having surgery was also relatively low. At eight years 2.4% of the surgery patients had had a second operation and 29.3% of the angioplasty patients had undergone surgery (p< 0.001).

Source of funding:

Supported by a grant from the National Heart, Lung, and Blood Institute.

Does the study answer the question?/Further Comments

Yes. The primary focus of this 8 year follow up was all cause mortality and requirement for repeat vascularization procedures. The follow up data show that long-term survival is not significantly different between angioplasty and surgery, and late (three to eight year) revascularization procedures were infrequent. Patients without treated
diabetes had similar survival in both groups.

King SB;Lembo NJ;Weintraub WS;Kosinski AS;Barnhart HX;Kutner MH;Alazraki NP;Guyton RA;Zhao XQ;

A randomized trial comparing coronary angioplasty with coronary bypass surgery. Emory Angioplasty versus Surgery Trial (EAST)

Ref ID 1799 **RID:** 539 1994 Oct 20

QUALITY

A. Selection bias (systematic differences between the comparison groups)

A4 Based on your answers t, in your opinion was selection bias present? If so, what is the likely direction of its effect?:

Low risk of bias **Direction =**

B. Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)

B4 Based on your answers to the above, in your opinion was performance bias present? If so, what is the likely direction of its effect?:

Low risk of bias **Direction =** Clinical investigators were independent and blind to patients' treatment.

C. Attrition bias (systematic differences between the comparison groups with respect to loss of participants)

C4 Based on your answers to the above, in your opinion was attrition bias present? If so, what is the likely direction of its effect?:

Low risk of bias **Direction =**

D. Detection bias (bias in how outcomes are ascertained, diagnosed or verified)

D6 Based on your answers to the above, in your opinion was detection bias present? If so, what is the likely direction of its effect?:

Low risk **Direction =**

Overall Study Quality -Strengths and Weaknesses: Randomisation methods were not well described although an independent centre collected all data. Clinical investigators were independent and blind to treatment. Analyses was on an intent-to-treat basis and no patients were lost to follow up.

DETAILS

# of patients: n=392 (n=194 in the CABG group and n=198 in the PTCA group)

Prevalence (Diagnostic):

Patient Characteristics

	CABG N=194	PTCA n=198
Age (yr)	61.4(10.0)	61.8(10.1)
Male sex	141(72.7)	148(74.7)
White race	183(94.3)	184(92.9)

No. of diseased vessels		
Two	117(60.3)	119(60.1)
Three	77(39.7)	79(39.9)
Proximal LAD stenosis		
>=50%	143(73.7)	140(70.7)
No. of lesions per patients	3.4(1.4)	3.4(1.2)
Prior myocardial infarction	79(40.7)	81(40.9)
Congestive heart failure	8(4.1)	5(2.5)
Angina		
No angina	8(4.2)	8(4.2)
CCS class I	9(4.8)	11(5.8)
CCS class II	17(9.0)	24(12.6)
CCS class III	33(17.5)	35(18.4)
CCS class IV	122(64.6)	112(58.9)
Diabetes mellitus	41(21.2)	49(24.7)
Hypertension	100(51.5)	106(53.5)

Interventions/ Test/ Factor being investigated

Percutaneous transluminal coronary angioplasty (PCTA). PTCA was performed by standard methods.

Comparisons

PCTA versus CABG (CABG was performed in a standard fashion.)

Length of Study/ Follow-up

Three years after randomisation.

Outcome measures studied

The primary end point was a composite of death, Q-wave myocardial infarction within the previous three years, and detection of a large ischemic defect on thallium scanning at three years. Secondary end points involved the degree of revascularization at one and three years, ventricular function, exercise performance, the need for subsequent revascularization procedures, the quality of life, and costs.

Results

Effect Size

	CABG N=194	PTCA n=198
	No. of patients (%)	
Vital status		
Dead	12(16.2)	14(7.1)
Alive	182(93.8)	184(92.9)
Q-wave MI within 3 yrs		
Yes	38(19.6)	29(14.6)
No	134(69.1)	144(72.7)
Dead, no preceding MI	9(4.6)	12(6.1)
Alive, no 3 year ECG	13(6.7)	13(6.6)
Large ischemic defect on thallium scan		
Yes	11(5.7)	19(9.6)
No	136(70.1)	137(69.2)
No thallium scan		
Dead	12(6.2)	14(7.1)
Alive	35(18.0)	28(14.1)
Composite primary end point		
Yes	53(27.3)	57(28.8)
No	118(60.8)	120(60.6)
Alive, incomplete data	23 (11.9)	21(10.6)

Secondary outcomes

Further revascularisation
Only one additional operation was required among the patients in the CABG group, whereas 42 operations were needed in the PTCA group. Approximately half these operations occurred during the initial hospitalization, and most of the others occurred over the next 12 months. After three years, 1 percent of the patients in the CABG group and 22 percent of those in the PTCA group had undergone additional surgery (P<0.001).

Outcomes by number of diseased vessels
Because of the concern that patients with more diffuse disease might have better outcomes with surgery, the
patients were randomized according to the presence of three-vessel disease (40% of the patients) or two-vessel
disease (60% of the patients). At three years neither the three-vessel disease patients nor the two-vessel disease
patients showed better survival by treatment assignment (three-vessel: surgery 93.5%, angioplasty 91.1%; two-vessel: surgery 94.0%, angioplasty 94.1%).

Source of funding: Supported by a grant from the National Heart, Lung, and Blood Institute.

Does the study answer the question?/Further Comments Yes. CABG and PTCA did not differ significantly with respect to the occurrence of the composite primary end point.

Kurbaan AS;Bowker TJ;Ilsley CD;Sigwart U;Rickards AF;

Difference in the mortality of the CABRI diabetic and nondiabetic populations and its relation to coronary artery disease and the revascularization mode

Ref ID 3144 **RID:** 675 2001

QUALITY

A. Selection bias (systematic differences between the comparison groups)

A4 Based on your answers t, in your opinion was selection bias present? If so, what is the likely direction of its effect?:

Low risk of bias **Direction =**

B. Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)

B4 Based on your answers to the above, in your opinion was performance bias present? If so, what is the likely direction of its effect?:

Low risk of bias **Direction =**

C. Attrition bias (systematic differences between the comparison groups with respect to loss of participants)

C4 Based on your answers to the above, in your opinion was attrition bias present? If so, what is the likely direction of its effect?:

Low risk of bias **Direction =**

D. Detection bias (bias in how outcomes are ascertained, diagnosed or verified)

D6 Based on your answers to the above, in your opinion was detection bias present? If so, what is the likely direction of its effect?:

Low risk of bias

Direction =

Overall Study Quality -Strengths and Weaknesses:

Strengths: Multicentre, randomised (computerised random number generation), allocation concealment reported, baseline comparisons made,no loss to follow-up , Intention to treat analysis reported.
Weakness: No blinding.*
*This is a sub-group analysis of the CABRI study for patients with diabetes.

DETAILS

# of patients:

N=1054 - in the CABRI trial (n=125 patients with diabetes – n=62 in PTCA and n=63 in CABG)

Prevalence (Diagnostic):

Patient Characteristics

Baseline characteristics:
The mean age of the diabetics was 61.0 years and 75.2% were men. Diabetics were evenly randomised to PTCA (49.6%) and CABG (50.4%). (No further details reported).

Interventions/ Test/ Factor being investigated

PTCA

Comparisons

CABG

Length of Study/ Follow-up

4 years

Outcome measures studied

Primary and Secondary outcomes not stated. Outcomes assessed were mortality and measures of location for each pre revascularisation and post revascularisation coronary score.

Results

Effect Size

Results:
Outcome: PTCA diabetes (n=62) vs. CABG diabetes (n=63)
Mortality: 14 (22.6%) vs. 8 (12.5%); RR 1.81 (95% CI 0.80 -4.08)

Entire group (n=1054): Diabetics vs. Non diabetics
Mortality: 17.8 % vs. 8.1%; RR 2.19 (1.39 -3.44); p=0.001

Source of funding:

The CABRI trial was sponsored by educational and research grants from CR Bard (USCI) Inc., Minneapolis, Minnesota; The World Health Organisation, Geneva

Does the study answer the question?/Further Comments

Yes. Diabetics had significantly double the mortality of non-diabetics. Among diabetics there was no significant difference between PTCA and CABG for mortality.

Legrand VM;Serruys PW;Unger F;van Hout BA;Vrolix MC;Fransen GM;Nielsen TT;Paulsen PK;Gomes RS;de Queiroz e Melo JM;Neves JP;Lindeboom W;Backx B;Arterial Revascularization Therapy Study (ARTS) Investigators;

Three-year outcome after coronary stenting versus bypass surgery for the treatment of multivessel disease

Ref ID 1001 **RID:** 692 2004 Mar 9

QUALITY

A. Selection bias (systematic differences between the comparison groups)

A4 Based on your answers t, in your opinion was selection bias present? If so, what is the likely direction of its effect?:

Low risk of bias **Direction =**

B. Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)

B4 Based on your answers to the above, in your opinion was performance bias present? If so, what is the likely direction of its effect?:

Low risk of bias **Direction =**

C. Attrition bias (systematic differences between the comparison groups with respect to loss of participants)

C4 Based on your answers to the above, in your opinion was attrition bias present? If so, what is the likely direction of its effect?:

Low risk of bias **Direction =**

D. Detection bias (bias in how outcomes are ascertained, diagnosed or verified)

D6 Based on your answers to the above, in your opinion was detection bias present? If so, what is the likely direction of its effect?:

Low risk of bias **Direction =**

Overall Study Quality -Strengths and Weaknesses:

Strengths*: Multi centre, randomised, allocation concealment reported, sample size calculation reported, baseline comparisons made. Nos. lost to follow-up reported (0.4%; 6/1205**). Intention to treat analysis reported. Clinical events adjudicated by an independent committee.
Weakness: None

* This study is a 3 year follow-up of the ARTS trial.
** 1 patient was lost to follow-up, 3 were alive but withdrew their consent from further participation in the trial, and 2 patients were never treated by either modality.

DETAILS

# of patients: n=1205 (stenting (n=600) vs. Bypass surgery (n=605). Diabetes n=208 (n=112 stent and n=96 in CABG).

Prevalence (Diagnostic):

Patient Characteristics

Baseline characteristics:
Characteristics: stenting (n=600) vs. Bypass surgery (n=605)
Male (%): 77; 76
Age (yr):61 ±10; 61±9
Previous MI (%): 44; 42
Diabetes: 19; 16
Stable angina (%): 57; 60
Unstable angina (%):37; 35
No. of diseased vessels (%) of patients
1: 2; 0
2: 68; 67
3:30; 33
Vessel territory with stenosis (% of patients)
Right coronary artery: 71; 72
Left anterior descending artery: 90; 90
Left circumflex artery: 71; 71
Left main coronary artery: 0; 0
Total occlusion (%) of patients: 3; 5

Interventions/ Test/ Factor being investigated

PCI with stenting

Comparisons

CABG

Length of Study/ Follow-up

3 years

Outcome measures studied

The primary endpoint was defined as the absence of any of the following MACCE's within 12 months after randomisation: death, CVA, documented non fatal MI or repeat revascularisation by coronary stenting or CABG.
Secondary objectives of the study were to compare both strategies at 3 years.
Secondary measures of efficacy were assessed by means of the EQ-5D questionnaire, which allows patients to grade their general health status.

Results

Effect Size

Results: 3 years
Outcome: Stent (n=600) vs. CABG (n=605)
Death n (%):22 (3.7) vs. 28 (4.6); RR 0.79 (0.46-1.37)
CVA n (%): 20 (3.3) vs. 20 (3.3); RR 1.01 (0.55-1.86)
Q-wave MI n(%) : 36 (6) vs. 30 (5.0) ; RR 1.21 (0.76-1.94)
Non-Q-wave MI n(%) : 8 (1.3) vs. 4 (0.7); RR 2.02 (0.61-6.67)
CABG n (%): 55 (9.3) vs. 7(1.2); RR 7.92 (3.64-17.3)
Repeat PCI n (%): 120 (20) vs. 37 (6.1); RR 3.27 (2.30-4.65)
Angina free: 18.4% vs. 12.8%; p=0.01
Use of Anti anginal medication (BB, CCB, and/or nitrates): 78.4% vs. 65.4%; p<0.001
Quality of life*
EQ-5D summary: 85±17 vs. 86±17; p=0.74
EQ-5D domain
Mobility: 1.7±3.0 vs. 1.5±2.9; p=0.46
Self-care: 0.6±2.5 vs. 0.5±2.3; p=0.87
Usual activity: 1.0±1.9 vs. 0.8±1.7; p=0.09
Pain or discomfort: 4.9±6.9 vs. 5.2±7.7; p=0.78
Anxiety or depression: 2.4±4.8 vs. 2.2±4.4; p=0.77

*Higher scores on the EQ-5D summary indicate a good quality of life, where as low scores on the 5 items of EQ-5D domain reflect a favourable assessment of each component.

Patients with diabetes:
Outcome: Stent (n=112) vs. CABG (n=96)
Death, n (%): 8 (7.1) vs. 4(4.2); RR 1.714 (0.533-5.517)
CVA n (%): 6 (5.4) vs. 7 (7.3); 0.735 (0.256-2.112)
MI n (%): 11 (9.8) vs. 6 (6.3); RR 1.571 (0.604-4.090)

CABG n (%): 15 (13.4) vs. 2 (2.1);RR 6.429 (1.508-27.406)
Repeat PCI n (%): 31 (27.7) vs. 6 (6.3); RR 4.429 (1.930 -10.162)
Event free survival, n (%): 59 (52.7) vs. 78 (81.3); p<0.0001

Source of funding: Cordis Corporation

Does the study answer the question?/Further Comments Yes. There was no significant difference between stent and CABG groups for death, stroke or MI. There was significantly more repeat revascularisation in stent group compared to CABG. There were no differences in quality of life assessed by the self-rated EQ-5D questionnaire. More specifically, the benefit observed after CABG in specific domains such as 'mobility' and 'anxiety or depression' at 1 year disappeared by 3 years. The incidence of death, stroke, and MI were similar between patients with or without diabetes assigned to stenting or CABG. However, in diabetics assigned to stenting, the need for revascularisation was higher compared to CABG.

Martuscelli E;Clementi F;Gallagher MM;D'Eliseo A;Chiricolo G;Nigri A;Marino B;Romeo F;

Revascularization strategy in patients with multivessel disease and a major vessel chronically occluded; data from the CABRI trial

Ref ID 3285 **RID:** 493 2008

QUALITY

A. Selection bias (systematic differences between the comparison groups)

A4 Based on your answers t, in your opinion was selection bias present? If so, what is the likely direction of its effect?:

Low risk of bias **Direction =**

B. Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)

B4 Based on your answers to the above, in your opinion was performance bias present? If so, what is the likely direction of its effect?:

Low risk of bias **Direction =**

C. Attrition bias (systematic differences between the comparison groups with respect to loss of participants)

C4 Based on your answers to the above, in your opinion was attrition bias present? If so, what is the likely direction of its effect?:

Low risk of bias **Direction =**

D. Detection bias (bias in how outcomes are ascertained, diagnosed or verified)

D6 Based on your answers to the above, in your opinion was detection bias present? If so, what is the likely direction of its effect?:

Low risk of bias

Direction =

Overall Study Quality -Strengths and Weaknesses:

Strengths : Multicentre, randomised (computerised random number generation), allocation concealment reported, baseline comparisons made, Intention to treat analysis reported.
Weakness: No blinding of outcome assessors.*
*This a sub group of the CABRI study at 30 months follow-up. From the database of the CABRI study patients with chronic occlusion of a major coronary vessel (left anterioir descending artery, circumflex artery or right coronary artery) with the aim of determining whether the success of revascularisation in the territory of this vessel would influence the long term outcome regardless of the revascularisation strategy

DETAILS

# of patients:

n= 223 (CABG (n=103) ; PTCA (n=120))

Prevalence (Diagnostic):

Patient Characteristics

Baseline characteristics:
Variable: CABG (n=103) ; PTCA (n=120)
Age (yrs); 58 ; 60
Male: 84.5% ;90%
Angina grade
1: 13.6% ; 15.9%
2: 20.4% ;23.5%
3: 38.8% ; 375
4: 27.2% ; 23.5%
Previous MI: 54.4% ;47.5%
Diabetes: 16.5% ;10.8%
Hypertension: 37.9% ; 26.7%
Vessel occluded
CX: 17.5% ; 24.2%
RC: 62.1% ;55.8%
LAD : 20.4% ;20%

Inclusion criteria: From the CABRI database all patients with chronic occlusion of one of the three major coronary vessels (left anterior descending artery, circumflex artery or right coronary artery) were selected.

Interventions/ Test/ Factor being investigated

PTCA

Comparisons

CABG

Length of Study/ Follow-up

30 months (mean follow-up 30.7 months for PTCA compared to 28.1 months for CABG)

Outcome measures studied

Primary outcomes to be compared were mortality and symptom status (based on angina class) at 1 year. Secondary outcomes were MI, requirement for medication, and subsequent revascularisation procedures after the initial revascularisation.

Results

Effect Size

Results:
Outcome: CABG (n=103) vs. PTCA (n=120)
Q-Wave Myocardial Infarction: 3 (2.9%) vs. 8 (6.7%) ;p=ns
Death: 5 (4.9%) vs. 15 (12.5%): p=0.06

Death or Q wave MI: 7 (6.8%) vs. 21 (17.5%);p=0.05
Angina grade
1 : 89.3% vs. 83.7%
2 : 8.7% vs. 12.1%
3: 1.9% vs. 4.3%

Second Intervention
CABG: 0 vs. 30 (25%); p<0.01
PTCA: 6 (5.8%) vs. 26 (21.7%)

Third intervention
CABG: 0 vs. 7 (5.8%) ; p<0.05
PTCA: 1 (1%) vs. 5 (4.2%)

Completeness of revascularisation: 72.8 % vs. 7.8% ; p<0.001

Source of funding:

CABRI was sponsored by educational and research grants from CR Bard (USCI) Inc, the World Health Organisation, and the European Society of Cardiology

Does the study answer the question?/Further Comments

Yes. The incidence of composite endpoint of death or MI was significantly lower in the CABG group than in the PTCA group. More patients in the PTCA required a second and third revascularisation. More patients in the CABG group had significantly complete revascularisation compared to PTCA.

Morice MC;Serruys PW;Kappetein AP;Feldman TE;Stahle E;Colombo A;Mack MJ;Holmes DR;Torracca L;van Es GA;Leadley K;Dawkins KD;Mohr F;

Outcomes in patients with de novo left main disease treated with either percutaneous coronary intervention using paclitaxel-eluting stents or coronary artery bypass graft treatment in the Synergy Between Percutaneous Coronary Intervention with TAXUS and C

Ref ID 25 **RID:** 1181 2010 Jun 22

QUALITY

A. Selection bias (systematic differences between the comparison groups)

A4 Based on your answers t, in your opinion was selection bias present? If so, what is the likely direction of its effect?:

Low risk of bias **Direction =**

B. Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)

B4 Based on your answers to the above, in your opinion was performance bias present? If so, what is the likely direction of its effect?:

Low risk of bias **Direction =**

C. Attrition bias (systematic differences between the comparison groups with respect to loss of participants)

C4 Based on your answers to the above, in your opinion was attrition bias present? If so, what is the likely direction of its effect?:

Low risk of bias

Direction =

D. Detection bias (bias in how outcomes are ascertained, diagnosed or verified)

D6 Based on your answers to the above, in your opinion was detection bias present? If so, what is the likely direction of its effect?:

Low risk of bias

Direction =

Overall Study Quality -Strengths and Weaknesses:

Strengths – Randomised, allocation concealment reported. n=12 withdrew consent in CABG group (N=336, 96.6% follow-up at 12 months) and n=1 lost to follow-up and n=1 discontinued treatment in PCI group (n=355, 99.4% follow-up at 12 months). Baseline comparisons made.
Limitations- ITT not reported.
*This study presents the outcomes in the pre-specified subgroup of patients (n=705) with LM disease in the SYNTAX trial.

DETAILS

# of patients:

n=705 (with left main disease) [n=348 in CABG and n=357 in PCI]
All randomised patients n=1800; n=1095 patients with 3 vessel disease and

Prevalence (Diagnostic):

Patient Characteristics

Eligible patients had de novo LM and/or 3 vessel disease and ≥50% stenosis by visual assessment in the with stable or unstable angina. LM disease was defined as at least 50% stenosis by visual assessment in the LM vessel or LM equivalent (defined as atleast50% stenosis of the ostium of the left anterior descending artery and the ostium of the left circumflex) with or without stenosis in other vessels. Key exclusion criteria were previous PCI or CABG, acute MI or the need for concomitant cardiac\surgery. Patients were evaluated by a local heart team, consisting of an interventional cardiologist and a cardiothoracic\ surgeon, for suitability for either PCI with TAXUS Express paclitaxel-eluting stents or CABG.

Baseline clinical characteristics in Left main patients
Variable: CABG (n=348) ; PCI (n=357)
Age: 65.6±0.1; 65.4±9.8
Men (%): 75.6; 72
Diabetes mellitus (%): 25.6; 23.8
Prior MI (%): 25.4; 28.5
Unstable angina (%):29.0; 30.5
Left ventricular ejection fraction < 30% (%):1.4;1 .4
Isolated LM, (%):14.1; 11.8
LM+1 vessel (%):20.4; 18.8
LM+2 vessels (%): 30.5; 31.4
LM+3 vessels (%): 35.1; 38.1
Mean SYNTAX score: 30.2±12.7; 29.6±13.5

In the LM subset, 2 patients randomised to CABG received medical treatment (worsening clinical status, n=1; investigator decision that patient was not suitable for surgical treatment, n=1), and 5 received PCI (worsening clinical status, n=1; patient preference, n=3; disappearance of LM stenosis on second angiogram, n=1). In the PCI arm, 3 patients received medical therapy (patient preference, n=1; disappearance of LM stenosis on second angiogram, n=2) and 5 received CABG (patient preference, n=3; investigator decision that patient was not suitable for PCI, n=2)

The SNTAX study also used a novel scoring system (SYNTAX score) to predict outcomes on the basis of coronary anatomic risk factors including number of

	lesions, total occlusion, bi/trifurcations, aorto-ostial stenosis, tortuosity, lesion length >20mm, calcification, thrombus and small vessels/diffuse disease.
Interventions/ Test/ Factor being investigated	PCI with TAXUS Express paclitaxel-eluting stents. Clopidogrel was mandated for at least 6 months after the procedure, with aspirin therapy indefinitely.
Comparisons	CABG. Minimally invasive surgery was not performed, arterial revascularisation was preferred per protocol and the decision of on-or off pump surgery was left to surgical judgement.
Length of Study/ Follow-up	1 year
Outcome measures studied	The primary end-point was the composite of major adverse cardiovascular and cerebro vascular events (MACCE) at 1 year, which included all-cause death, cerebrovascular accident/stroke (CVA), MI and repeat revascularisation.
Results	
Effect Size	At 1 year Overall LM disease: Outcomes: PCI (N=357) vs. CABG (N=348) MACCE: 15.8%vs. 13.6% All causes death: 4.2% vs. 4.4% (change -0.2 [95% CI-3.2 to 2.8]) Cardiac death: 3.9%vs. 2.4% (change 1.6% [95%CI-1.0% to 4.2%]) MI: 4.3% vs.4.1 % (change 0.2 [95% CI -2.8 to 3.2]) CVA (stroke): 0.3% vs.2.7% (change -2.4% [95% CI-4.3% to-0.5%]) Repeat revascularisation: 12% vs. 6.7% (change 5.3%[95% CI1% TO 9.6%]) Of the repeat revascularisations the majority were via repeat PCI, with only 3.1% (11/355) of LM patients initially treated with PCI undergoing repeat revascularisation by CABG within 12 months. Outcomes at 1 year in Left main patients by number of diseased vessels: Subgroup, % (n/N): CABG (N=348) vs. PCI (N=357); difference; p-value 1. Overall MACCE:P=.50* All LM patients: 13.7 (46/336) vs. 15.8 (56/355); 2.1 (-3.2 to7.4); 0.44 LM isolated: 8.5 (4/47) vs. 7.1(3/42);-1.4% (-14.8 to 11.9); 1.00 LM+1 vessel: 13.2 (9/68) vs.7.1 (5/67); -5.8 (-16.0 to 4.40); 0.27 LM+2 vessel: 14.4(15/04) vs. 19.8 (22/111); 5.4(-4.6 to 15.4); 0.29 LM +3 vessels: 15.4 (18/117) vs. 19.3 (26/135); 3.9(-5.5 to 13.2); 0.42 2. Death/CVA/MI: P=0.53 All LM patients: 9.2(31/336) vs. 7.0(25/355);-2.2(-6.3 to 1.9); 0.29 LM isolated: 2.1 (1/47) vs.0 (0/42);-2.1 (N/A); 1.00 LM+1 vessel: 7.4 (5/68) vs. 4.5 (3/67);-2.9(N/A); 0.72 LM+2 vessels: 7.7(8/104) vs.9.9 (11/111); 2.2 (-5.3to 9.8); 0.57 LM +3 vessels: 14.5(7/117) vs. 8.1 (11/135);-6.4 (-14.3 to1.5); 0.11 3. Revascularisation: P=0.33 All LM patients: 6.5(22/336) vs. 11.8(42/355); 5.3 (1.0 to 9.6); 0.02 LM isolated: 6.4(347) vs.7.1 (3/42); 0.8(N/A); 1.00 LM+1 vessel: 5.9(4/68) vs. 3.0 (2/67);-2.9(N/A); 0.68 LM+2 vessels: 7.7 (8/104) vs.15.3 (17/111); 7.6 (-0.8 to 16.1); 0.08 LM +3 vessels: 6.0 (7/117); 14.8(20/135); 8.8(1.5to16.2) *Interaction p-value Outcomes stratified by baseline SYNTAX score: 1.Death SYNTAX score: CABG vs. PCI 0-22: 3% vs.0.9% 23-32:6.7% vs. 1.0% ≥33:4.1%vs.9.7% 2.MI

SYNTAX score: CABG vs. PCI
0-22: 2.0% vs.1.7%
23-32: 3.4% vs. 2.9%
≥33: 6.1% vs. 7.5%

3.CVA
SYNTAX score: CABG vs. PCI
0-22: 2% vs. 0%
23-32: 2.2% vs. 0%
≥33: 3.4% vs. 0.7%

4.Death/CVA/MI
SYNTAX score: CABG vs. PCI
0-22: 6.1% vs. 1.7%
23-32: 10.1% vs. 3.9%
≥33: 10.9%vs. 14.2%

5.Repeat revascularisation
SYNTAX score: CABG vs. PCI
0-22: 8.1% vs. 7.7%
23-32: 7.9%vs. 9.7%
≥33: 4.8% vs.17.2%

Patients were sub divided by baseline SYNTAX score in to 3 terciles: low (Syntax score 0 to 22), intermediate (23 to32), or high (≥33) scores. In the LM sub group, MACCE outcomes at 1 year were comparable between PCI and CABG with low or intermediate baseline SYNTAX score, with the exception of significantly increased all-cause death in CABG patients with an intermediate SYNTAX score compared with PCI patients with an intermediate SYNTAX score. In the tercile with the highest baseline score, MACCE outcomes were significantly higher for patients treated with PCI. Increased MACCE rates in the highest SYNATX score tercile were driven primarily by significantly increased repeat revascularisation.

Source of funding:

Research supported by Boston Scientific Corp.

Does the study answer the question?/Further Comments

Yes. Patients with LM disease who had revascularisation with PCI had safety and efficacy outcomes comparable to CABG at 1 year.
Authors note: Although the study was adequately powered to test the difference in MACCE between groups, it is underpowered to detect differences in the individual components of MACCE, so these results must be interpreted with caution. The sub set of LM patients in this study was a heterogeneous group that consisted of patients with isolated LM disease or LM plus additional disease. The clinical events committee did not adjudicate repeat revascularisation according to lesion location (i.e., LM or elsewhere), which may have confounded the results presented here. Follow-up was available only through 1 year, hence longer follow-up is required to determine whether these 2 revascularisation strategies offer comparable medium-term outcomes in this group of patients.

Pocock SJ;Henderson RA;Seed P;Treasure T;Hampton JR;

Quality of life, employment status, and anginal symptoms after coronary angioplasty or bypass surgery. 3-year follow-up in the Randomized Intervention Treatment of Angina (RITA) Trial

Ref ID 4260 **RID:** 552 1996

QUALITY

A. Selection bias (systematic differences between the comparison groups)

A4 Based on your answers t, in your opinion was selection bias present? If so, what is the likely direction of its effect?:

Low risk of bias

Direction =

B. Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)

B4 Based on your answers to the above, in your opinion was performance bias present? If so, what is the likely direction of its effect?:

Low risk of bias

Direction = Patients and clinicians were not blind to treatment due to the nature of the study. However, the primary

C. Attrition bias (systematic differences between the comparison groups with respect to loss of participants)

C4 Based on your answers to the above, in your opinion was attrition bias present? If so, what is the likely direction of its effect?:

Low risk of bias

Direction =

D. Detection bias (bias in how outcomes are ascertained, diagnosed or verified)

D6 Based on your answers to the above, in your opinion was detection bias present? If so, what is the likely direction of its effect?:

Low risk.

Direction =

Overall Study Quality -Strengths and Weaknesses:

This is a well conducted RCT. Methods of randomisation and concealment well described. It was not appropriate to blind patients or clinicians but primary endpoint was assessed by independent, blinded investigators. No patients lost to follow up for survival. An intent-to-treat analysis was performed.

DETAILS

# of patients:

n=1011 (n=501 in the CABG arm and n=510 in the PTCA arm)

Prevalence (Diagnostic):

Patient Characteristics

	CABG N=501	PTCA N=510
Treatment vessels		
One	222	234
Two	218	213
Three	61	63
Age (yr):		
<40	13	14
40-49	88	91
50-59	207	225
60-69	169	156
70-79	21	23
Women:	107	88
Angina:		
None	33	36

Grade 1	33	44
Grade 2	128	140
Grade 3	155	159
Grade 4	149	130
At rest	275	282
Causing hospital admission:	187	189
Median time since onset (lower and upper quartiles):	8(4,24)	9(5,24)
Previous MI:	210	217
Not working due to coronary disease:	191	193
Current medication:		
Beta-blocker	369	383
Calcium antagonist	363	365
Long-acting nitrate	314	334
Aspirin	353	370
Antianginal drugs:		
None	14	13
One	116	95
Two	174	216
Three	194	185

Interventions/ Test/ Factor being investigated

Percutaneous transluminal coronary angioplasty (PTCA). (PTCA was conventional balloon angioplasty.)

Comparisons

PTCA versus coronary artery bypass surgery (CABG)

Length of Study/ Follow-up

2.5 years since randomisation.

Outcome measures studied

Primary outcome: 5-year incidence of death and definite non-fatal myocardial infarction. Secondary outcomes in this study include quality of life, employment status, anginal symptoms.

Results

Effect Size

Data are not presented in tables but are in graph form. Therefore, results are reported as they appear in the text of the study.

Primary outcome
After 3 years of follow-up, there was no difference in mortality (18 and 17 deaths in the PTCA and CABG groups, respectively) and nonfatal myocardial infarction (34 and 27 in the PTCA and CABG groups, respectively.)

Secondary outcomes

Angina
For the CABG group, there was a steadily increasing prevalence of angina over time, from 1.4% grade >=2 at 1 month after the procedure to 16.4% at 3 years after randomization. In the PTCA group, the prevalence of grade >=2 remained steady at approx 20%, but this was achieved because some PTCA patients underwent further procedures: 108 patients (21%) required CABG and an additional 77 patients (15%) required further PTCA within 3 years of randomization. The 3-year reintervention rates in the CABG group were much lower: 4(1%) required additional CABG, and a further 17(3%) underwent PTCA.

Self reported health status (Nottingham Health Profile (NHP)
For both groups there was a marked improvement from baseline in all domains: energy, pain, emotional reactions, sleep, social isolation and physical mobility. There was no significant difference between the groups for individual domains. When all items were combined, the treatment difference at 2 years was 0.79 item (p=0.10) in favour of the CABG group. This compares with a treatment difference of 1.21 items (p=0.007) at 3 months post randomisation.

Relationship between health status and angina
There is a clear trend whereby the higher the angina grade, the greater the impairment in each domain (part 1 of NHP) and the greater the impact on life

aspects (part 2 NHP).

Employment status
Percentages not working at 3 years are 51.8% in the CABG group and 47.7% in the PTCA group.

Source of funding: British Heart Foundation, British Cardiac Society and Department of health. Additional financial support has been provided by Advanced Cardiovascular

Does the study answer the question?/Further Comments

Serruvs PW;Morice MC;Kappetein AP;Colombo A;Holmes DR;Mack MJ;Stahle E;Feldman TE;van d;Bass EJ;Van D;Leadley K;Dawkins KD;Mohr FW;

Percutaneous coronary intervention versus coronary-artery bypass grafting for severe coronary artery disease

Ref ID 3717 **RID:** 508 2009

QUALITY

A. Selection bias (systematic differences between the comparison groups)

A4 Based on your answers t, in your opinion was selection bias present? If so, what is the likely direction of its effect?:

Low risk of bias **Direction =**

B. Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)

B4 Based on your answers to the above, in your opinion was performance bias present? If so, what is the likely direction of its effect?:

Low risk of bias **Direction =**

C. Attrition bias (systematic differences between the comparison groups with respect to loss of participants)

C4 Based on your answers to the above, in your opinion was attrition bias present? If so, what is the likely direction of its effect?:

Low risk of bias **Direction =**

D. Detection bias (bias in how outcomes are ascertained, diagnosed or verified)

D6 Based on your answers to the above, in your opinion was detection bias present? If so, what is the likely direction of its effect?:

Low risk of bias

Direction =

Overall Study Quality -Strengths and Weaknesses:

Strengths- Randomised, allocation concealment reported, baseline comparisons made, nos. lost to follow-up reported ((5.4% in CABG and 1.3% in PCI group), Intention to treat analysis reported. Blind outcome assessment (adjudicated by an independent Clinical Events Committee).
Weakness: Patients aware of the intervention allocated.

DETAILS

# of patients:

n=1800 (n=897 in CABG and n=903 in PCI) at the sites in USA and Europe. PCI , N=903 [11 underwent CABG, 6 underwent neither PCI nor CABG] . CABG, N=897

Prevalence (Diagnostic):

Patient Characteristics

Baseline characteristics: (Patients with previously untreated 3 vessel or Left Main coronary artery disease)
Characteristic: PCI (N=903) ; CABG (N=897)
Age (yr): 65.2 ±9.7; 65.0±9.8
Male (%): 76.4; 78.9
Medically treated diabetes (%): 25.6; 24.6
Previous MI (%): 31.9; 33.8
Stable Angina (%): 56.9; 57.2
Unstable angina (%): 28.9; 28
European System for Cardiac operative Risk Evaluation (euro SCORE): 3.8 ±2.6 ;3.8 ±2.7
A total of 38.8% of patients in the CABG group and 39.5% in the PCI group had left main coronary artery disease, with or without additional diseased vessels.

Cardiac related medications given after the study procedure:
Medication: PCI vs. CABG
Any (%): 98.9; 98.6
Aspirin (%):
At discharge (%): 96.3; 88.5
1 month after procedure (%): 95.5;18.4
Thienopyridine:
At discharge (%): 96.8 ;19.5
1 month after procedure (%) : 95.5; 18.4
Statin (%): 86.7; 74.5
BB (%) : 81.3; 78.6
ACE inhibitor (%): 55.1; 44.6
CCB (%): 25.8; 18.4
ARB (%): 13.3; 7

Patients who underwent CABG received less pharmacologic treatment, whereas those who underwent PCI were consistently treated with antiplatelet medications.
Inclusion criteria:
1.Stable or unstable angina pectoris with ischemia; or patients with atypical chest pain or asymptomatic with demonstrated myocardial ischemia (e.g. exercise stress test, radionuclide scintigraphy, stress echocardiography).
2.Denovo lesions.
3.Eligible for coronary revascularisation (both PCI and CABG).
4.At least 1 significant stenosis in all 3 major epicardial territories supplying viable myocardium; or significant stenosis in the LM or LM equivalent with or without stenosis in one of the other vessels.
5.Patients with hypoplastic right coronary artery with absence of a posterior descending artery and presence of a lesion in the left anterior descending and left circumflex territories may be included in the trial as a 3 vessel equivalent.
6.Vessel size should be at least 1.5mm diameter as assessed by diagnostic angiogram.

Exclusion criteria:
1.Younger than 21 years.

	2.Previous PCI or CABG. 3.Pregnancy or intention to become pregnant. 4.Ongoing acute MI and cardiac enzymes >2 times the upper limit of normal. 5.Inability to follow the patient over the period of 1 year after enrolment, as assessed by the investigator. 6.Planned need for concomitant other cardiac surgery (e.g. valve surgery or resection of aortic or left ventricular aneurysms. Etc.) 7.Psychiatric illness or organic brain disease rendering the subject unable to understand the nature, scope, and possible consequences of the study or mental retardation or language barrier such that the patient is unable to give informed consent. 8.Single or 2 vessel disease without LM disease. 9.Participation or planned participation in another cardiovascular clinical study before completion of 1 year follow-up.
Interventions/ Test/ Factor being investigated	PCI (Percutaneous coronary intervention) with drug eluting stents -(PCI with polymer-based, paclitaxel-eluting TAXUS stents)
Comparisons	CABG.(Coronary artery bypass grafting)
Length of Study/ Follow-up	12 months
Outcome measures studied	Primary end point:Composite of major adverse cardiac and cerebrovascular events (i.e., death from any cause, stroke, MI or repeat revascularisation) throughout the 12 month period after randomisation.
Results	
Effect Size	Results:** Variable: PCI vs. CABG (RR with PCI (95% CI)) Major adverse cardiac or cerebrovascular event in hospital: 39/896 vs. 47/870 (0.81 (0.53-1.22)) Major adverse cardiac or cerebrovascular event after 6 months: 111/893 vs. 85/860 (1.26 (0.96-1.64)) Major adverse cardiac or cerebrovascular event after 12 months: 159/891 vs. 105/849 (1.44 (1.15-1.81)) Death, stroke or MI: 68/891 vs. 65/849 (1.00 (0.72-1.38)) Death from cardiac causes: 33/891 vs. 18/849 (1.75 (0.99-3.08)) Death from cardiovascular causes: 1/891 vs. 3/849 (0.32 (0.03-3.05)) Death from non cardiovascular causes: 5/891 vs. 9/849 (0.53 (0.18-1.57)) MI: 43/891 VS. 28/849 (1.46 (0.92-2.33)) Repeat revascularisation*: 120/891 vs. 50/849 (2.29 (1.67-3.14)) CABG: 25/891 vs. 11/849 (2.17 (1.07-4.37)) PCI: 102/891 vs. 40/849 (2.43 (1.71-3.46)) *One patient randomly assigned to undergo CABG and seven patient randomly assigned to undergo PCI underwent repeat PCI and repeat CABG. **Data for patients who were assigned to one treatment but underwent the other and for those who did not undergo either revascularisation procedure were analysed in an intention to treat manner. Sub-group- Patients with Left main coronary artery disease***: 12 months Outcome: CABG vs. PCI Major adverse cardiac or cerebrovascular events: 13.7% vs. 15.8% (p=0.44) Repeat revascularisation: 6.5% vs. 11.8% (p=0.02) Sub-group- 3 vessel disease in the absence of left main coronary artery disease***: 12 months Outcome: CABG vs. PCI Major adverse cardiac or cerebrovascular events: 11.5% vs. 19.2% (p<0.0001) Repeat revascularisation: 5.5% vs. 14.6% (p<0.001) Death from any cause, stroke, or MI: 6.6% vs. 8% (p=0.39) *** Exact number of patients in the subgroup of patients with left main coronary artery disease and with 3 vessel disease not reported.

Source of funding: Supported by Boston Scientific.

Does the study answer the question?/Further Comments

Yes. Rates of major adverse cardiac or cerebrovascular events at 12 months were significantly higher in the PCI group. At 12 months the rates of death and MI were similar between the 2 groups. The rates of repeat revascularisation at 12 months was significantly higher among patients in the PCI group than among those in the CABG group. Most patients who underwent repeat revascularisation were treated with PCI rather than CABG.

The 12 month rate of major adverse cardiac or cerebrovascualr events among patients with left main coronary artery disease was similar in CABG and PCI groups, although the rate of repeat revascularisation was significantly higher in the PCI group.
The 12 month rate of major adverse cardiac or cerebrovascular events among patients with 3 vessel disease was significantly increased in the PCI group as compared to CABG group, as was the rate of repeat revascularisation. The rate of death from any cause, stroke, or MI in this subgroup was similar with PCI and CABG.

Serruys PW;Ong AT;van Herwerden LA;Sousa JE;Jatene A;Bonnier JJ;Schonberger JP;Buller N;Bonser R;Disco C;Backx B;Hugenholtz PG;Firth BG;Unger F;

Five-year outcomes after coronary stenting versus bypass surgery for the treatment of multivessel disease: the final analysis of the Arterial Revascularization Therapies Study (ARTS) randomized trial

Ref ID 9140 **RID:** 611 2005 Aug 16

QUALITY

A. Selection bias (systematic differences between the comparison groups)

A4 Based on your answers t, in your opinion was selection bias present? If so, what is the likely direction of its effect?:

Low risk of bias **Direction =**

B. Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)

B4 Based on your answers to the above, in your opinion was performance bias present? If so, what is the likely direction of its effect?:

Low risk of bias **Direction =**

C. Attrition bias (systematic differences between the comparison groups with respect to loss of participants)

C4 Based on your answers to the above, in your opinion was attrition bias present? If so, what is the likely direction of its effect?:

Low risk of bias **Direction =**

D. Detection bias (bias in how outcomes are ascertained, diagnosed or verified)

D6 Based on your answers to the above, in your opinion was detection bias present? If so, what is the likely direction of its effect?:

Low risk of bias

Direction =

Overall Study Quality -Strengths and Weaknesses:

Strengths*: Multi centre, randomised, allocation concealment reported, baseline comparisons made. Nos. lost to follow-up reported (1.6%; 10/600 in stent and 3.1%; 19/605 in CABG). Intention to treat analysis reported. Clinical events adjudicated by an independent committee.
Weakness: None
Weaknesses reported by the authors: the study was underpowered to detect a significant difference in the endpoint; because of the strict inclusion and exclusion criteria, patients treated in this study represent a small segment of patients treated by the study surgeons.

* This study is a 5 year follow-up of the ARTS trial.

DETAILS

# of patients:

n=1205 (n=600 in stent and n=605 in CABG) ; n=208 diabetic patients (n=112 in stent and n=96 in CABG)

Prevalence (Diagnostic):

Patient Characteristics

Baseline characteristics:
Characteristics: stenting (n=600) vs. Bypass surgery (n=605)
Male (%): 77; 76
Age (yr):61 ±10; 61±9
Previous MI (%): 44; 42
Diabetes: 19; 16
Stable angina (%): 57; 60
Unstable angina (%):37; 35
No. of diseased vessels (%) of patients
1: 2; 0
2: 68; 67
3:30; 33
Vessel territory with stenosis (% of patients)
Right coronary artery: 71; 72
Left anterior descending artery: 90; 90
Left circumflex artery: 71; 71
Left main coronary artery: 0; 0
Total occlusion (%) of patients: 3; 5

Interventions/ Test/ Factor being investigated

Stent implantation (bare metal)

Comparisons

CABG

Length of Study/ Follow-up

5 years

Outcome measures studied

Primary endpoint was defined as the absence of any of the following major adverse cardiac and cerebral events (MACCE) within 12 months after randomisation: death (All cause mortality), cerebrovascular accident, documented non fatal MI, or repeat revascularisation. Secondary objectives of the study were to compare both strategies at 5 years. In addition, anginal status and use of medications were assessed.

Results

Effect Size

Results:
Outcomes: Stenting (n=600) vs. CABG (n=605)
Death, n (%): 48 (8%) vs. 46 (7.6%); RR 1.05 (0.71-1.55); p=0.83
CVA n (%): 23 (3.8%) vs. 21 (3.5%); RR 1.10 (0.62-1.97); p=0.76
Q-wave MI n(%) : 40 (6.7%) vs. 34 (5.6%) ;RR 1.19 (0.76-1.85); p=0.47
Non Q-wave MI n(%) : 11 (1.8%) vs. 5 (0.8%); RR 2.22 (0.78-6.35);p=0.14
CABG n (%): 63 (10.5%) vs. 7 (1.2%); RR 9.08 (4.19-19.7); p<0.001

Repeat PCI n (%): 139 (23.2%) vs. 50 (8.3%); RR 2.80 (2.07-3.80);p<0.001
Any revascularisation n (%): 182 (30.3%) vs.53 (8.8%); RR 3.46 (2.61-4.60); p<0.001
Presence of anginal symptoms: 21.2% vs. 15.5%; p<0.05
Patients on short acting nitrates: 6.1% vs. 2.4%; p=0.003
Patients on long acting nitrates: 19.6% vs. 11.6%; p<0.001
Patients on BB: 53.9% vs. 46.5%; p=0.016
Patients on CCB: 29.1% vs. 18.9%; p<0.001

Patients with diabetes:
Outcomes: Stenting (n=112) vs. CABG (n=96)
Death, n (%): 15 (13.4%) vs. 8 (8.3%); RR 1.61 (0.713.63);p=0.27
CVA n(%) : 7 (6.3) vs. 7 (7.3%); RR 0.86 (0.31-2.36); P=0.79
MI n (%): 12 (10.7%) vs. 7 (7.3); RR 1.47 (0.60-3.59); p=0.47
Repeat CABG n (%): 17 (15.2%) vs. 2 (2.1%); RR 7.29 (1.73-30.7); p=0.001
Repeat PCI n (%): 34 (30.4%) vs. 9(9.4%); RR 3.24 (1.64-6.41); p<0.001
Any revascularisation n (%): 48 (42.9%) vs. 10 (10.4%); RR 4.11 (2.20-7.68); p<0.001

Source of funding:

Cordis, a Johnson & Johnson company.

Does the study answer the question?/Further Comments

Yes. Overall freedom from death, stroke, or MI was not significantly different between groups. Presence of anginal symptoms and use of anti anginal medication was significantly lower in the CABG group compared to stent group. The incidence of repeat revascularisation was significantly higher in the stent group than in the CABG group.

Author's conclusion: Based on the available evidence, surgery should continue to be viewed as the preferred therapy for diabetic patients with multivessel disease when using bare metal stents. The authors also state that when interpreting the results, it is important to realise that improvements in both surgical and percutaneous techniques have occurred, calling in to question the validity of these earlier conclusions. The advent of drug eluting stents has drastically reduced the need for repeat revascularisation in both diabetic and non diabetic patients.

Serruys PW;Unger F;Sousa JE;Jatene A;Bonnier HJRM;Schonberger JPAM;Buller N;Bonser R;van d;Van H;Morel MAM;Van H;

Comparison of coronary-artery bypass surgery and stenting for the treatment of multivessel disease

Ref ID 3726 **RID:** 537 2001

QUALITY

A. Selection bias (systematic differences between the comparison groups)

A4 Based on your answers t, in your opinion was selection bias present? If so, what is the likely direction of its effect?:

Low risk of bias

Direction =

B. Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)

B4 Based on your answers to the above, in your opinion was performance bias present? If so, what is the likely direction of its effect?:

Low risk of bias

Direction =

C. Attrition bias (systematic differences between the comparison groups with respect to loss of participants)

C4 Based on your answers to the above, in your opinion was attrition bias present? If so, what is the likely direction of its effect?:

Low risk of bias

Direction =

D. Detection bias (bias in how outcomes are ascertained, diagnosed or verified)

D6 Based on your answers to the above, in your opinion was detection bias present? If so, what is the likely direction of its effect?:

Low risk of bias

Direction =

Overall Study Quality -Strengths and Weaknesses:

Strengths*: randomised, allocation concealment reported, loss to follow-up (1/600 (0.1%) in stenting and 4/605 (0.6%)**, Intention to treat analysis reported. Clinical events adjudicated by an independent committee.
Weakness: None
*this study is the 1 year follow-up of the ARTS trial.
**Five patients , one assigned to stenting to and four assigned to surgery did not undergo coronary revascularisation and instead continued to receive pharmacologic treatment.

DETAILS

# of patients:

n=1205 (n=600 stenting group; n=605 surgery group)

Prevalence (Diagnostic):

Patient Characteristics

Baseline characteristics:
Characteristics: stenting (n=600) vs. Bypass surgery (n=605)
Male (%): 77; 76
Age (yr):61 ±10; 61±9
Previous MI (%): 44; 42
Diabetes: 19; 16
Stable angina (%): 57; 60
Unstable angina (%):37; 35
No. of diseased vessels (%) of patients
1: 2; 0
2: 68; 67

	3:30; 33 Vessel territory with stenosis (% of patients) Right coronary artery: 71; 72 Left anterior descending artery: 90; 90 Left circumflex artery: 71; 71 Left main coronary artery: 0; 0 Total occlusion (%) of patients: 3; 5 Inclusion criteria: Patients who had not previously undergone bypass surgery or angioplasty were eligible for coronary revascularisation if they had either stable angina (CCS class I,II,III or IV) or unstable angina or if they had silent ischemia and at least 2 new lesions that were located in different vessels and territories (not including the left main coronary artery) and that were potentially amenable to stent implantation. Exclusion criteria: Patients had to have a left ventricular ejection fraction of more than 30%, and patients with overt congestive heart failure were excluded. Patients were also excluded if they had a history of cerebrovascualr accident; if they had had transmural myocardial infarction in the previous week; if they had severe hepatic or renal disease, diseased saphenous veins, neutropenia or thrombocytopenia or an intolerance or contraindication to acetylsalicylic acid or ticlodipine; or if they needed concomitant major surgery (e.g. valve surgery, resection of an aortic or left ventricular aneurysm, carotid endarterectomy, or surgery for an abdominal aortic aneurysm). 5 patients, 1 assigned to stenting and 4 assigned to surgery did not undergo coronary revasc and instead continued to receive pharmacologic treatment. 6 patients in stent group were instead treated surgically and 19 patients in surgery group were instead treated with stent implantation
Interventions/ Test/ Factor being investigated	Stent implantation
Comparisons	Bypass surgery
Length of Study/ Follow-up	1 year
Outcome measures studied	Primary endpoint was freedom, for 12 months after randomisation, from major adverse cardiac or cerebrovascular events, defined as death, stroke, transient ischemic attacks, and reversible ischemic neurologic deficits ;documented non fatal MI; and repeated revascularisation by percutaneous intervention or surgery.Secondary endpoint was angina status, use of medications, quality of life, a combined endpoint of death, MI, or stroke; and the rates of death, MI, stroke and revascularisation procedures.
Results	
Effect Size	Results - Outcome: Stenting (n=600) vs. Surgery (n=605) Death: 15 (2.5%) vs. 17 (2.8%); RR 0.89 (0.45 -1.77) Cerebrovascular accident: 10 (1.7%) vs. 13 (2.1%); RR0.78 (0.34-1.76) MI: 37 (6.2%) vs. 29 (4.8%); RR 1.29 (0.80-2.06) Repeated revascularisation: 126 (21.0) vs. 23 (3.8); RR 5.52 (3.59-8.49) CABG: 40 (6.7) vs. 4 (0.7); 10.08 (3.63-28.01) PTCA: 94 (15.7) vs. 20 (3.3); RR 4.74 (2.96-7.58) Event free-survival: 443 (73.8%) vs. 531 (87.8%) Free of angina (%): 78.9 vs. 89.5; p<0.001 Free of anti anginal medication (%): 21.1 vs. 41.5; p<0.001 EuroQol summary *:86±16 vs. 87± 16; p=0.24 EuroQol domain: Mobility: 1.4±2.8 vs. 1.1±2.8; p=0.05 Self-care:0.4±2.1 vs. 0.4±2.5; p=0.53 Usual activity: 1.0±1.9 vs. 0.8±1.8; p=0.01 Pain or discomfort: 4.4±7.1 vs. 4.6±7.4; p=0.82 Anxiety or depression: 2.5±4.5 vs. 2.0±4.1; p=0.04

The data from the self-rated EuroQol questionnaire indicated a slight difference in favour of surgery after 12 months. The difference at 12 months was attributable to significant differences in the ratings for 'usual activity' and 'anxiety or depression' and a non significant difference in ratings for mobility.

*Information elicited on the five EuroQol domains is converted in to a single EuroQol summary (range, 0 to 100) after the individual scores have been weighted to account for differences in the importance of the various domain to the patient.

Source of funding:

Supported by Cordis, a Johnson & Johnson company

Does the study answer the question?/Further Comments

Yes. At one year, there was no significant difference between the two groups in terms of the rates of death, stroke, or MI. Significantly more patients in the stenting group underwent revascularisation compared to CABG. Event free survival was significantly better in the CABG group compared to stenting. There was no significant difference between the groups for quality of life.Significantly more no. of patients in the surgery group were free of angina and free of anti anginal medication compared to stenting group.

Sigwart U;Stables R;Booth J;Erbel R;

Coronary artery bypass surgery versus percutaneous coronary intervention with stent implantation in patients with multivessel coronary artery disease (the Stent or Surgery trial): A randomised controlled trial

Ref ID 3794 **RID:** 702 2002

QUALITY

A. Selection bias (systematic differences between the comparison groups)

A4 Based on your answers t, in your opinion was selection bias present? If so, what is the likely direction of its effect?:

Low risk of bias **Direction =**

B. Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)

B4 Based on your answers to the above, in your opinion was performance bias present? If so, what is the likely direction of its effect?:

Low risk of bias **Direction =**

C. Attrition bias (systematic differences between the comparison groups with respect to loss of participants)

C4 Based on your answers to the above, in your opinion was attrition bias present? If so, what is the likely direction of its effect?:

High risk of bias **Direction =**

D. Detection bias (bias in how outcomes are ascertained, diagnosed or verified)

D6 Based on your answers to the above, in your opinion was detection bias present? If so, what is the likely direction of its effect?:

Low risk of bias

Direction =

Overall Study Quality -Strengths and Weaknesses:

Strengths*- Multi centre (Europe and Canada), Randomisation method reported, allocation concealment reported, sample size calculation reported, baseline comparisons made, Numbers lost to follow (1 year- 8/488 (1.6%) in PCI and 13/500 (2.6%) in CABG; At 2 years – 188/488 (38.5%) in PCI and 199/500 (39.8%) in CABG; At 3 years- 404/488 (82.2%) in PCI and 408/500 (81.6%) in CABG) reported, Intention to treat analysis reported. Blind outcome assessment (A clinical events committee, consisting of study interventionists and surgeons, adjudicated all outcome measures. The members of the clinical events committee did not adjudicate patients treated at their own centres and were blinded to the randomisation allocation and of the identities of patients and centres.)

Weakness- High attrition. Patients aware of treatment allocation. Author reported weaknesses in the study: Small sample size, patients and investigators aware of the treatment allocation.

* This study reports 1 and 2 year follow-up of the SoS trial.

DETAILS

# of patients:

n=988 (n=488 in PCI and n=500 in CABG)

Prevalence (Diagnostic):

Patient Characteristics

Baseline characteristics:
Characteristics: PCI (n=488); CABG (n=500)
Men: 390 (80%); 392 (78%)
Age: 61; 62
Previous MI: 214 (44%); 234 (47%)
Type 1 diabetes: 19 (4%); 9 (2%)
Type 2 non-insulin dependent diabetes: 40 (10%); 65 (13%)
Hypertension: 212 (43%); 235 (47%)
CCS class IV: 94 (19%); 108 (22%)
CCS class III: 116 (24%); 133 (27%)
Two vessel disease: 303 (62%); 262 (52%)
Three vessel disease: 183 (38%); 236 (47%)
Diseased vessel territory
Left main stem: 4(1%); 3 (1%)
Left anterior descending (proximal): 235 (48%); 222 (44%)
Left anterior descending (other): 214(44%); 241 (48%)
Circumflex: 342 (70%); 374 (75%)
Right coronary artery: 361 (74%); 395 (79%)
One occluded vessel: 77 (16%); 70 (14%)
Two occluded vessels: 4(1%); 12 (2%)

Inclusion criteria: Symptomatic patients with multivessel coronary artery disease were considered for inclusion and enrolled if the consensus view of the trial surgeon and interventionist was that revascularisation was clinically indicated and appropriate by either strategy. The interventionist had to identify at least one lesion as suitable for stent implantation.
Exclusion criteria: Previous thoracotomy or coronary revascularisation. Patients

	who required intervention for pathology of the valves, great vessels, or aorta were also excluded. In the PCI group, one patient died while waiting for revasc and 7 received CABG as the index procedure. In the CABG group, 2 patients refused any revascularisation procedure and were treated medically. A further 11 patients, randomised to CABG received a PCI procedure as the index revascularisation.
Interventions/ Test/ Factor being investigated	PTCA (with the primary implantation of intra coronary stents).- Bare metal stents
Comparisons	CABG
Length of Study/ Follow-up	1 year and 2 years.
Outcome measures studied	Primary outcome was the rate of repeat revascularisation. Secondary outcomes were: death or Q-wave MI; all cause mortality; symptoms of angina; cardiac medication requirements; left ventricular function.
Results	
Effect Size	Results: At 1 year: Outcome: PCI (n=417) vs. CABG (n=493) CCS class 0: 309 (66%) vs. 387 (79%); p<0.0001% I: 105 (22%) vs. 73 (15%) II: 46 (10%) vs. 24 (5%) III: 8 (2%) vs. 7 (1%) IV: 2(0%) vs. 1 (0%) Outcome: PCI (n=488) vs. CABG (n=500) Death: 12 (3%) vs. 4 (1%) Cerebro vascular accident: 7 (1%) vs. 8(2%) Q-wave MI: 21 (4%) vs. 34 (7%) Surgery: 38 (8%) vs. 5 (1%) PCI: 55 (11%) vs. 16 (3%) Anti anginal medication (number of drugs) 0: 87 (18%) vs. 173 (35%); p<0.0001 1: 210 (45%) vs. 218 (44%) 2: 136 (29%) vs. 90 (18%) 3: 37 (8%) vs. 11 (2%) 4: 1 (0%) vs. 0(0%) At 2 years: Outcome: PCI (n=488) vs. CABG (n=500) Causes of death Cardiac: 9 vs. 4 Other vascular: 2 vs. 1 Non cardiovascular: 9 vs. 3 Unknown: 2 vs. 0 Total: 22 vs. 8 * The definition of MI was restricted to the development of new-wave morphology.
Source of funding:	The work was supported by funding from a consortium of stent manufacturers: Bard (now Medtronic), Guidant ACS, and Schneider (now Boston Scientific)
Does the study answer the question?/Further Comments	Yes. There were fewer deaths in the CABG group compared to PCI. Repeat revascularisation was higher in the PCI group compared to CABG. The incidence of Q-wave MI was similar in both groups.

Unger F;Serruys PW;Yacoub MH;Ilsley C;Paulsen PK;Nielsen TT;Eysmann L;Kiemeneij F;

Revascularization in multivessel disease: comparison between two-year outcomes of coronary bypass surgery and stenting

Ref ID 1120 RID: 613 2003 Apr

QUALITY

A. Selection bias (systematic differences between the comparison groups)

A4 Based on your answers t, in your opinion was selection bias present? If so, what is the likely direction of its effect?:

Low risk of bias **Direction =**

B. Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)

B4 Based on your answers to the above, in your opinion was performance bias present? If so, what is the likely direction of its effect?:

Low risk of bias **Direction =**

C. Attrition bias (systematic differences between the comparison groups with respect to loss of participants)

C4 Based on your answers to the above, in your opinion was attrition bias present? If so, what is the likely direction of its effect?:

Low risk of bias **Direction =**

D. Detection bias (bias in how outcomes are ascertained, diagnosed or verified)

D6 Based on your answers to the above, in your opinion was detection bias present? If so, what is the likely direction of its effect?:

Low risk of bias **Direction =**

Overall Study Quality -Strengths and Weaknesses:

Strengths**: Multi centre, randomised, allocation concealment reported, sample size calculation reported, baseline comparisons made. Nos. lost to follow-up reported *(1.1 % (7/600) in stent and (4.2%) 26/605 in CABG). Intention to treat analysis reported. Clinical events adjudicated by an independent committee.
Weakness:None
*5 patients (1 assigned to undergo stented angioplasty and 4 assigned to undergo surgery) did not undergo coronary revascularisation and instead continued to receive pharmacologic treatment; 3 patients died on waiting list (all 3 in CABG); 6 patients cross over from stent to CABG (3 patients withdrew consent, 2 patients had significant left main disease and in 1 case inappropriate patient selection occurred); 19 patients cross over from CABG to stent (8 patients withdrew consent, in 8 cases the inclusion criteria were not met, in 1 case there was a miscommunication between the

investigator and the study co-ordinator about the random assignment, 1 patient had a Q-wave MI while on the waiting list, and 1 patient had unstable angina develop while on the waiting list and was treated with stented angioplasty); 6 patients unavailable for follow-up at 2 years (1 patient was unavailable for follow-up, 3 were alive but had withdrawn their consent from further participation in the trial, and 2 patients were never treated with either modality.
** this is a 2 year follow-up of the ARTS trial.

DETAILS

# of patients:

N=1205 (n=600 in stent implantation and n=605 in CABG)

Prevalence (Diagnostic):

Patient Characteristics

Baseline characteristics:
Characteristics: stenting (n=600) vs. Bypass surgery (n=605)
Male (%): 77; 76
Age (yr):61 ±10; 61±9
Previous MI (%): 44; 42
Diabetes: 19; 16
Stable angina (%): 57; 60
Unstable angina (%):37; 35
No. of diseased vessels (%) of patients
1: 2; 0
2: 68; 67
3:30; 33
Vessel territory with stenosis (% of patients)
Right coronary artery: 71; 72
Left anterior descending artery: 90; 90
Left circumflex artery: 71; 71
Left main coronary artery: 0; 0
Total occlusion (%) of patients: 3; 5

Interventions/ Test/ Factor being investigated

Stented angioplasty

Comparisons

CABG

Length of Study/ Follow-up

2 years

Outcome measures studied

Primary endpoint: Absence of any of the following major adverse cardiac and cerebrovascular events within 12 months after random assignment: death, cerebrovascular event, documented non fatal MI, or repeated revascularisation by precutaneous intervention or bypass surgery. In the primary comparison of the two treatment strategies, all deaths (cardiac and non cardiac causes) were reported. Cerebrovascualr events were classified in to three major categories: stroke, transient ischemic attack, and reversible ischemic neurologic deficit. Secondary objectives of the study were to compare both strategies at 2 years with respect to the following: anginal status, medication use, the combined endpoint of death, MI and stroke, and the itemised outcomes of death, MI, stroke, or revascularisation procedure.

Results

Effect Size

Results: 2 years (Patient with events)
Outcome*: Stent (n=600) vs. CABG (n=605)
Death: 17 (2.8%) vs. 22 (3.6%); RR 0.78 (0.42-1.45)
CVA: 16 (1.7%) vs. 13 (2.1%); RR 0.95 (0.48-1.86)
MI: 40 (6.7%) vs. 31 (5.1%); RR 1.30 (0.83-2.05)
Re-intervention: 147 (24.5%) vs. 33 (5.5%); RR4.49 (3.13-6.44)
Re-operative CABG: 53 (8.8%) vs. 7 (1.2%); RR 7.64 (3.50-16.66)

Re-intervention PTCA: 107 (17.8%) vs. 30 (5.0%); RR 3.60 (2.44-5.31)
Event free: 417 (69.5%) vs. 513 (84.8%); p=0.0001

For diabetic patients: (Patients with events)
Outcome*: Stent (n=112) vs. CABG (n=96)
Death: 8 (7.1%) vs. 3 (3.1%); RR 2.29 (0.62-8.38)
CVA: 4 (3.6%) vs. 6 (6.3%); RR 0.57 (0.17-1.97)
MI: 40 (6.7%) vs. 31 (5.1%); RR 1.30 (0.83-2.05)
Re-intervention: 40 (35.7%) vs. 5 (5.2%); RR 6.86 (2.82-16.68)
Re-operative CABG: 14 (12.5%) vs. 2 (2.1%); RR 6.00 (1.40-25.74)
Re-intervention PTCA: 28 (25%) vs. 4 (4.2%); RR 6.00 (2.18-16.50)
Event free: 63 (56.3%) vs. 79 (82.3%); p=0.0001
Angina free: 79.7% vs. 87.2%; p=0.001
Angina medication free: 22.9% vs. 39.6%; p<0.001

*If a patient required repeat angioplasty and later CABG, the total count at 365 days would reflect both events, not just the first that occurred.

Source of funding: Cordis Corporation

Does the study answer the question?/Further Comments Yes. At 2 years there were no significant differences between stent and surgery group for death, stroke or MI. There was significantly more repeat revascularisation; there was significantly more event free survival, and angina free survivors in the CABG group compared to stent. There were significantly more patients free of antianginal medication in the CABG group compared to stent. In the diabetes subgroup significantly more patients were free from any events in the CABG group compared to stent.

Zhang Z;Mahoney EM;Spertus JA;Booth J;Nugara F;Kolm P;Stables RH;Weintraub WS;

The impact of age on outcomes after coronary artery bypass surgery versus stent-assisted percutaneous coronary intervention: one-year results from the Stent or Surgery (SoS) trial

Ref ID 532 **RID:** 651 2006 Dec

QUALITY

A. Selection bias (systematic differences between the comparison groups)

A4 Based on your answers t, in your opinion was selection bias present? If so, what is the likely direction of its effect?:

Low risk of bias **Direction =**

B. Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)

B4 Based on your answers to the above, in your opinion was performance bias present? If so, what is the likely direction of its effect?:

Low risk of bias **Direction =**

C. Attrition bias (systematic differences between the comparison groups with respect to loss of participants)

C4 Based on your answers to the above, in your opinion was attrition bias present? If so, what is the likely direction of its effect?:

Low risk of bias

Direction =

D. Detection bias (bias in how outcomes are ascertained, diagnosed or verified)

D6 Based on your answers to the above, in your opinion was detection bias present? If so, what is the likely direction of its effect?:

Low risk of bias

Direction =

Overall Study Quality -Strengths and Weaknesses:

Strengths*- Multi centre, Randomisation method reported, allocation concealment reported, sample size calculation reported, baseline comparisons made, Numbers lost to follow reported (1 year- 8/488 (1.6%) in PCI and 13/500 (2.6%) in CABG) (not reported separately for >65 yrs of age), Intention to treat analysis reported. Blind outcome assessment (A clinical events committee, consisting of study interventionists and surgeons, adjudicated all outcome measures. The members of the clinical events committee did not adjudicate patients treated at their own centres and were blinded to the randomisation allocation and of the identities of patients and centres). Not reported if blind outcome assessment for quality of life.

Weakness- Patients aware of treatment allocation.

* This study reports 1 year follow-up of the SoS trial reporting outcomes in the subgroup of people aged ≥ 65 years.

DETAILS

# of patients: n=395 (PCI (n=190); CABG (n=205))

Prevalence (Diagnostic):

Patient Characteristics

Baseline variables of patients ≥ 65 years
Variable: PCI (n=190); CABG (n=205)
Age (yrs): 70.4; 70.6
Female: 28.4%; 26.8%
Hypertension: 44.2%; 55.1%
CCS class IV: 20.5%; 22%
Prior MI: 45.6%; 40.5%
Diabetes: 12.6%; 16.6%
3 vessel disease: 39%; 46.8%

Interventions/ Test/ Factor being investigated: PCI

Comparisons: CABG

Length of Study/ Follow-up: 1 year

Outcome measures studied: The clinical outcomes included the rate of all cause mortality, Q-wave MI and repeat revascularisation.

Results

Effect Size	Results: Patients ≥ 65 yrs Outcomes: PCI (n=190) vs. CABG (n=205); Hazard ratio (95% CI); p value Death (%): 2.1% vs. 0.5%; 2.7 (0.66 to 10.6); p=0.16 Q-wave MI (%): 6.8% vs. 8.3%; 0.99 (0.53 to 1.89); p=0.99 Cerebrovascular accident (%): 2.6% vs. 2.4%; 1.6 (0.54 to 5.00); p=0.388 Repeat revascularisation (%): 19.5% vs. 3.4%; 5.0 (2.92 to 8.53); p<0.0001
Source of funding:	The work was supported by funding from a consortium of stent manufacturers: Bard (now Medtronic), Guidant ACS, and Schneider (now Boston Scientific)
Does the study answer the question?/Further Comments	Yes. The analysis from the SoS trial shows that CABG had similar clinical outcomes to PCI, but had lower need for repeat revascularisation.

Zhang Z;Mahoney EM;Stables RH;Booth J;Nugara F;Spertus JA;Weintraub WS;

Disease-specific health status after stent-assisted percutaneous coronary intervention and coronary artery bypass surgery: one-year results from the Stent or Surgery trial

Ref ID 1049 **RID:** 532 2003 Oct 7

QUALITY

A. Selection bias (systematic differences between the comparison groups)

A4 Based on your answers t, in your opinion was selection bias present? If so, what is the likely direction of its effect?:

Low risk of bias **Direction =**

B. Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)

B4 Based on your answers to the above, in your opinion was performance bias present? If so, what is the likely direction of its effect?:

High risk of bias **Direction =**

C. Attrition bias (systematic differences between the comparison groups with respect to loss of participants)

C4 Based on your answers to the above, in your opinion was attrition bias present? If so, what is the likely direction of its effect?:

Low risk of bias **Direction =**

D. Detection bias (bias in how outcomes are ascertained, diagnosed or verified)

D6 Based on your answers to the above, in your opinion was detection bias present? If so, what is the likely direction of its effect?:

High risk of bias

Direction =

Overall Study Quality -Strengths and Weaknesses:

Strengths*- Multi centre, Randomisation method reported, allocation concealment reported, sample size calculation reported, baseline comparisons made, Numbers lost to follow reported (12/488 (2.4%) in PCI and 4/500 (0.8%) in CABG), Intention to treat analysis reported.

Weakness- No blinding of outcome assessors. Patients aware of treatment allocation.
Author reported weakness: One year follow-up may not reflect of CABG versus PCI on cardiac related health status. Patient's knowledge of the procedure they received may have influenced responses to the SAQ questionnaire.

*This study is a 1 year follow-up of the SoS trial.

DETAILS

# of patients:

n=988 (n=488 in PCI and n=500 CABG)

Prevalence (Diagnostic):

Patient Characteristics

Baseline characteristics:
Characteristics: PCI (n=488); CABG (n=500)
Men: 390 (80%); 392 (78%)
Age: 61; 62
Previous MI: 214 (44%); 234 (47%)
Type 1 diabetes: 19 (4%); 9 (2%)
Type 2 non-insulin dependent diabetes: 40 (10%); 65 (13%)
Hypertension: 212 (43%); 235 (47%)
CCS class IV: 94 (19%); 108 (22%)
CCS class III: 116 (24%); 133 (27%)
Two vessel disease: 303 (62%); 262 (52%)
Three vessel disease: 183 (38%); 236 (47%)
Diseased vessel territory
Left main stem: 4(1%); 3 (1%)
Left anterior descending (proximal): 235 (48%); 222 (44%)
Left anterior descending (other): 214(44%); 241 (48%)
Circumflex: 342 (70%); 374 (75%)
Right coronary artery: 361 (74%); 395 (79%)
One occluded vessel: 77 (16%); 70 (14%)
Two occluded vessels: 4(1%); 12 (2%)

Interventions/ Test/ Factor being investigated

Stent assisted PCI

Comparisons

CABG

Length of Study/ Follow-up

1 year

Outcome measures studied

Primary outcome: Cardiac related health status assessed with the Seattle Angina Questionnaire (SAQ), a 19 item self-administered questionnaire that measures 5 domains of CAD related health status: physical limitation, angina stability, angina frequency, treatment satisfaction, and disease perception/quality of life. Scores range from 0 to 100 for each domain, with higher scores indicating better functioning. The physical limitation subscale measures how daily activities are limited by symptoms of CAD. The angina stability subscale assesses patient's most strenuous level of activity, whereas the angina frequency subscale quantifies the frequency of angina over the preceding 4 weeks. The treatment satisfaction

	subscale evaluates the patient's level of satisfaction with their current angina treatment and the quality of life subscale characterises the patient's perception of the impact of CAD on their quality of life. Each domain measures a unique dimension of CAD, and no summary score is available. A clinically important change is between 5 and 8 points.
Results	
Effect Size	Results: SAQ domains*: PCI (n=476) vs. CABG (n=496) Physical limitation: 75.2±21.3 vs. 76.6±20.7; p=0.36 Angina frequency: 86.9±19.8 vs. 89.6±18.2; p=0.03 Treatment satisfaction: 91.2±13.1 vs. 90.0±16.0; p=0.73 Quality of life: 69.8±23.0 vs. 71.5±21.4; p=0.41 *Higher scores indicating better functioning.
Source of funding:	The work was supported by funding from a consortium of stent manufacturers: Bard (now Medtronic), Guidant ACS, and Schneider (now Boston Scientific)
Does the study answer the question?/Further Comments	Yes. Both CABG and stent assisted PCI resulted in significant improvement in angina related health status at 1 year after intervention. Angina frequency scores significantly higher in CABG compared to PCI group.

Evidence Table

Question: In adults with angina, what is the clinical/cost effectiveness of aspirin or clopidogrel to alleviate angina symptoms and to improve long term outcomes?

Study Type	Randomised Controlled Trial

Juul-Moller S;Edvardsson N;Jahnmatz B;Rosen A;Sorensen S;Omblus R;

Double-blind trial of aspirin in primary prevention of myocardial infarction in patients with stable chronic angina pectoris

Ref ID 637 **RID:** 449 1992

QUALITY

A. Selection bias (systematic differences between the comparison groups)

A4 Based on your answers t, in your opinion was selection bias present? If so, what is the likely direction of its effect?:

Unclear/unknown risk **Direction =**

B. Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)

B4 Based on your answers to the above, in your opinion was performance bias present? If so, what is the likely direction of its effect?:

Unclear/unknown risk **Direction =**

C. Attrition bias (systematic differences between the comparison groups with respect to loss of participants)

C4 Based on your answers to the above, in your opinion was attrition bias present? If so, what is the likely direction of its effect?:

Unclear/unknown risk **Direction =**

D. Detection bias (bias in how outcomes are ascertained, diagnosed or verified)

D6 Based on your answers to the above, in your opinion was detection bias present? If so, what is the likely direction of its effect?:

Low risk of bias **Direction =**

Overall Study Quality -Strengths and Weaknesses:

Strengths: Multicentre Randomised, double blind, low drop out rate (0.5% drop out after 50 months), sample size calculation reported, baseline comparisons made.
Weakness: Allocation concealment not reported, Intention to treat analysis not reported.

DETAILS

# of patients: n=2035 (n=1009 in Aspirin+sotalol group and n=1026 placebo+sotalol group)

Prevalence (Diagnostic):

Patient Characteristics	All 2035 patients with symptoms of chronic stable angina pectoris and were treated with increasing doses of sotalol until optimal symptom control was obtained. Baseline characteristics: Aspirin +sotalol (n=1009); Placebo +sotalol (n=1026) Male (%): 51; 53 Age (yr) (Mean (SD): 67 (8); 67 (8) Duration of angina (yr) (Mean (SD): 4.6 (5); 4.7 (5) Treated with CCB (%): 9; 9 Treated with Diuretics (%): 27; 25 Sotalol median dose (mg): 160 (80-160); 160 (80-60) The inclusion criteria was a history of exertinal chest pain for atleast a month in patients aged 30-80. Patients already on treatment with or requiring aspirin, anticoagulants, verapamil, or non steroid anti inflammatory drugs were excluded; as were to avoid the risk of hypokalaemia, patients needing more than 50 mg of hydrochlorthiazide, 5 mg bendroflumethiazide or 40mg frusemide daily. Further exclusion criteria were a resting heart rate below 55/min, ongoing treatment with class 1 antarrhythmic drugs, a history of MI, atriventricular block, symptoms of obstructive lung disease, active peptic ulcer, hypersensitivity to aspirin , juvenile diabetes, and uncontrolled late onset diabetes.
Interventions/ Test/ Factor being investigated	Aspirin 75 mg dailiy. All patients in both the groups were treated with sotalol for control of symptoms.
Comparisons	Placebo
Length of Study/ Follow-up	Median follow-up 50 months.
Outcome measures studied	Primary endpoints: first occurrence of non fatal MI or fatal MI (during hospitalisation) or sudden death. Secondary endpoints: vascular events (first occurrence of MI, stroke, or vascular death), vascular death (ie, fatal vascular events), all cause mortality, and stroke.
Results	
Effect Size	Primary endpoint: Aspirin +sotalol (n=1009) vs.Placebo+sotalol (n=1026) Non fatal MI : 7 vs. 78 (p=0.006) Fatal MI: 15 vs. 15 Sudden death: 19 vs. 31(p=0.09) Secondary endpoint: Vascular events: 108 vs. 161 (p<0.001) Vascular deaths: 51 vs. 70 (p=0.11) All cause mortality: 82 vs. 106 Non haemorrhagic adverse events*: 174 vs. 168 Haemorrhagic adverse events (bleed): 27 vs. 16 Fatal haemorrhagic events (bleeds): 9 vs. 5 *cold extremities, bradycardia, bronchial spasm, gastrointestinal, central nervous system, skin.
Source of funding:	Not reported.
Does the study answer the question?/Further Comments	Yes.There was a significant reduction in non fatal MI and vascular events in Aspirin+sotalol compared to placebo+sotalol group, while the numbers of fatal MI's during hospitalisation were identical in the two groups. There was no significant difference between the two groups for sudden deaths, vascular deaths and all cause mortality.

Ridker PM;Manson JE;Gaziano JM;Buring JE;Hennekens CH;

Low-dose aspirin therapy for chronic stable angina. A randomized, placebo-controlled clinical trial

Ref ID 392 **RID:** 348 1991 May 15

QUALITY

A. Selection bias (systematic differences between the comparison groups)

A4 Based on your answers t, in your opinion was selection bias present? If so, what is the likely direction of its effect?:

Unclear/unknown risk **Direction =**

B. Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)

B4 Based on your answers to the above, in your opinion was performance bias present? If so, what is the likely direction of its effect?:

Unclear/unknown risk **Direction =**

C. Attrition bias (systematic differences between the comparison groups with respect to loss of participants)

C4 Based on your answers to the above, in your opinion was attrition bias present? If so, what is the likely direction of its effect?:

Low risk of bias **Direction =**

D. Detection bias (bias in how outcomes are ascertained, diagnosed or verified)

D6 Based on your answers to the above, in your opinion was detection bias present? If so, what is the likely direction of its effect?:

Low risk of bias **Direction =**

Overall Study Quality -Strengths and Weaknesses:

Strengths: Randomised, double blind, baseline comparisons made, Intention to treat analyses used.
Weakness: Allocation concealment not reported.

DETAILS

# of patients: n=333 (n=178 in aspirin and n=155 in placebo group).

Prevalence (Diagnostic):

Patient Characteristics	Baseline characteristics: aspirin; placebo Mean age (yr) (mean (SE): 63.6±9.3; 62.4±8.6 Patients with diabetes mellitus (%): 14.1; 6.5 (p=0.03) All 333 participants had history of chronic stable angina*. No significant differences between aspirin and placebo groups, except for diabetes mellitus. *The study included 333 men with baseline chronic stable angina, who were enrolled in the Physicians Health study, a trial of aspirin among 22071 male physicians.
Interventions/ Test/ Factor being investigated	Aspirin 325 mg (alternate day)
Comparisons	Placebo.
Length of Study/ Follow-up	Follow-up average 60.2 months.
Outcome measures studied	Endpoint (reported): MI (fatal, non fatal), stroke and death (acute infarction, cardiovascular)
Results	
Effect Size	Aspirin (n=178) vs. placebo (n=155) fatal MI: 0/178 vs. 4/155; Non fatl MI: 7/178 vs. 16/155; RR 0.37 (0.16 -0.84) (p=0.019) Cardiovascular death: 6/178 vs. 7/155; RR 0.75 (0.25- 2.33) Sub group analysis: for Confirmed MI among 221 participants with chronic stable angina without previous coronary revascularisation. Aspirin group (n=119) vs. placebo (n=102) Fatal MI: 0/119 vs. 2/102 Non fatal MI: 5/119 vs. 13 /102 ; RR 0.33 (0.13- 0.82)
Source of funding:	Not reported.
Does the study answer the question?/Further Comments	Yes. Data indicated that alternate day aspirin therapy significantly reduced the non fatal MI among patients with chronic stable angina, a group of patients at high risk for cardiovascular death (p<0.001).

Evidence Table

Question: What is the clinical /cost effectiveness of using statin therapy in patients with normal coronary arteries (syndrome X) ?

Study Type	Randomised Controlled Trial

Fabian E;Varga A;Picano E;Vajo Z;Ronaszeki A;Csanady M;

Effect of simvastatin on endothelial function in cardiac syndrome X patients

Ref ID 9041 **RID:** 428 2004 Sep 1

QUALITY

A. Selection bias (systematic differences between the comparison groups)

A4 Based on your answers t, in your opinion was selection bias present? If so, what is the likely direction of its effect?:

Unclear/unknown risk **Direction =**

B. Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)

B4 Based on your answers to the above, in your opinion was performance bias present? If so, what is the likely direction of its effect?:

High risk of bias **Direction =**

C. Attrition bias (systematic differences between the comparison groups with respect to loss of participants)

C4 Based on your answers to the above, in your opinion was attrition bias present? If so, what is the likely direction of its effect?:

High risk of bias **Direction =**

D. Detection bias (bias in how outcomes are ascertained, diagnosed or verified)

D6 Based on your answers to the above, in your opinion was detection bias present? If so, what is the likely direction of its effect?:

unclear risk of bias **Direction =**

Overall Study Quality -Strengths and Weaknesses:

Strengths: Randomised, baseline comparisons made.
Weakness: Allocation concealment not reported, blinding not reported, drop out rate not reported, intention to treat analysis not reported.

DETAILS

# of patients: n=40 (n=20 placebo; n=simvastatin)

Prevalence (Diagnostic):

Patient Characteristics	The patient population consisted of 40 prospectively enrolled patients with cardiac syndrome x with mild hypercholesterolemia. Baseline characteristics: Placebo (n=20); Simvastatin (n=20) Age (yrs): 55.7; 55 Men/women: 13/7 ; 12/8 Medication use- Aspirin: 100%; 100% ACE inhibitor: 0 ;0 CCB: 85%; 90% B-Blocker: 80%; 75% Nitrates: 0;0 None of them were on long acting nitrates , nitric oxide donor, trimetazidine, or ACE inhibitor therapy. Only sublingual nitrates were allowed for the relief of chest pain during the study. Patients were not allowed to take BB or sublingual nitrates 24 hours before the exercise stress tests. Inclusion criteria: Patients with normal coronary angiographic results, positive exercise electrocardiographic test results, positive myocardial perfusion scintigraphic results, normal regional and global left ventricular function at rest, and a mildly elevated total serum cholesterol level (>5.2 mmol/L). Exclusion criteria: Previous MI, valvular heart disease, including mitral valve prolapse, congestive heart failure,cardiomyopathy, sinus node dysfunction, or conduction disturbances , diabetes mellitus, impaired renal or liver function, and smoking.
Interventions/ Test/ Factor being investigated	simvastatin 20 mg/day at bed time.
Comparisons	placebo
Length of Study/ Follow-up	Follow-up 12 weeks.
Outcome measures studied	Primary and secondary endpoints not stated. Outcomes: Time to >1mm ST segment depression.
Results	
Effect Size	Time to 1mm ST segment depression: (placebo n=20; simvastatin n=20) Simvastatin vs. Placebo 5.33±0.27 mins vs. 4.45±0.39 min (p<0.0001)
Source of funding:	Not reported
Does the study answer the question?/Further Comments	Yes. In the simvastatin group the time to 1mm ST segment depression during stress testing was significantly longer by the end of the study compared to placebo (p<0.0001).

Kayikcioglu M;Payzin S;Yavuzgil O;Kultursay H;Can LH;Soydan I;

Benefits of statin treatment in cardiac syndrome-X1.[see comment]

Ref ID 9040 **RID:** 388 2003 Nov

QUALITY

A. Selection bias (systematic differences between the comparison groups)

A4 Based on your answers t, in your opinion was selection bias present? If so, what is the likely direction of its effect?:

Unclear/unknown risk

Direction =

B. Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)

B4 Based on your answers to the above, in your opinion was performance bias present? If so, what is the likely direction of its effect?:

High risk of bias

Direction =

C. Attrition bias (systematic differences between the comparison groups with respect to loss of participants)

C4 Based on your answers to the above, in your opinion was attrition bias present? If so, what is the likely direction of its effect?:

Unclear/unknown risk

Direction =

D. Detection bias (bias in how outcomes are ascertained, diagnosed or verified)

D6 Based on your answers to the above, in your opinion was detection bias present? If so, what is the likely direction of its effect?:

low risk of bias

Direction =

Overall Study Quality -Strengths and Weaknesses:

Strengths: Single blind, randomised, baseline comparisons made
Weakness: allocation concealment not reported, 0.5% drop out, intention to treat analysis not reported.

DETAILS

# of patients:

n=40 (exact participants in each group not reported). After 3 months n=38 (n=19 placebo group; n=19 Pravastatin group)

Prevalence (Diagnostic):

Patient Characteristics

Baseline characteristics:
Study population consisted of 40 prospectively enrolled consecutive patients with diagnosis of cardiac syndrome x.
Number of patients: placebo (n=19); Pravastatin (n=19)
Age (yrs): 45; 47
F/M: 10/9; 12/7

Clinical characteristics did not differ significantly between the two groups.
All patients were receiving antianginal treatment before entry in to the study. The medication was withdrawn at least one week before the study. Only sublingual nitrates were allowed for relief of chest pain during pharmacological wash out period.

	Exclusion criteria: Previous MI, congestive heart failure, diabetes mellitus, valvular heart disease including mitral valve proplapse, overt cardiomyopathy, sinus node dysfunction or conduction disturbance , impaired renal or liver functions, hyperlipidemia and thyroid disease.
Interventions/ Test/ Factor being investigated	Pravastatin 40 mg daily for 3 months.Compliance with medication was regimen was 100% for Pravastatin group and 95% for placebo group.
Comparisons	Placebo
Length of Study/ Follow-up	Follow-up after 3 months.
Outcome measures studied	Outcomes used in the study: Lipid measurements, symptom limited exercise tests and vascular ultrasound images.
Results	
Effect Size	After 3 months Exercise duration (sec): Placebo (n=19) ; Pravastatin (n=19) 507±110; 585 ±165 (p=0.025) Time to 1mm ST depression (sec) 256±102; 419±162 (p=0.001) complete disappearance of chest pain: 0/19 vs. 5/19 Hopsitalisation: 1/19 vs. 1/19 In the placebo group, CCS angina classification improved one or more categories in 8 patients (42%), whereas it deteriorated or remained in the same category in 11 patients (58%). Mean while, the Pravastatin group the CCS angina classification improved one or more categories in 15 patients (79%), whereas it deteriorated or remained in the same category in 4 patients.
Source of funding:	Not reported.
Does the study answer the question?/Further Comments	Yes. Authors conclusion : At the end of 3 months, both exercise duration and time to 1mm ST segment depression were significantly longer in patients receiving Pravastatin than the placebo group.Moreover, complete disappearance of chest pain was noted in 5 patients on statin treatment. During that period, 2 patients had been hospitalised for the worsening of angina (one in placebo and in pravastatin group) and no other side effects developed in both groups.

Evidence Table

Question: What is the clinical /cost effectiveness of ACE inhibitors or ARBs for the management of angina?

Study Type	Randomised Controlled Trial

Braunwald E;Domanski MJ;Fowler SE;Geller NL;Gersh BJ;Hsia J;Pfeffer MA;Rice MM;Rosenberg YD;Rouleau JL;PEACE T;

Angiotensin-converting-enzyme inhibition in stable coronary artery disease.[see comment]

Ref ID 9074 **RID:** 386 2004 Nov 11

QUALITY

A. Selection bias (systematic differences between the comparison groups)

A4 Based on your answers t, in your opinion was selection bias present? If so, what is the likely direction of its effect?:

Unclear/unknown risk **Direction =**

B. Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)

B4 Based on your answers to the above, in your opinion was performance bias present? If so, what is the likely direction of its effect?:

Unclear/unknown risk **Direction =**

C. Attrition bias (systematic differences between the comparison groups with respect to loss of participants)

C4 Based on your answers to the above, in your opinion was attrition bias present? If so, what is the likely direction of its effect?:

Low risk of bias **Direction =**

D. Detection bias (bias in how outcomes are ascertained, diagnosed or verified)

D6 Based on your answers to the above, in your opinion was detection bias present? If so, what is the likely direction of its effect?:

Low risk of bias **Direction =**

Overall Study Quality -Strengths and Weaknesses:

Strengths - block randomisation, double blind, sample size calculation reported, large sample (n=8290), Loss to follow-up (1.6% (68) in the placebo group and 1.6% (66) in the Trandolapril group) and intention to treat analysis used.
Weakness- Allocation concealment not reported.

DETAILS

# of patients: n=8290 (n=4158 in Trandolapril group, n=4132 in Placebo).

Prevalence (Diagnostic):

Patient Characteristics

Baseline characteristics: Trandolapril (n=4158); Placebo (n=4132)
Age (yr): 64±8; 64±8
Age>75 yrs (% of patients): 11; 11
Females (%): 19; 17 (p<0.05)
White (%): 92; 93
Angina pectoris (%): 70: 71
Diabetes (%): 18; 16 (p<0.05)
Medication (% of patients)
CCB: 36; 35
BB: 60; 60
Lipid lowering drug: 70; 70
Aspirin or antiplatelet medication: 90; 91
Diuretic agent: 13; 13
Digitalis: 4; 4
Antiarrhythmic agent: 2; 2
Anti coagulant: 5; 5
Insulin: 4:4

Inclusion criteria: Age 50 yrs or older; Coronary artery disease documented by at least one of the following: MI at least 3 months before enrolment, CABG or PTCA at least 3 months before enrolment, obstruction of>50% of the luminal diameter of at least one native vessel on coronary angiography; Left ventricular ejection fraction >40% on contrast or radionuclide ventriculography or echocardiography, a qualitatively normal left ventriculogram, or the absence of left ventricular wall motion abnormalities on echocardiography; toleration of the medication and successful completion of the run-in phase with >80% compliance with the medication.
Exclusion criteria: Current condition requiring use of ACE inhibitor or a contraindication to use of ACE inhibitor, hospitalisation for unstable angina within the preceding 2 months, valvular heart disease deemed to require surgical intervention, CABG or PTCA within the preceding 3 months, planned elective coronary revascularisation, female sex of childbearing potential and not using contraception.

Interventions/ Test/ Factor being investigated

Trandolapril 2-4 mg/day.

Comparisons

Placebo.

Length of Study/ Follow-up

Median 4.8 years

Outcome measures studied

Primary endpoint: Death from cardiovascular causes or nonfatal MI.
Secondary endpoint: Composite of death from cardiovascular causes , nonfatal MI or coronary revascularisation.

Results

Effect Size

Results:
Outcome: Trandolapril (n=4158) vs. Placebo (n=4132); Hazard ratio (95% CI) P-value
Primary (death from CV causes, nonfatal MI, CABG or PCI) : 909 vs.929; 0.96 (0.88-1.06) (p=0.43)
Death from CV causes: 146 vs. 152; 0.95 (0.76-1.19) p=0.67
Non fatal MI: 222 vs. 220; 1.00 (0.83-1.20) p=0.09
Death from non cardiovascular or unknown causes: 153 vs. 182; 0.83 (0.67-1.03) p=0.13
Death from any cause: 299 vs. 334; 0.89 (0.76-1.04) p=0.13
Death from cardiovascular causes, non fatal MI, revascularisation, or unstable angina: 1060 vs. 1068; 0.98 (0.90-1.07) p=0.64
Death from cardiovascular causes or non fatal MI (original outcome in PEACE trial): 344 vs. 352; 0.97 (0.83-1.12)

Post hoc analyses:

	Death from cardiovascular causes, non fatal MI, or stroke (outcome in HOPE): 396 vs. 420; 0.93 (0.81-1.07) (P=0.32) Death from cardiovascular causes, non fatal MI, or cardiac arrest (outcome in EUROPA): 346 vs. 356; 0.96 (0.83-1.12) p=0.62 CHF as primary cause of hospitalisation: 105 vs. 134; 0.77 (0.60-1.00) p=0.05
Source of funding:	Supported by a contract from the National Heart, Lung, and Blood Institute and by Knoll Pharmaceuticals and Abbot Laboratories, which also provided the study
Does the study answer the question?/Further Comments	Yes. In patients with stable coronary heart disease and preserved left ventricular function who are receiving 'current standard' therapy , there was no evidence that the addition of an ACE inhibitor provides further benefit in terms of death from cardiovascular causes, MI or coronary revascularisation .

Klein WW;Khurmi NS;Eber B;Dusleag J;

Effects of benazepril and metoprolol OROS alone and in combination on myocardial ischemia in patients with chronic stable angina.[see comment]

Ref ID 312 **RID:** 412 1990 Oct

QUALITY

A. Selection bias (systematic differences between the comparison groups)

A4 Based on your answers t, in your opinion was selection bias present? If so, what is the likely direction of its effect?:

Unclear/unknown risk **Direction =**

B. Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)

B4 Based on your answers to the above, in your opinion was performance bias present? If so, what is the likely direction of its effect?:

Unclear/unknown risk **Direction =**

C. Attrition bias (systematic differences between the comparison groups with respect to loss of participants)

C4 Based on your answers to the above, in your opinion was attrition bias present? If so, what is the likely direction of its effect?:

High risk of bias **Direction =**

D. Detection bias (bias in how outcomes are ascertained, diagnosed or verified)

D6 Based on your answers to the above, in your opinion was detection bias present? If so, what is the likely direction of its effect?:

Low risk of bias.

Direction =

Overall Study Quality -Strengths and Weaknesses:

Strengths-Randomised, cross over, double blind, baseline comparisons made. 6% (2/31) lost to follow-up.
Weakness- Allocation concealment not reported, Intention to treat analysis not used.

DETAILS

# of patients:

N=31 (cross over trial).

Prevalence (Diagnostic):

Patient Characteristics

31 patients (28 men and 3 women, 42-74 years of age) with established grade II or III stable effort induced angina pectoris. The duration of angina ranged from 4 to 120 months (mean 29.8). Coronary artery disease was confirmed in all 31 patients with selective coronary arteriography, which demonstrated >75% occlusion of one or more major coronary arteries. The left ventricular function as assessed by ejection fraction was normal in all patients (mean 65%, range 53% to 80%). Ten patients had previous MI.

The previous anti anginal treatment was nifedipine (n=1 patient), verapamil (n=3), diltiazem (n=7), gallopamil (n=2), sotalol (n=1), atenolol (n=2), metoprolol (n=7) and isosorbide mono nitrate (n=15). All patients were gradually and completely withdrawn from their current anti anginal treatment other than sub lingual nitroglycerin to control anginal pain for at least 1 week before the start of the study.

Inclusion criteria:
Patients were required to develop angina on treadmill exercise testing accompanied by>1mm horizontal or down sloping ST segment depression at the J point in one of the monitored bipolar ECG leads CM5, and CC5. If the ST segment slope was <0.1 mV/s, they were required to have >1mm ST segment depression. If the ST slope was >1 mV/s, the patients were excluded, whereas for those whose ST slope was between 0.1mV and 1mV/s, >2mm ST segment depression was required. The patients were required to have had for >4 months symptomatic stable angina that was relieved by rest and sublingual nitroglycerin with an average incidence of 4 anginal attacks/week. Patients also had to have unequivocal evidence of coronary artery disease by selective coronary arterigraphy or previous MI. All patients were required to be physically capable of undertaking regular exercise tests.
Exclusion criteria:
Patients were excluded from the study if they were receiving any drug likely to influence heart rate or ST segment level, such as digitalis or diuretic drugs, or if they had a rest blood pressure >170/105 mm Hg, left ventricular hypertrophy or bundle branch block. Patients with a history of recent MI within the preceding 4 months, unstable angina, clinical congestive heart failure, bronchial asthma, peripheral vascular disease, insulin dependent diabetes or the labile ST-T syndrome were also excluded, as were patients >75 years of age and women of child bearing age. Any patient not developing classic anginal pain and >1mm ST segment depression during the initial control test or who had an exercise time during the placebo run-in test >8 min or exercise time variability on two tests > 20%, or both, was excluded.

Interventions/ Test/ Factor being investigated

Benazepril 20 mg twice daily.

Comparisons

Metoprolol OROS 14/190 mg once daily.

Length of Study/ Follow-up

Follow-up 12 weeks

Outcome measures studied

Primary and secondary endpoints not stated.Outcomes: Exercise time (min), 1mm ST segment depression (min).

Results

Effect Size

The 4 trial treatments 1) Benazepril 20 mg twice daily 2) Metoprolol OROS*, 14/190 mg (release rate/total dose) once daily 3) Benazepril, 10mg twice daily, plus Metoprolol OROS, 14/190 mg once daily 4) Placebo.
*Metoprolol OROS is a sustained release formulation of metoprolol fumarate.

Results:
Outcome: Placebo (n=23**) vs. Benazepril (n=23) vs. Metoprolol OROS (n=23) vs. Benazepril +Metoprolol OROS (N=23)
Exercise time (min): 8.5± 3.29 vs. 8.3±2.82 (-1.06 to 0.54) vs. 9.4±2.35 (-0.32 to 2.14) vs. 9.6±2.35 (-0.25 to 2.47)
1 mm ST depression (min): 6.0 ±2.82 vs. 6.3±2.82 (-0.93 to 1.45) vs. 7.9±2.35 (0.83 to 3.0) vs. 8.1±2.82 (0.88 to 3.29).

Anginal attacks and sublingual nitroglycerin consumption:
During the 3 week treatment period, 342 anginal attacks were recorded with placebo, the number of attacks was reduced to 326 with benazepril, 318 with metoprolol OROS and 268 with the combination of benazepril and metoprolol OROS. Similarly, the consumption of nitroglycerin tablets was 174 with placebo and was reduced to 171 with benazepril, 128 with metoprolol OROS and 129 with the combination of benazepril and metoprolol OROS.
These data were evaluated only descriptively and no statistical tests were performed because some patients failed to return or fill in the diary card completely. However, the authors report that the changes observed during active treatment are neither clinically relevant nor statistically significant.

**One patient withdrew consent during the first treatment period, one patient died suddenly during the first double blind treatment period, 4 patients were considered protocol violators because their exercise time during the initial control tests was either > 8 min or the variability of exercise time in two tests was >20%. Two patients took sublingual nitroglycerin tablets before the exercise test and their data could not be used for efficacy analysis. There fore only 23 patients were analysed for exercise test data.

Source of funding:

This study was supported in part by a grant from Ciba-Geigy Pharmaceuticals, Basel, Switzerland

Does the study answer the question?/Further Comments

Yes.
Authors conclusion:
Metoprolol is an effective anti ischemic agent. Benazepril did not produce any clinical benefit in terms of exercise test variables. The data also confirm that benazepril did not impair the anti ischemic effects of metoprolol OROS.

Pitt B;O'Neill B;Feldman R;Ferrari R;Schwartz L;Mudra H;Bass T;Pepine C;Texter M;Haber H;Uprichard A;Cashin HL;Lees RS;QUIET Study Group;

The QUinapril Ischemic Event Trial (QUIET): evaluation of chronic ACE inhibitor therapy in patients with ischemic heart disease and preserved left ventricular function.[see comment]

Ref ID 195 RID: 451 2001 May 1

QUALITY

A. Selection bias (systematic differences between the comparison groups)

A4 Based on your answers t, in your opinion was selection bias present? If so, what is the likely direction of its effect?:

Unclear/unknown risk

Direction =

B. Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)

B4 Based on your answers to the above, in your opinion was performance bias present? If so, what is the likely direction of its effect?:

Unclear/unknown risk

Direction =

C. Attrition bias (systematic differences between the comparison groups with respect to loss of participants)

C4 Based on your answers to the above, in your opinion was attrition bias present? If so, what is the likely direction of its effect?:

Low risk of bias

Direction =

D. Detection bias (bias in how outcomes are ascertained, diagnosed or verified)

D6 Based on your answers to the above, in your opinion was detection bias present? If so, what is the likely direction of its effect?:

Low risk of bias

Direction =

Overall Study Quality -Strengths and Weaknesses:

Strengths – randomised, baseline comparisons made, sample size calculation reported, four patients lost to follow-up at 3 years, intention to treat analysis used,
Weakness- Allocation concealment not reported, blinding not reported.

DETAILS

# of patients:

TOTAL: n=1750 (n=878 in Quinapril , n=872 in placebo)

Prevalence (Diagnostic):

Patient Characteristics

Baseline characteristics:
Variable: placebo (n=872); Quinapril (n=1750)
Mean age (yrs): 58 ; 58
Men: 702 (81%) ; 717 (82%)
White: 819 (94%); 812 (94%)
History of angina: 803 (92%) ; 804 (92%)
Concomitant medications:
Lipid lowering agents: 1(0.1%); 1(0.1%)
B-blocker:218 (25%); 237 (27%)
Calcium antagonist: 0 ; 0
Nitrates: 358 (41%); 369 (42%)
Aspirin: 619 (71%); 650 (74%)

Inclusion criteria-
Eligible patients were 18 to 75 years of age, had undergone successful coronary

	angioplasty or atherectomy at baseline, and had at least 1 coronary artery that had not been subjected to mechanical revascularisation. Exclusion criteria- The protocol excluded patients with any of the following: low density lipo protein cholesterol >4.3 mmol/L (165 mg/dl) , coronary artery bypass graft surgery, systolic blood pressure <100 mm Hg or >160 mm Hg and/or diastolic blood pressure >100 mm Hg, ejection fraction <40% , myocardial infarction within 7 days, prior angioplasty within 3 months, and those receiving lipid lowering medications, ACE inhibitors, or calcium channel blockers.
Interventions/ Test/ Factor being investigated	Quinapril 20 mg/day
Comparisons	Placebo
Length of Study/ Follow-up	Follow-up 36 months (mean 27±0.3 months)
Outcome measures studied	Primary endpoints- Time to the first cardiac event Secondary endpoints- 1)Time to first major cardiac event (cardiac death, non fatal MI, resuscitated cardiac arrest) 2)Time to first cardiac event in the first 6 months 3)Time to first cardiac event in months 7 to 36 months
Results	
Effect Size	Event: Placebo (n=872) vs. Quinapril (n=878) Cardiac death: 13 vs. 12 Non fatal MI: 40 VS. 36 Hospitalised with unstable angina: 45 vs. 52 All patients with nay event: 329 vs. 338 All patients with any event at months 7-36: 203 vs. 189 Causes of death in randomised patients: placebo (n=872) vs. Quinapril (n=878) Cardiovascular- Cardiac : 13 vs. 12 Vascular/ stroke: 1 vs. 1 Non cardio vascular: 13 vs. 14 All cause mortality: 27 vs. 27 Safety and tolerability: The frequency and reasons for withdrawal observed between patients treated with placebo and those treated with quinapril were similar. Cough was the only treatment associated adverse event leading to a significantly higher percentage of withdrawals in the quinapril (3.8%)than in the placebo group (0.2%).
Source of funding:	This study was supported by Parke-Davis Pharmaceutical Research, Ann Abor, Michigan
Does the study answer the question?/Further Comments	Yes. Quinapril 20 mg/day did not significantly reduce cardiac death, non fatal MI, or hospitalisation for angina pectoris. The authors report that the absence of demonstrable effect of Quinapril may be due to several limitations in study design-small sample size, low dose of quinapril, short follow-up, occurrence of lipid lowering drug drop ins.

Yui Y;Sumiyoshi T;Kodama K;Hirayama A;Nonogi H;Kanmatsuse K;Origasa H;Iimura O;Ishii M;Saruta T;Arakawa K;Hosoda S;Kawai C;

Nifedipine retard was as effective as angiotensin converting enzyme inhibitors in preventing cardiac events in high-risk hypertensive patients with diabetes and coronary artery disease: the

Japan Multicenter Investigation for Cardiovascular Diseases-B (JM

Ref ID 9065 **RID:** 442 2004 Jul

QUALITY

A. Selection bias (systematic differences between the comparison groups)

A4 Based on your answers t, in your opinion was selection bias present? If so, what is the likely direction of its effect?:

Unclear/unknown risk **Direction =**

B. Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)

B4 Based on your answers to the above, in your opinion was performance bias present? If so, what is the likely direction of its effect?:

High risk of bias **Direction =**

C. Attrition bias (systematic differences between the comparison groups with respect to loss of participants)

C4 Based on your answers to the above, in your opinion was attrition bias present? If so, what is the likely direction of its effect?:

Low risk of bias **Direction =**

D. Detection bias (bias in how outcomes are ascertained, diagnosed or verified)

D6 Based on your answers to the above, in your opinion was detection bias present? If so, what is the likely direction of its effect?:

Low risk of bias **Direction =**

Overall Study Quality -Strengths and Weaknesses:

Strengths- Randomised, open, blinded endpoint design, sample size calculation reported, Intention to treat analysis used.
Weakness- Allocation concealment not used.

DETAILS

# of patients: n=1650 (n=372 in diabetic group and 1278 in non diabetic group; n=828 in nifedipine group and 822 in ACE inhibitor group)

Prevalence (Diagnostic):

Patient Characteristics

Of the 1,650 patients analysed in the JMIC-B study, 372 (23%) were diabetic at treatment baseline.

Patients with diabetes*
Patients characteristics:– Nifedipine (n=199) ; ACE inhibitor (n=173)
Age(yrs): 63; 64
M/F: 137/62; 120/53

	MI: 36%; 59% Angina pectoris: 65% ; 60% No. of diseased vessels: 1 vessel- 34%; 29% 2 vessel- 21%; 24% 3 vessel- 7%; 12% LMT- 0; 2% Patients without diabetes Patients characteristics: – Nifedipine (n=199); ACE inhibitor (n=173) Age (yrs): 65; 64 M/F: 423/206; 455/194 MI: 39%; 43% Angina pectoris: 69%; 62% No. of diseased vessels: 1 vessel- 36%; 36% 2 vessel- 19%; 16% 3 vessel- 5%; 5% LMT- 0.3%; 0.6% No significant difference in patient characteristics was noted between the Nifedipine and ACE inhibitor groups. *The present study utilizes subgroup analysis by dividing data from the JMIC-B patients in to diabetic and non diabetic categories.
Interventions/ Test/ Factor being investigated	ACE inhibitor (enalapril 5-10 mg/day, imidapril 5-10 mg/day, or lisinopril 10-20 mg/day as recommended in JAPAN).
Comparisons	Nifedipine retard (a long acting Nifedipine formulation that is given at a dose of20-40 mg/day in Japan).
Length of Study/ Follow-up	Follow-up 3 years.
Outcome measures studied	Primary endpoint: Overall incidence of cardiac events, defined as 1)cardiac death or sudden death 2) MI (initial or recurrent) 3) Angina pectoris requiring hospitalisation 4)HF requiring hospitalisation 5) serious arrhythmia 6) performance of coronary interventions. Secondary end points: Cerebrovascular accidents, worsening of renal dysfunction, non cardiovascular events such as cancer, and total mortality.
Results	
Effect Size	Results: Outcome: Nifedipine vs. ACE; RR (95% CI) Cardiac death or sudden death: 1 vs. 3; 0.31 (0.03 to 3.37); p=0.332 MI: 4 vs.4; 1.08 (0.25 to 4.65); p=0.916 Hospitalisation for angina pectoris: 16 vs.12; 1.03 (0.47 to 2.27); p=0.946 Hospitalisation for HF: 8 vs. 5; 1.55 (0.47 to 5.05); p=0.470 Total mortality: 2 vs. 5; 0.33 (0.06 to 1.77); p=0.195 Primary endpoints (combined) : Nifedipine vs. ACE inhibitor Patients with diabetes: 30/199 vs. 26/173 Patients without diabetes: 86/629 vs. 80/649 Secondary endpoints (combined): Nifedipine vs. ACE inhibitor With diabetes: 10/199 vs. 9/173 Without diabetes: 17/629 vs. 33/1278
Source of funding:	The study was supported by a grant from the Preventive Arteriosclerosis Research Association

Does the study answer the question?/Further Comments	Yes. The results showed no significant difference in primary and secondary endpoints between the Nifedipine and ACE inhibitor group in both diabetic and non diabetic patients.

Yui Y;Sumiyoshi T;Kodama K;Hirayama A;Nonogi H;Kanmatsuse K;Origasa H;Iimura O;Ishii M;Saruta T;Arakawa K;Hosoda S;Kawai C;Japan Multicenter Investigation for Cardiovascular Diseases;

Comparison of nifedipine retard with angiotensin converting enzyme inhibitors in Japanese hypertensive patients with coronary artery disease: the Japan Multicenter Investigation for Cardiovascular Diseases-B (JMIC-B) randomized trial

Ref ID 9064 **RID:** 406 2004 Mar

QUALITY

A. Selection bias (systematic differences between the comparison groups)

A4 Based on your answers t, in your opinion was selection bias present? If so, what is the likely direction of its effect?:

Unclear/unknown risk **Direction =**

B. Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)

B4 Based on your answers to the above, in your opinion was performance bias present? If so, what is the likely direction of its effect?:

High risk of bias **Direction =**

C. Attrition bias (systematic differences between the comparison groups with respect to loss of participants)

C4 Based on your answers to the above, in your opinion was attrition bias present? If so, what is the likely direction of its effect?:

Low risk of bias **Direction =**

D. Detection bias (bias in how outcomes are ascertained, diagnosed or verified)

D6 Based on your answers to the above, in your opinion was detection bias present? If so, what is the likely direction of its effect?:

Low risk of bias **Direction =**

Overall Study Quality -Strengths and Weaknesses:	Strengths- Randomised, open, blinded endpoint design, sample size calculation reported ,Intention to treat analysis used. Weakness- concealment of allocation not reported

DETAILS

# of patients:

n=1650 (n=828 in Nifedipine Retard group and n=822 in ACE inhibitor group).

Prevalence (Diagnostic):

Patient Characteristics

The subjects were outpatients aged 75 years who had diagnoses of both hypertension and coronary artery disease. Patients who did not undergo CAG were diagnosed as having coronary artery diseases when both of the following criteria were met: 1) a history of more than 2 anginal attacks per week with a stable frequency 2) ST segment depression of 1mm or more during the treadmill exercise test using the multistage gradual increase method according to the Bruce protocol.
Patients with acute MI or unstable angina were excluded.

Characteristics: Nifedipine (n=828); ACE inhibitor (n=822)
M/F: 560/268 ; 575//247
Age: 65; 64
Angina pectoris: 566 (68.4%); 507 (61.7%)
No. of diseased vessels:
1 vessel- 275 (33.2%); 267 (32.5%)
2 vessel – 152 (18.4%); 136 (16.6%)
3 vessel- 43 (5.2%); 53 (6.5%)

Use of concomitant medications:
The number of patients who concomitantly received a nitrate preparation to treat angina pectoris was 587 (70.9%) in the nifedipine group and 567 (69%) in the ACE inhibitor group, with no significant difference between the two groups. The number of patients who were co-administered a B-blocker was 205 (24.8%) in the nifedipine group 192 (23.4%) in the ACE inhibitor group, with no significant difference observed between the two groups. The number of patients who were concomitantly treated with an α blockers was 52 (6.3%) in the nifedipine group and 88 (10.7%) in the ACE inhibitor group, and the difference was statistically significant.

Interventions/ Test/ Factor being investigated

ACE inhibitor (Enalapril 5-10mg, imidapril 5-10 mg, or lisinopril 10-20 mg, once daily as recommendedin Japan for 3 years.)

Comparisons

Nifedipine Retard (a long acting nifedipine formulation that is given at a dose of 10-20 mg twice daily in Japan for 3 years).

Length of Study/ Follow-up

Follow-up after 3 years

Outcome measures studied

Primary endpoint: Overall incidence of cardiac events, which were defined as 1)cardiac or sudden death 2) MI 3)Angina pectoris requiring hospitalisation 4)HF requiring hospitalisation 5)serious arrhythmia 6)Performance of coronary interventions.
Secondary endpoints: Cerebrovascular accidents, renal dysfunction, non cardio vascular events such as cancer, and total mortality.

Results

Effect Size

Outcome: Nifedipine (n=828) vs. ACE inhibitor (n=822); Relative risk
Cardiac events: 116 vs. 106; 1.05 (0.81-1.37) (p=0.75)
Sudden death/cardiac death: 6 vs. 6; 0.96 (0.31-3.04) (p=0.95)
MI: 16 vs. 13; 1.31 (0.63-2.74) (p=0.47)
Angina pectoris requiring hospitalisation: 50 vs. 56; 0.80 (0.55-1.18) (p=0.26)
HF requiring hospitalisation: 12 vs. 9; 1.25 (0.52-2.98) (p=0.62)
Non-cardiac death: 6 vs. 9; 0.64 (0.23-1.81) (p=0.40)
Total mortality: 12 vs. 15; 0.76 (0.35-1.63) (p=0.48)
Adverse events*: 76 vs. 121
Rate of withdrawal due to adverse events**: 41 vs. 72 (p=0.002)

	*The major adverse events occurring in the Nifedipine group were those related to vasodilatory effect, including hypotension, facial erythema, and hot flushes. On the other hand dry cough accounted for most of the adverse events occurring in the ACE inhibitor group. **The main reasons for withdrawal were vasodilatory effect in the Nifedipine group and predominantly cough in the ACE inhibitor group.
Source of funding:	The study was supported from a grant from the Preventive Arteriosclerosis Research Association
Does the study answer the question?/Further Comments	Yes. The incidence of cardiac events and mortality did not differ between the nifedipine retard and ACE inhibitor therapies. However there were significantly more withdrawal due to adverse effects in the ACE inhibitor group.

Evidence Table

Question: Which tables, equations, engines, models or scoring systems are most effective for prognostic -risk stratification in prediction of adverse cardiac outcomes in adults with stable angina?

Study Type	Prognostic

Clayton TC;Lubsen J;Pocock SJ;Voko Z;Kirwan BA;Fox KAA;Poole-Wilson PA;

Risk score for predicting death, myocardial infarction, and stroke in patients with stable angina, based on a large randomised trial cohort of patients

Ref ID 9352 **RID:** 1069 2005

QUALITY

A. Selection bias (systematic differences between the comparison groups)

A4 Based on your answers t, in your opinion was selection bias present? If so, what is the likely direction of its effect?:

Direction =

B. Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)

B4 Based on your answers to the above, in your opinion was performance bias present? If so, what is the likely direction of its effect?:

Direction =

C. Attrition bias (systematic differences between the comparison groups with respect to loss of participants)

C4 Based on your answers to the above, in your opinion was attrition bias present? If so, what is the likely direction of its effect?:

Direction =

D. Detection bias (bias in how outcomes are ascertained, diagnosed or verified)

D6 Based on your answers to the above, in your opinion was detection bias present? If so, what is the likely direction of its effect?:

Direction =

Overall Study Quality -Strengths and Weaknesses:

Strengths- The study sample represents the population of interest with regard to key characteristics sufficient to limit potential bias to the results. The outcome of interest was adequately measured in study participants. The statistical analysis was appropriate for the design of the study.
Limitations- Small sample size. Highly selective group of patients. This study used data from the ACTION trial (a coronary disease trial investigating outcome with nifedipine GITS), which followed 7665 patients with stable symptomatic angina for a mean of 4.9 years, to develop a score for predicting the combined risk of death from any cause, MI or stroke.
Design- Multivariate Cox regression analysis of data from a large multicentre trial.

DETAILS

# of patients:

N= 7311. Model is based on 7311 patients with values for all variables in model, of whom 1063 had the combined event of death, MI, or disabling stroke.

Prevalence (Diagnostic):

Patient Characteristics

Baseline data:
Inclusion criteria in the ACTION trial, eligible patients had stable symptomatic angina requiring treatment and either previous MI or proved angiographic coronary artery disease. Patients without a previous MI or coronary angiography could participate only if there was a positive result on an exercise or perfusion test. Key exclusions were ejection fraction below 40%, clinically significant heart failure, major cardiovascular event or intervention within the past 3 months, planned coronary angiography or intervention, and known intolerance to dihydropyridines. Individual baseline data available included demographics, medical history, cardiovascular risk factors, current symptoms of angina and functional status, past use of calcium channel blockers, results of non-fasting laboratory tests, left ventricular ejection fraction mostly measured by echocardiography, standard 12 lead electrocardiography findings, routine cuff blood pressure, pulse rate, and the results of previous angiography if available. (Data not reported in this paper)
Setting: Outpatient cardiology clinics in Western Europe, Israel, Canada, Australia, and New Zealand.

Interventions/ Test/ Factor being investigated

Assessing individual risk factors to derive a risk score for the combination of death from all causes, MI, and disabling stroke for patients with stable angina.

Comparisons

Length of Study/ Follow-up

4.9 years.

Outcome measures studied

Death from any cause or MI or disabling stroke

Results

Effect Size

The first table shows the 16 variables, with there risk scores and Cox regression coefficients, that were in the final model as derived for 7311 patients (95%) with complete information.

The second table presents hazard ratios for the individual events of death, MI, and diabling stroke with the same variables as for the combined endpoint.

Predictors of death, MI, or disabling stroke for 7311 participants in the ACTION trial (cox proportional hazard analysis) – figures are numbers (%)
Risk factors: Death, MI or stroke (n=1063) ;No death, MI, or stroke (n=6248);Z score*; Co-efficient ; Contribution to risk score
Mean age SD (year):66.5 (9.5); 63 (9.2); 10.77; 0.55; 0 when age≤60 years or add per 10 years>60 years
Mean SD (ejection fraction); 46.7 (6.6); 48.6 (6.3);6.47; 0.17; 0 when ≤60 years or add per 5% <60%
Smoking
Never: 260 (24); 1784 (29); -;-
Ex smoker: 560 (53); 3417 (55); 1.54; 0.12; Add if applicable
Current : 243 (23); 1047 (17); 6.12; 0.60; Add if applicable
Mean (SD) white blood cells: (109 /l): 7.4 (2.5); 7 (1.8); 6.07; 0.068; 0 when ≤5109/l >5
Diabetes
No diabetes: 848 (80); 5393 (86)
Non- ID diabetes: 167 (16); 727 (12); 1.06; 0.13; Add if applicable
ID diabetes : 48 (5); 128 (2); 5.61; 0.85; Add if applicable
Mean (SD) glucose, no diabetes (mg/dl): 103 (26); 99 (20); 4.68; 0.072; 0 when ≤100 mg/dl or add per 10mg/dl >100 mg/dl.
Mean (SD) glucose, non-ID diabetes (mg/dl): 189 (79); 168 (65); 3.36; 0.032; 0

when ≤100 mg/dl or add per 10mg/dl >100 mg/dl.
Mean (SD) creatinine (mg/dl): 1.14 (0.25); 1.08 (0.21); 4.27; 0.078; 0 when ≤1.15 mg/dl or add per 0.1 mg/dl >1.15 mg/dl.
Previous stroke : 50 (5); 116 (2); 3.59; 0.53; Add if yes
Angina attack ≥1 /week: 364 (34); 1750 (28); 3.42 ; 0.22; Add if applicable
Previous angiography
Never done: 350 (33); 1842 (29); 1.50; 0.11; Add if applicable
0-2 vessel disease: 421 (40); 3069 (49); -; -; Add 0 if applicable
≥3 vessel disease: 292 (27); 1337 (21); 3.23; 0.25; Add if applicable
No lipid lowering therapy: 406 (38); 1950 (31); 3.20; 0.21; Add if applicable
QT interval (12 lead ECG) ≥ 430msec: 238 (22); 1096 (18); 3.05; 0.23; Add if applicable
Systolic blood pressure ≥ 155 mmHg: 275 (26); 1097 (18); 2.84; 0.21; Add if applicable
No of drugs for angina
0: 8 (1); 53 (1);-;-
1: 268(25) ;1953 (31); 2.76; 0.13 ; Add once for each drug used
2: 626 (59); 3487 (56);-
3:161 (15); 755 (12)
Previous MI: 597 (56); 3118 (50); 2.16; 0.14; Add if yes
Male: 863 (81); 4944 (79); 1.87; 0.16; Add if male
* Each variables strength of predictive contibution is expressed by its Z-score. Z score is calculated as- co-efficient divided by its SE. Larger values indicate more highly significant risk factor: z scores of 1.96, 2.58, 3.29 and 3.89 correspond to p=0.05, p=0.01, p=0.001 and p=0.0001. Each variables predictive is quantified as a hazard ratio with 95% CI.

Note: Age was the strongest predictor. Male sex was of borderline significance (p=0.06) but was retained for completeness. Diabetes and stroke were the strongest predictors from clinical history. Patients with known three or more vessel disease had raised risk.Other predictors included were left ventricular ejection fraction, a prolonged QT interval, use of lipid lowering drugs, and the number of drugs used for angina (including past use of CCB).

Multivariate Cox proportional hazard models used for the outcome time to death, MI, or disabling stroke as adjudicated by the critical events committee, using patients who had no missing values for the predictor variables.
Predictors of death, MI, and disabling stroke (Cox proportional hazard analysis). Figures are hazard ratios (95% CI).

Risk factor : Death, MI, or stroke (n=1063); Death (n=569); MI (n=495); Stroke (n=170)
Age per 10 years >60: 1.73 (1.57 to 1.92); 2.30 (2.01 to 2.64); 1.45 (1.25 to 1.69); 1.75 (1.37 to 2.24)
Ejection fraction per 5%<60: 1.19 (1.13 to 1.25);1.26 (1.17 to 1.35);1.14 (1.06 to 1.23);1.24 (1.09 to 1.41)
Smoking
Never:1.00;1.00;1.00;1.00
Ex smoker:1.13 (0.97 to1.32); 1.19 (0.96 to 1.48); 0.99 (0.79 to 1.24);1.42 (0.95 to 2.13)
current: 1.82 (1.50 to 2.20);2.20 (1.69 to 2.85);1.39 (1.05 to 1.84);2.44 (1.49 to 3.99)
White blood cells per 109 /l>5:1.07 (1.05 to 1.09); 1.09 (1.07 to 1.12); 1.05 (1.01 to 1.10); 1.00 (0.92 to 1.09)
Diabetes
No diabetes: 1.00; 1.00;1.00;1.00
Non ID diabetes: 1.14 (0.90 to 1.44); 0.93 (0.66 to 1.32); 1.14 (0.81 to 1.60); 1.75 (1.06 to 2.90)
ID diabetes: 2.33 (1.74 to 3.14); 3.44 (2.40 to 4.94); 2.62 (1.75 to 3.93); 0.56 (0.14 to 2.29)
Glucose per 10 mg/dl >100† (no diabetes): 1.08 (1.04 to 1.11); 1.10 (1.06 to 1.14);1.05 (1.00 to 1.10);1.07 (0.98 to 1.15)
Glucose per 10 mg/dl >100† (non-ID diabetes):1.03 (1.01 to 1.05); 1.04 (1.01 to 1.01 to 1.07);1.03 (1.00 to 1.06); 1.03 (0.99 to 1.07)
Creatinine per 0.1 mg/dl >1.5: 1.08 (1.04 to 1.12); 1.09 (1.04 to 1.14); 1.08 (1.02 to 1.14);1.06 (0.97 to 1.16)
Previous stroke: 1.70 (1.27 to 2.28); 1.74 (1.19 to 2.54); 1.50 (0.95 to 2.36); 4.28 (2.60 to 7.06)

Angina attack ≥1 /week: 1.25 (1.10 to 1.42); 1.27 (1.07 to 1.51);1.21 (1.00 to 1.46); 1.16 (0.84 to 1.61)
Previous angiography
Never done: 1.12 (0.97 to 1.30); 1.16 (0.95 to 1.41); 1.20 (0.96 to 1.49); 1.10 (0.77 to 1.58)
0-2 vessel disease: 1.00; 1.00; 1.00; 1.00
≥3 vessel disease: 1.28(1.10 to 1.50); 1.14 (0.92 to 1.41);1.50 (1.21 to 1.87); 1.06 (0.72 to 1.57)
No lipid lowering therapy: 1.23 (1.08 to 1.40); 1.33 (1.12 to 1.58); 1.10 (0.91 to 1.33); 1.09 (0.79 to 1.51)
QT interval (12 lead ECG) ≥ 430msec: 1.26 (1.08 to 1.45); 1.52 (1.26 to 1.84); 1.08 (0.87 to 1.35);1.69 (1.22 to 2.36)
Systolic blood pressure ≥ 155 mmHg: 1.23 (1.07 to 1.42); 1.18 (0.98 to 1.43); 1.09 (0.88 to 1.35);1.69 (1.22 to 2.36)
For each additional drug for angina: 1.14 (1.04 to 1.25); 1.09 (0.96 to 1.24); 1.20 (1.05 to 1.38);1.21 (0.96 to 1.54)
Previous MI: 1.15 (1.01 to 1.30); 1.10 (0.92 to 1.30); 1.16 (0.96 to 1.39); 1.01 (0.74 to 1.38)
Male: 1.17 (0.99 to 1.39); 1.21 (0.96 to 1.52); 1.24 (0.97 to 1.59); 0.88 (0.59 to 1.30)

Note: Patterns of risk factors were broadly similar, though risk of stroke was more strongly linked to raised blood pressure but unrelated to white cell count, angiographic data, previous MI and sex.

Source of funding:

The ACTION trial was supported by Bayer Health care AG, Wupertal, Germany.

Does the study answer the question?/Further Comments

Yes. Large variation in risk of death, MI, and disabling stroke between patients can be determined from an easily calculated risk score using standard clinical information. The risk score combined 16 routinely available variables: age, left ventricular ejection fraction, smoking, white blood cell count, diabetes, casual blood glucose concentration, creatinine concentration, previous stroke, at least one attack a week, coronary angiographic findings (if available), lipid lowering treatment, QT interval, systolic blood pressure ≥ 155 mm Hg, number of drugs used for angina, previous MI, and sex .
Authors note: The patients in the top 10% of risk had ten times the risk of patients in the bottom 10% of risk. Hence, risk stratification using the ACTION score helps to identify patients with stable angina for whom elective revascularisation might improve prognosis. Risk stratification aids decisions on secondary preventive medical management, especially when limited resources exist for coronary angiography and revascularisation. Patients at high risk of serious clinical events can be given priority so as to avoid such events while they are waiting fro an invasive procedure. However, the risk score did not seem to predict the nature of the event (death in 39%, MI in 46% and disabling stroke in 15%).
The present risk score is limited to patients with preserved left ventricualr function who did not have any condition, other than coronary artery disease, that limits life expectancy.

Daly CA;De SB;Sendon JL;Tavazzi L;Boersma E;Clemens F;Danchin N;Delahaye F;Gitt A;Julian D;Mulcahy D;Ruzyllo W;Thygesen K;Verheugt F;Fox KM;

Predicting prognosis in stable angina--results from the Euro heart survey of stable angina: prospective observational study

Ref ID 9370 RID: 976 2006 Feb 4

QUALITY

A. Selection bias (systematic differences between the comparison groups)

A4 Based on your answers t, in your opinion was selection bias present? If so, what is the likely direction of its effect?:

Direction =

B. Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)

B4 Based on your answers to the above, in your opinion was performance bias present? If so, what is the likely direction of its effect?:

Direction =

C. Attrition bias (systematic differences between the comparison groups with respect to loss of participants)

C4 Based on your answers to the above, in your opinion was attrition bias present? If so, what is the likely direction of its effect?:

Direction =

D. Detection bias (bias in how outcomes are ascertained, diagnosed or verified)

D6 Based on your answers to the above, in your opinion was detection bias present? If so, what is the likely direction of its effect?:

Direction =

Overall Study Quality -Strengths and Weaknesses:

Strengths-n=3779 enrolled. n=748 follow-up not complete vital status during follow-up was ascertained in 3259 (86%) patients, and data were suitable for survival analysis for the primary outcome of interest, which included non fatal MI, in 3031. The outcome of interest is adequately measured in study participants. The statistical analysis is appropriate for the design for the study. Cox's proportional hazards models was used to determine the effects of clinical and investigative variables on the occurrence of death or non fatal MI in both univariate and multivariate analysis.
Limitations –Small sample. The Euro heart survey of stable angina population differs from a general selection of people with angina in the community, many of whom may not have a diagnosis, and differs from the overall primary care angina population in that they have been selected for specialist assessment. However, the population is comparatively less highly selected than those in randomised controlled trials.
The Euro heart survey of stable angina was designed as a prospective observational cohort study of patients presenting to cardiology services with stable angina. Participating centres were a mix of academic and non academic institutions, and hospitals with and without interventional and cardiac surgical facilities.

DETAILS

# of patients: N=3031 patients enrolled from 156 centres in 34 countries.

Prevalence (Diagnostic):

Patient Characteristics

Baseline data:
No substantial differences existed between the patients with and without follow-up information in terms of clinical characteristics or regional distribution.

Variable : Follow-up incomplete (n=748); Follow-up complete (n=3031); P value (btw with/without follow-up)
Mean (SD) age (yrs): 61 (11) ;61 (11); 0.85
Female sex: 311/748 (42); 1271 /3031 (42); 0.83
CCS class: N=706; N=2766
Class I:251 (36);1096 (40);0.15
Class II:360 (51); 1331 (48)
Class III: 95 (13); 339 (12)
Duration of angina symptoms: N=706;N=2814
<1 month: 4 (<1); 48 (2); 0.18
1-5 months: 365 (52); 1494 (53)
6-11 months:155 (22); 585 (21)
>12 months: 182 (26); 687 (24)
Previous MI (>1 year before): 13/445 (3); 117 2456 (5);0.08
Peripheral vascular disease: 51/748 (7);216/3031; 0.76
Previous TIA or CVA: 46/748 (6);151/3031 (8); 0.20
Renal failure: 7/748 (1); 47/3031(2); 0.20
Diabetes : 122/713 (17); 530/2953 (18); 0.59
Hypertension:458 /727(63); 1809/2949 (61);0.39
Mean SD systolic BP (mm Hg): 144 (22)n=748; 145 (21) n=3001; 0.43
Drugs at baseline:N=748 ; N=3031
Aspirin:374 (50); 1602 (47); 0.16
Statin:184 (25); 1429 (21); 0.04
BB: 262 (35); 1142 (38);0.18

Inclusion criteria: Patients attending cardiology services with a new presentation of stable angina were considered for enrolment, and consecutive patients in whom the cardiologist made a clinical diagnosis of stable angina caused by myocardial ischemia due coronary disease were included in the survey. Exclusion criteria included unstable angina, admission to hospital within 24 hours of assessment, myocardial infarction within one year, previous revascularisation, or a cause of angina other than coronary disease.

Interventions/ Test/ Factor being investigated

Objective: To investigate the prognosis associated with stable angina, to identify the key prognostic features, and from this to construct a simple score to assist risk prediction.

Comparisons

Length of Study/ Follow-up

Follow-up was done by clinical review or telephone contact as close as possible to one year from initial assessment median -13 months (interquartile range 12-15 months).

Outcome measures studied

The occurrence and dates of occurrence of death or cardiovascular events were recorded, as well as the cause of death if available. The local investigators adjudicated clinical endpoints according to pre specified definitions. Severity of angina was assessed by using the Canadian Cardiovascular Society classification.

Results

Effect Size

Major clinical events occurring during follow-up in the overall population with stable angina.
N=3031
Endpoint: no. of events; event rate (95% CI) per 100 patient years
Death*: 50 ; 1.5 (1.1 to 1.9)
Non cardiovascular death: 14 (28%)
Non fatal MI: 48; 1.4 (1.1 to 1.9)
Death and non fatal MI: 93 ; 2.3 (1.9 to 2.8)
Cerebrovascular event: 34; 1.1 (0.8 to 1.5)
Heart failure: 49: 1.5 (1.1 to 2.0)
Unstable angina: 164; 5.2 (4.4 to 6.0)
All cardiovascular events: 328; 10.3 (9.3 to 11.5)

*of 50 deaths, the cause of death was classified as unknown or missing in 6 and cardiac or cardiovascular in 29.
Note: Comparisons with clinical trial populations with stable angina: The annual incidence of death in the survey was 1.5% and the incidence of non fatal MI was 1.4%. In the subgroup with proved coronary disease these rates were 1.8% and 3.2%. Estimates of annual mortality from modern clinical trials of secondary prevention, anti anginal treatment, or revascularisation range from 0.9% to 1.7%, with a higher mortality in populations with more severe symptoms. Reported annual incidences of non fatal MI range from 1.1% to 1.5%.

Unadjusted hazard ratio of death or MI associated with clinical and investigative parameters in general population with stable angina (n=3031)
Variables: Hazard ratio; p value
Clinical variables:
Age (per 1 year increment): 1.03 (1.01 to 1.05); 0.001
Sex (Female vs. Male):1.19 (0.79 to 1.79); 0.40
Diabetes: 2.40 (1.55 to 3.70); <0.001
Hypertension: 2.12 (1.29 to 3.48); 0.002
Ever smoked: 1.53 (1.00 to 2.36); 0.05
Previous MI: 3.24 (1.72 to 6.13); 0.002
Co-morbidity: 2.98 (1.98 to 4.52); <0.001
Symptom severity:
Class II versus class I: 2.34 (1.37 TO 4.00); 0.0002
Class III versus class I: 3.44 (1.80 to 6.55); 0.0002
Symptom duration >6 months: 0.60 (0.39 to 0.94); 0.03
Signs of heart failure: 2.67 (1.56 to 4.57); 0.001
Investigative variables
Left bundle branch block: 1.50 (0.66 to 3.43); 0.34
Q wave: 2.37 (1.38 to 4.06); 0.002
ST or T wave changes: 2.26 (1.50 to 3.41); <0.001
Ischemic ECG changes: 2.27 (1.50 to 3.43); <0.001
Results of individual stress tests
Positive exercise ECG (n=2299): 1.44 (0.80 to 2.61); 0.22
Positive stress echocardiogram (n=119): 1.24 (0.24 to 6.40); 0.80
Positive perfusion scan (n=420): 3.55 (0.77 to 16.47); 0.07
Result of any stress test
Positive test: 1.50 (0.82 to 2.73); <0.0001
No test done: 4.42 (2.50 to 7.82)
Echocardiography (before events)
Abnormal left ventricular function: 5.21(3.19 to 8.49); <0.001

Clinical and investigative parameters independently predictive of death or MI, determined by using stepwise selection procedures in general population with stable angina**
Variables: Hazard ratio (95% CI); p value
Clinical variables (n=2183)
Co-morbidity: 2.41 (1.49 to 3.91) ;< 0.001
Signs of heart failure: 1.62 (0.85 to 3.07); 0.14
Previous MI: 2.19 (1.08 to 4.42); 0.03
Diabetes: 2.03 (1.25 to 3.31); 0.004
Symptom duration >6 months: 0.54 (0.33 to 0.87); 0.01
Symptom severity:
Class II versus class i: 1.95 (1.07 to 3.54); 0.005
Class III versus class I: 2.65 (1.29 to 5.50); 0.005
Investigating variables (n=2963)
Stress testing
Positive test: 1.43 (0.76 to 2.70); 0.0001
No stress test done: 3.78 (2.04 to 7.00); 0.0001
Echocardiography:
Abnormal left ventricular function: 2.57 (1.62 to 4.08); <0.0001
Electrocardiography
ST or T wave changes: 1.63 (1.06 to 2.50); 0.03
Combines clinical and investigative variables (n=2528)
Co-morbidity: 2.25 (1.43 to 3.56); 0.0008
Diabetes: 1.95 (1.22 to 3.11); 0.007
Previous MI:-
Symptoms >6 months: 0.48 (0.30 to 0.77); 0.002
Symptom severity:

Class II versus class I: 1.76 (1.00 to 3.09); 0.05
Class III versus class I: 2.18 (1.10 to 4.33); 0.05
ST or T wave changes: 1.56 (0.99 to 2.45); 0.05
Stress test:
Positive stress test result: 1.29 (0.63 to 2.67); <0.0001
No stress test done: 3.48 (1.71 to 7.07) ;< 0.0001
Abnormal left ventricular function: 2.11 (1.29 to 3.46); 0.004
** As non performance of a test is not an objective measure of a patient but can be influenced by many physician related and non clinical factors. A further stepwise selection process was used to consider only the non invasive investigations that had been done. A positive versus negative or inconclusive non-invasive stress test result was not selected as a significant predictor of outcome when combined with information from echocardiography and resting echocardiography. Thus in the model developed to derive the clinical risk score the final predictors of death or MI were co-morbidity, diabetes, severity of symptoms, duration of symptoms, resting electrocardiogram abnormalities, and abnormal ventricular function. Applying the model developed on 75% of the population to the remaining 25% of the population gave a C-statistic for the angina score to predict outcome of 0.74.

Cox's proportional hazards models were used to determine the effects of clinical and investigative variables on the occurrence of death or non fatal MI in both univariate and multivariate analysis.

To develop a scoring system for predicting probability of death or infarction during the first year after presentation that was based only on objective information generally available to clinicians and not on whether a test was done a further multivariate model was developed without the stress test done/not done variable. The performance of the model was assessed by calculating the Harrels C-statistics (comparable to the area under the receiver operating characteristics curve).

Note: Coronary angiography was done at least once during follow-up in 1253 (41%) patients. At the end of the follow-up period, approximately one third (n=994) of patients had had coronary disease confirmed angiographically and a further third (n=1023) had negative investigations.

Source of funding:

Servier Laboratories was the principal financial sponsor for the study.

Does the study answer the question?/Further Comments

Yes. The clinical and investigative factors most predictive of adverse outcome were comorbidity, diabetes, shorter duration of symptoms, increasing severity of symptoms, abnormal ventricular function, resting electrocardiographic changes, or not having any stress test done. Results of the non invasive stress tests did not significantly predict outcome in the population who had tests done. A score was constructed using the parameters predictive of outcome to estimate the probability of death or myocardial infarction within one year of presentation with stable angina.

Applying the model developed on 75% of the population to the remaining 25% of the population gave a C-statistic for the angina score to predict outcome of 0.74.

Data extraction for prognostic tests

Exercise Electrocardiography

Forslund 2000 (Exercise electrocardiography)

This paper investigated the exercise test in the APSIS study (Angina Prognosis Study in Stockholm) population. APSIS was a prospective, randomised, single centre trial involving treatment of patients with verapamil or metoprolol and here it is analysed as prospective cohort study.

Participants: A total of n=809 participants were involved in this study.

Selection: 1276 patients with a presumed diagnosis of stable angina were referred from the Danderyd Hospital or from primary care in the catchments area to the Heart Research Laboratory at the Danderyd Hospital. Based on history and physical examination by a cardiologist, 809 patients (248 women) were considered to have stable angina and were included.

Inclusion criteria: age <70 yrs, and a history of chronic stable angina. Exclusion criteria: MI within the last three years; anticipated need for revascularisation within one month after inclusion; significant valvular disease or severe congestive heart failure; other severe diseases; contraindications to either study drug; and risk of poor compliance (e.g. suspected alcohol abuse). After baseline investigations patients randomised to treatment with metoprolol or verapamil.

Tests: Exercise tolerance testing. A symptom limited exercise was performed on an electrically braked cycle ergometer, with a starting load of 30 W and 10 W increments every minute. The following parameters were registered: exercise duration (s); time to onset of chest pain (s); time to 1 mm ST segment depression (s); maximal ST segment depression (mm) both during exercise and at rest 2 min after exercise. The patients were urged to report chest pain immediately, as well as in increase in its severeity, as assessed by the 10 degree modified Borg scale. The exercise test was stopped when patients were unable to continue due to chest pain, general and/or leg muscle fatigue or dyspnoea. For safety reasons, the responsible cardiologist could also stop the test if there was a fall in systolic blood pressure (≤ 20 mm Hg in one measurement or ≥10 mm Hg in two consecutive measurements), a severe ST segment depression (4-5 mm in at least 3 leads), or a severe ventricular arrhythmia.

Follow-up: Follow-up varied from 6 months to 75 months (median 40 months).

End points: The endpoints in this study were cardiovascular death, and cardiovascular death+MI. Cardiovascular death was defined as death from acute MI, sudden death (within 2 hours of onset of symptoms) or death from other vascular causes (e.g. fatal cerebrovascular disease, pulmonary emboli).

Statistical analysis: To investigate associations between exercise test variables and events, univariate Cox regression analysis and log rank statistics were performed. In a second step exercise variables that showed relationships to events were further evaluated with adjustments for the following known risk factors: sex, previous MI, hypertension and diabetes mellitus. All analyses were performed according to the principle of intention to treat. The treatment effects of the drugs were taken in to account in a separate analysis.

Results: During follow-up, 32 patients (29 men) suffered a cardiovascular death and 29 (24 men) a MI. In addition, 91 patients were revascularised, 35 had unstable or worsening angina, 21 suffered a cerebrovascular event, and five had other vascular events. Nine patients died of cancer. Thus there were 509 (335 men) event free patients. Patients on treatment with cardiac glycosides or with left bundle branch block were excluded from analyses, leaving 731 patients with evaluable exercise tests.

Exercise variables in patients with different outcomes: Prognostic evaluation of exercise variables - univariate analysis. Patients suffering cardiovascular death had a shorter exercise duration ($p < 0.01$) and a lower maximal heart rate during exercise ($p<0.001$) than patients without this event. They reported chest pain and showed significant ST segment depression earlier ($p<0.05$ for both). Maximal ST segment depression did not differ, but ST segment depression at rest 2 min after exercise was significantly greater among patients suffering cardiovascular death ($p<0.01$). For patients suffering a non fatal MI , only maximal heart rate during exercise differed ($p<0.01$).

Prognostic evaluation of exercise variables - multivariate analysis: Results of the Cox proportional hazard analysis regarding the risk of suffering a cardiovascular endpoint. The calculations were performed with the following covariates: sex, previous MI, hypertension and diabetes mellitus. Calculations concerning exercise duration have been performed on male patients only due to the sex related differences in exercise capacity.

Table X: Prognostic evaluation of exercise variables –multivariate analysis for CV death

Prognostic factors	Odds ratio (95% CI)	p value
Maximal ST depression	1.450 (1.15 to 1.83)	0.0018
Maximal ST depression 1-2 mm	0.827 (0.30 to 2.30)	0.71
Maximal ST depression ≥ 2 mm	1.619 (0.73 to 3.59)	0.23
ST segment depression after exercise:	1.850 (1.43 to 2.39)	0.00
ST segment depression 1-2 mm	1.502 (0.63 to 3.59)	0.36
ST segment depression ≥2 mm	5.180 (2.12 to 12.67)	0.0003
Exercise duration (male patients)	0.786 (0.69 to 0.90)	0.0006
Exercise duration 9-13 min	0.358 (0.16 to 0.82)	0.015
Exercise duration ≥ 13	0.250 (0.08 to 0.77)	0.016

min		

Table X: Prognostic evaluation of exercise variables –multivariate analysis for CV death +MI:

Prognostic factors	Odds ratio (95% CI)	p value
Maximal ST depression	1.33 (1.12 to 1.58)	0.001
Maximal ST depression 1-2 mm	1.36 (0.66 to 2.80)	0.402
Maximal ST depression ≥ 2 mm	2.06 (1.11 to 3.83)	0.02
ST segment depression after exercise:	1.54 (1.26 to 1.91)	0.00
ST segment depression 1-2 mm	1.59 (0.89 to 2.85)	0.11
ST segment depression ≥2 mm	3.03 (1.46 to 6.31)	0.002
Exercise duration (male patients)	0.834 (0.76 to 0.92)	0.0002
Exercise duration 9-13 min	0.506 (0.28 to 0.92)	0.02
Exercise duration ≥ 13 min	0.314 (0.14 to 0.71)	0.005

Treatment effects: In order to assess the prognostic information of the treatment given and treatment effects, multivariate Cox model was employed described above, with further variables describing treatment effects added. The analyses were limited to treatment effects on maximal ST segment depression, as exercise duration, and time until 1 mm ST segment depression differed little between the baseline and 1 month investigations. The analysis showed that neither the type of drug given nor the effect of treatment on ischaemia, regardless of the drug given, had any independent prognostic impact. The slightly more marked reductions of ischaemia by verapamil did not influence prognosis significantly.

Summary: Prognostic implications of results from exercise tests were assessed in a multivariate Cox model which included sex, previous MI, hypertension and diabetes mellitus. After adjustment for these variables, maximal ST depression during exercise, ST segment depression 2 min after exercise, and exercise duration all carried independent relationships to both cardiovascular death and the combined endpoint of cardiovascular death + MI. When the treatment given and treatment effects on ST-segment depression were added to the Cox model, no impact on

prognosis could be detected for either cardiovascular death alone or combined with MI. Anginal pain carried no prognostic information.

Strength: The study sample represented the population of interest. Loss to follow-up was unrelated to key characteristics. The statistical analysis was appropriate for the study.

Limitations: Selected population sample. Very few events.

Sekhri 2008 (Exercise electrocardiogram)

Population: N= 1422

Overall, 8176 of 10 634 consecutive patients with new onset of chest pain referred by their doctor to six chest pain clinics from 1 January 1996 to 31 December 2002 were included in this study.

Patients without chest pain, with previously diagnosed coronary artery disease (n=858), with incomplete data on pre-specified covariates (n=685), not traced by central registries (n=40), and whose ethnicity was black or not specified (n=875) were excluded. From among these 8176 patients (cohort), a total of 4873 (60%) who had an exercise ECG recorded were stratified into two subsets: 4848 patients with a summary test result recorded (positive, negative, equivocal for ischaemia) and 1422 with additional detailed test data recorded. These groups comprised the summary ECG subset and detailed ECG subset for exercise electrocardiography, respectively. The exercise ECG (Bruce treadmill protocol) was obtained in all but 7% of patients on the day of the clinic visit.

Angina was diagnosed in 29% of the cohort, 32% of the summary ECG subset and 28% of the detailed ECG subset.

Test: resting 12 lead ECG for every patient, recorded as normal or abnormal depending on entries in the database for rhythm, conduction, regional change in ST segment or T wave, left ventricular hypertrophy, and Q waves.

In the summary ECG subset only the clinicians' assessment of ischaemia was recorded (positive, negative, or equivocal). In the detailed ECG subset, data recorded included exercise time, maximum workload, maximum heart rate, maximum blood pressure, diagnostic change in ST segment, arrhythmias, and reason for stopping (limiting symptoms, ST segment displacement of more than 1 mm 0.08 seconds after the J point, or target heart rate achieved).

Outcome: The primary end point was a composite of death due to coronary heart disease or non-fatal acute coronary syndrome

Follow-up: median follow-up of 2.46 years.

Statistical analysis: Multivariable Cox analysis was carried out for the primary end point using factors that were statistically significant at the 20% level in univariable analysis for each of three separate models: clinical model (age, sex, typicality of symptoms, heart rate, systolic blood pressure, history of hypertension, diabetes, smoking status), ECG model (QRS axis deviation, pathological Q waves, change in ST segment or T wave, left ventricular hypertrophy, bundle branch block), summary exercise ECG model (positive, negative, or equivocal), and detailed exercise ECG model (exercise time, maximum workload, percentage predicted heart rate, maximum blood pressure, reason for stopping exercise, diagnostic change in ST segment, exertional arrhythmias). The covariates that remained statistically significant at the 5% level in each model were used to build three incremental models: basic clinical assessment, basic clinical assessment plus resting ECG, and basic clinical assessment plus resting ECG plus either summary exercise ECG or detailed exercise ECG. Then prognostic indices were calculated for each of the incremental models using the regression coefficients.

Results:

Patient outcomes
Typical chest pain and abnormalities on the resting ECG and exercise ECG were all associated with adverse outcomes. Thus point estimates of the probability of the primary end point at three years were 16% for patients with typical chest pain, 15% for patients with an abnormal resting ECG, and 19% for patients with an abnormal exercise ECG, compared with 3%, 5%, and 9% for patients with non-specific chest pain and normal resting and exercise ECGs. However, 47% (n=166) of the events during follow-up occurred in patients with a "normal" exercise ECG, emphasising the limitations of exercise ECGs for risk assessment. Thus in both the summary ECG and the detailed ECG subsets, risk stratified cumulative probabilities of the primary end point at one year and six years for all three prognostic indices (basic clinical assessment, basic clinical assessment plus resting ECG, basic clinical assessment plus resting ECG plus exercise ECG) showed only small differences at all time points and in all thirds of risk.

Table X: Sekhri 2008, ECG Univariate analysis

Covariate	Univariable hazard ratio (95% CI)	P value	Adjusted hazard ratio* (95% CI)	P value
Whole cohort (n=8167) risk of composite end point(events=576)				
Basic clinical assessment:				
Age (10 year increase)	1.04 (1.03 to 1.05)	<0.001	1.02 (1.02 to 1.03)	<0.001
Sex (female v male)	0.75 (0.64 to 0.88)	<0.001	0.76 (0.65 to 0.90)	<0.001
Typicality	3.94 (3.33 to 4.67)	<0.001	3.17 (2.66 to 3.79)	<0.001

Typical v atypical	0.61 (0.45 to 0.83)		0.68 (0.50 to 0.93)	
Non-specific v atypical	0.98 (0.92 to 1.05)	0.53	NA	NA
Heart rate per 10 second increase	1.10 (1.06 to 1.14)	<0.001	1.02 (0.98 to 1.06)	0.313
Systolic blood pressure	0.71 (0.61 to 0.84)	<0.001	1.01 (0.85 to 1.21)	0.870
Hypertension	1.90 (1.55 to 2.32)	<0.001	1.48 (1.20 to 1.83)	<0.001
Diabetes	1.04 (0.86 to 1.25)	0.71	NA	NA
Current smoker				
Resting ECG:	2.25 (1.53 to 3.31)	<0.001	1.40 (0.94 to 2.08)	0.12
Abnormal axis	3.73 (2.67 to 5.23)	<0.001	2.62 (1.85 to 3.70)	<0.001
Q waves	2.77 (2.29 to 3.35)	<0.001	2.43 (1.98 to 2.98)	<0.001
Change in ST segment or T wave	1.72 (1.23 to 2.40)	0.0032	1.09 (0.77 to 1.54)	0.63
Left ventricular hypertrophy	2.18 (1.57 to 3.02)	<0.001	1.96 (1.40 to 2.73)	<0.001
Bundle branch block	3.94 (3.33 to 4.67)	<0.001	3.17 (2.66 to 3.79)	<0.001
Summary ECG subset (n=4848), (events=351)				
Exercise ECG:				
Positive result v negative result	4.58 (3.68 to 5.72)	<0.001	NA	NA
Equivocal v negative result	2.16 (1.48 to 3.14)			

Detailed ECG subset (n=1422), (events=110)				
Exercise ECG:				
Exercise time (minutes)	0.80 (0.75 to 0.86)	<0.001	0.84 (0.77 to 0.93)	0.0025
Maximum workload	0.84 (0.79 to 0.90)	<0.001	0.99 (0.93 to 1.07)	0.87
% predicted heart rate	0.99 (0.98 to 1.00)	0.0078	0.99 (0.98 to 1.00)	0.25
Maximum blood pressure	1.00 (0.99 to 1.01)	0.66	NA	NA

Multivariate analysis:

Adjusted hazard ratios for three incremental models: basic clinical assessment, basic clinical assessment plus resting electrocardiogram (ECG), and basic clinical assessment plus resting ECG plus exercise ECG are shown in the table below.

Table X: Sekhri 2008, ECG Multivariate analysis

Covariate	Coefficient	Adjusted hazard ratio (95% CI)	P value
Clinical assessment with significant variables (cohort)			
Age (10 year increase)	0.26	1.30 (1.21 to 1.39)	<0.001
Sex (female v male)	–0.28	0.75 (0.64 to 0.89)	0.0008
Typicality of chest pain:			
Typical v atypical	1.13	3.09 (2.58 to 3.71)	<0.001
Non-cardiac v atypical	–0.38	0.68 (0.50 to 0.93)	
Diabetes	0.45	1.58 (1.28 to 1.94)	<0.001
Clinical assessment plus resting ECG (cohort)			
Age (10 year increase)	0.23	1.26 (1.17 to 1.35)	<0.001

Sex (female v male)	–0.27	0.76 (0.65 to 0.90)	0.0013
Typicality of chest pain:			
Typical v atypical	1.04	2.82 (2.34 to 3.40	<0.001
Non-cardiac v atypical	–0.37	0.69 (0.50 to 0.95)	
Diabetes	0.41	1.50 (1.22 to 1.86)	0.0002
Q waves	0.57	1.77 (1.24 to 2.53)	0.0037
Bundle branch block	0.30	1.36 (0.95 to 1.94)	0.1089
Change in ST segment or T wave	0.45	1.57 (1.28 to 1.94)	<0.001
Clinical assessment plus resting ECG plus summary exercise ECG*			
Age (10 year increase)	0.10	1.11 (1.00 to 1.22)	0.048
Sex (female v male)	–0.05	0.95 (0.76 to 1.18)	0.64
Typicality of chest pain:			
Typical v atypical	0.75	2.12 (1.66 to 2.71)	<0.001
Non-cardiac v atypical	–0.54	0.58 (0.29 to 1.19)	
Diabetes	0.36	1.44 (1.09 to 1.89)	0.0134
Q waves	0.75	2.12 (1.28 to 3.49)	0.051
Bundle branch block	–0.11	0.90 (0.40 to 2.02)	0.79
Change in ST segment or T wave	0.29	1.34 (1.01 to 1.79)	0.0078
Positive v negative exercise ECG	0.92	2.53 (1.95 to 3.30)	<0.001

Equivocal v negative exercise ECG	0.44	1.55 (1.06 to 2.28	
Clinical assessment plus resting ECG plus detailed exercise ECG*			
Age (10 years increase)	0.03	1.03 (0.85 to 1.25)	0.76
Sex (female v male)	–0.59	0.55 (0.37 to 0.83)	0.0036
Typicality of chest pain:			
Typical v atypical	0.90	2.45 (1.62 to 3.70)	<0.001
Non-cardiac v atypical	–0.52	0.59 (0.14 to 2.45)	
Diabetes	0.03	1.03 (0.63 to 1.70)	0.9023
Q waves	0.49	1.64 (0.64 to 4.18)	0.3338
Bundle branch block	0.42	1.53 (0.48 to 4.89)	0.5022
Change in ST segment or T wave	0.32	1.37 (0.83 to 2.27)	0.2264
Exercise time (minutes)	–0.15	0.86 (0.79 to 0.93)	0.0005
Diagnostic change in ST segment	0.81	2.26 (1.44 to 3.53)	0.0005

**Covariates were those selected in whole cohort.*

Receiver operating characteristics curves and C statistic

In the cohort, receiver operating characteristics curves for the basic clinical assessment model alone and with iteration for the resting ECG were effectively superimposed with little or no increment in the C statistic (fig 1). With the iterations for the exercise ECGs the C statistic for the basic clinical assessment model increased in the summary ECG subset from 0.70 (95% confidence interval 0.68 to 0.73) to 0.74 (0.71 to 0.76) and in the detailed ECG subset from 0.74 (0.70 to 0.79) to 0.78 (0.74 to 0.82). When analysis was restricted to patients with an intermediate probability of coronary artery disease (20-80%), the receiver operating characteristics curves for the basic clinical assessment model alone and with iteration for the resting ECG remained effectively superimposed, reflecting poor discrimination. With the exercise

ECG iterations the C statistic (95% confidence interval) for the basic clinical assessment model increased in the summary ECG subset from 0.69 (0.65 to 0.73) to 0.74 (0.70 to 0.78) and in the detailed ECG subset from 0.69 (0.62 to 0.77) to 0.76 (0.70 to 0.82).

Summary: Receiver operating characteristics curves for the basic clinical assessment model alone and with the results of resting ECGs were superimposed with little difference in the C statistic. With the exercise ECGs the C statistic in the summary ECG subset increased from 0.70 (95% confidence interval 0.68 to 0.73) to 0.74 (0.71 to 0.76) and in the detailed ECG subset from 0.74 (0.70 to 0.79) to 0.78 (0.74 to 0.82). However, risk stratified cumulative probabilities of the primary end point at one year and six years for all three prognostic indices (clinical assessment only; clinical assessment plus resting ECG; clinical assessment plus resting ECG plus exercise ECG) showed only small differences at all time points and at all levels of risk.

Strengths:. Loss to follow-up is unrelated to key characteristics. The prognostic factor of interest and outcomes of interest is adequately measured in study participants. The statistical analysis was appropriate to the study. 353 combined events, however study does not report the individual number of events.

Limitations: Study sample does not entirely represent the population of interest. Loss to follow-up not reported

1.1 Exercise echocardiography

Antonello 2005 (Exercise stress echocardiography)

Participants: A total of 607 patients were included in the study.

The initial cohort included 640 consecutive patients who underwent exercise echocardiography clinically indicated from July 1997 to December 2003 for the evaluation of chest pain symptoms or for cardiac risk stratification. 22 patients who underwent coronary artery revascularisation within 3 months of ESE procedure, and 8 patients who were lost to follow-up (0.9%), were censored. Non cardiac death occurred in 3 patients: 2 for malignant cancer and 1 for a car accident.

The baseline characteristics of the sample were as follows: age (years): 58.5±10.9; males: 470 (77.4%); family history of CAD: 455 (75.8%); diabetes mellitus: 91 (14.9%); hypercholesterolemia: 361 (59.4%); arterial hypertension: 394 (64.9%); smokers: 355 (58.4%); angina: 520 (85.6%); previous AMI: 260 (42.8%); previous PTCA 61 (10.1%).

Exercise echo was performed for the diagnosis of suspected CAD in 267 patients (43.9%) and for risk stratification of known CAD in 340 patients (56.1%). Medical treatment if present was discontinued 3 days before the test.

Tests: Exercise stress echocardiography (ESE) was performed by bicycle ergometer in a supine position, using a standard Bruce protocol.

Echocardiographic analysis: All examinations were reviewed by 2 independent observers. For LV motion analysis, standard 16 segment LV model of the American Society of Echocardiography was used, and wall motion was scored as 1=normal; 2=hypo kinetic; 3=akinetic; 4= dyskinetic. LV wall motion score index (WMSI) was calculated a t baseline and at peak effort dividing the sum of individual segment scores by the number considered segments.

Outcomes: The primary outcomes were cardiac death, and cardiac death and non fatal MI.

Follow-up: Patients follow-up assessed for a mean period of 46.9 months (range 12-60 months).

Statistical analysis: Independent predictors of cardiac events (cardiac death, cardiac death+MI) were identified by univariate and multivariate Cox proportional hazard regression models. The 0.05 probability level was adopted for significant association between predictive variables and events. The risk associated with a given variable was expressed by a hazard ratio with a corresponding 95% CI. At multivariate analysis an automatic backward stepwise procedure was adopted.

Results: Cardiac events

During the follow-up there 48 deaths (21.6%) and 34 acute non fatal MIs (15.3%).

Univariate predictive value of clinical risk factors and Exercise stress echocardiography (ESE) results for cardiac events

Table X: Univariate predictive value of clinical risk factors and Exercise stress echocardiography (ESE) results for cardiac death

Risk factors:	**hazard ratio (95% CI)**	**p value**
Clinical data		
Age:	1.9 (1.5 to 4.8)	<0.01
Hypercholesterolemia:	1.3 (0.7 to 4.4)	ns
Cigarette smoking:	4.1 (2.3 to 4.8)	<0.001
Rest echocardiographic data		
Rest WMSI (wall motion score index) :	3.6 (2.3 to 6.1)	<0.01
ESE data		
Positive ESE:	5.1 (4.8 to 5.8)	<0.0001

Peak WMSI (wall motion score index):	4.8 (4.2 to 5.7)	<0.0001
Low workload;	4.1 (3.5 to 5.1)	<0.001
Angina during ESE:	2.2 (1.9 to 3.6)	NS

Table X: Univariate predictive value of clinical risk factors and Exercise stress echocardiography (ESE) results for cardiac death or MI

Risk factors:	**hazard ratio (95% CI)**	**p value**
Clinical data		
Age:	1.2 (1.1 to 5.2)	ns
Hypercholesterolemia:	4.7 (3.3 to 6.0)	<0.001
Cigarette smoking:	1.3 (1.2 to 4.6)	ns
Rest echocardiographic data		
Rest WMSI (wall motion score index)	3.8 (2.4 to 5.8)	< 0.01
ESE data		
Positive ESE:	5.3 (4.9 to 5.6)	<0.0001
Peak WMSI (wall motion score index):	5.0 (4.8 to 6.1)	<0.0001
Low workload:	2.3 (1.4 to 4)	ns
Angina during ESE:	4.1 (2.8 to 4.9)	<0.001

Table X: Multivariate predictive value of clinical risk factors and Exercise stress echocardiography (ESE) results for cardiac death

Variables	**Chi square (X^2)**	**p value**	**variables selected (partial X^2; 95% CI; p)**
Clinical	9.3	0.01	cigarette smoking (2.8; 1.8 to 4.1; <0.01)
Clinical +rest echo	11.8	0.001	rest WMSI (3.0; 2.1 to 4.1 ;< 0.01)
Clinical +rest echo+ ESE:	37.9	0.00001	positive ESE (4.1; 3.6 to 4.4;

			<0.0001) Peak WMSI (3.5; 2.8 to 4.1); <0.0001 Low workload (3.1; 2.7 to 3.7; <0.01)

Table X: Multivariate predictive value of clinical risk factors and Exercise stress echocardiography (ESE) results for cardiac death+MI

Variables:	**Chi-square (X^2)**	**p value**	**variables selected (partial X^2; 95% CI; p)**
Clinical	9.6	0.01	hypercholesterolemia (2.5; 1.6 to 3.3; <0.01)
Clinical +rest echo	12.5	0.001	rest WMSI (3.1; 2.4 to 3.8 ;< 0.01)
Clinical +rest echo+ ESE	39.6	0.00001	Positive ESE (4.5; 3.6 to 5.3 ;< 0.0001) Peak WMSI (3.7 ; 2.6 to 4.4; <0.0001) Angina during ESE (2.9; 2.3 to 3.8; <0.01)

Summary: At univariate analysis, the following variables were significant predictors of cardiac death (in descending order): ESE positive for ischaemia, peak WMSI, low workload, rest WMSI, cigarette smoking and age. Multivariate analysis identified ESE positive for ischaemia, peak WMSI, low workload and cigarette smoking as strongest independent predictors of cardiac death. The global **Chi-square** (X^2)of this combined clinical and stress test model was 37.9 ($p<0.00001$). For cardiac death+MI, the following variables were significant univariate predictors: positive stress test, peak WMSI, angina during the test, rest WMSI, hypercholesterolemia and cigarette smoking. However, multivariate analysis identified positive ESE, peak WMSI, angina during the test and hypercholesterolemia as the only independent determinants of cardiac death or MI. The global X^2 of this combined clinical and stress test model was 39.8 ($p<00001$). The results emphasise that information obtained by ESE is additional and independent to that provided by clinical and rest echocardiographic data.

Strengths: The study sample represented the population of interest with regard to key characteristics. Eight patients were lost to follow-up (0.9%) and were censored. The

statistical analysis is appropriate for the design of the study. All ESE examinations were reviewed by two independent observers and blinded to clinical data.

Elhendy 2004 (Exercise echocardiography):

Participants: A total of 437 (241 men and 196 women) patients were included in this study.

Inclusion criteria: The study included patients with a high pre test probability of CAD referred for exercise echocardiography. Exclusion criteria were a history MI; a previous coronary revascularisation procedure, CAD documented by angiography, and left ventricular hypertrophy. High pre- test probability of disease was defined as probability of >70%. This was considered in the presence of typical angina pectoris in women ≥ 50 years of age and in men ≥30 years of age.

Baseline characteristics: Mean age of the study patients was 65±10 years. Risk factors for CAD were hypertension in 208 patients (48%), diabetes mellitus in 32 (7%), hypercholesterolemia in 257 (59%) and smoking in 220 (50%).

Tests: Exercise echocardiography was done during symptom limited treadmill exercise testing (Bruce protocol 89%, Naughton protocol 6%, modified Bruce protocol 5%) with 12 channel electrocardiographic monitoring.

Exercise echocardiographic interpretation: Digitised and video tape-recorded images were used for interpretation. Regional wall motion was assessed semi quantitatively by an experienced echocardiographer who was blinded to clinical information. Wall motion at rest and during exercise was scored as 1 to 5 using a 16 segment model. Wall motion score index was determined at rest and during exercise as the sum of the segmental scores divided by the number of visualised segments. The difference between exercise and regional wall motion score index at rest was reported as mean wall motion score index. The development of new or increasing wall motion abnormality was considered indicative of myocardial ischaemia. A wall motion abnormality present at rest and unchanged with exercise was classified as fixed. Exercise echocardiographic results were defined as abnormal if there was ischaemia or fixed wall motion abnormalities. The exercise electrocardiogram was considered positive for ischaemia if there was horizontal or down sloping ST segment depression ≥1 mm at 80 ms after the J-point, non diagnostic if the baseline ST segment was abnormal, or negative for ischaemia in the absence of these criteria. Workload was measured in METs.

Follow-up: The follow-up was median 2.7 years (1 to 7.8 years).

Outcomes: The end points considered were 1) any cardiac events defined as coronary artery revascularization, non fatal MI and cardiac death 2) cardiac death and non fatal MI.

Statistical analysis: Univariable and multivariable associations of clinical and exercise echocardiographic variables with the end points were assessed in Cox's proportional hazards models.

Results: During a median follow-up of 2.7 years, cardiac events occurred in 68 patients (16%). Four cardiac deaths and 15 non fatal MIs occured a median of 2.7 years after the exercise echocardiogram. 53 patients underwent revascularisation procedures (4 subsequently had non fatal MI). Revascularisation was early (<1 month) in 24 patients and late (>1 month) in 29 patients.

Table X: Univariate association of clinical, exercise stress test, and echocardiographic variables with risk of cardiac events

Variable	Chi-square (X^2)	p-value; Risk ratio (95% CI)
Baseline characteristics		
Smoker	4.7	0.03; 1.72 (1.1 to 2.8)
Diabetes mellitus	5	0.02; 2.3 (1.4 to 4.6)
Men	19	0.0001; 0.25 (0.13 to 0.47)
Q waves on electrocardiogram	4.3	0.04; 2.15 (1.05 to 4.42)
Exercise test variables		
85% age predicted heart rate	10	0.001; 0.45 (0.3 to 0.7)
Heart rate during exercise	11	0.0009; 0.82 (0.74 to 0.90)
Systolic BP during exercise	11	0.001; 0.9 (0.82 to 0.90)
Rate pressure product during exercise	14	0.0002; 0.27 (0.14 to 0.53)
Workload (METs)	5	0.03; 0.9 (0.8 to 0.99)
Exercise induced angina	20	0.0001; 3 (1.9 to 4.9)
Ischaemic electrocardiographic changes	27	0.0001; 3.8 (2.3 to 6.2)
Echocardiographic variables		
Wall motion abnormality during exercise	28	0.0001; 5.7 (3 to 10.8)
New wall motion abnormality (ischaemia)	28	0.0001; 3.8 (2.3 to 6.3)
Percent ischaemic segments	47	0.0001; 1.97 (1.62 to 2.39)

Wall motion score index during exercise	45	0.0001; 4.4 (2.8 to 6.7)
Mean motion score index	48	0.0001; 7 (4 to 12)

Table X: Independent predictors of cardiac events using a three step multivariate analysis model

Parameters	**Chi-square (X^2)**	**p-value*; model chi-square ** **
Clinical (model)		
Age	0.01	0.9; 36
Gender	14	0.0002
Diabetes mellitus	1.9	0.2
Clinical and exercise tests (model)		
Ischaemic electrocardiographic changes	3.2	0.07; 62 ***
Workload	4.8	0.03
Clinical, exercise stress and echocardiography (model)		
Wall motion abnormalities		78 *****
In multi vessel regions****	13.4	0.0003
In single vessel region****	2.8	0.1

**Chi square and p value based on final model.*
*** Overall model chi-square at each phase of the modelling process*
**** p=0.0001 versus the clinical model.*
***** The reference group consisted of subjects with no wall motion abnormalities*
****** p=0.001 versus the clinical plus exercise stress model.*

Summary: During a median follow-up of 2.7 years, cardiac death or non fatal MI occurred in 19 patients and 53 patients underwent coronary revascularisation. Event free survival rates in patients with normal versus abnormal stress echocardiograms were 98% versus 83% at 1 year, 96% versus 75% at 3 years, and 87% versus 69% at 5 years, respectively. In a multivariate analysis of clinical, exercise, and echocardiographic parameters, independent predictors of cardiac death and non-fatal MI were Q waves on the electrocardiogram (Chi-square 8.7, p=0.003) and the presence of wall motion of abnormalities during exercise in multi vessel distribution

(Chi-square 5.3, p=0.02). In an incremental model of clinical, exercise and echocardiographic variables for the prediction of all cardiac events, the addition of echocardiographic data increased chi-square model from 62 to 78 (p=0.0003).

Strengths: The study sample represented the population of interest. The statistical analysis was appropriate for the design of the study.

Weakness: Loss to follow-up not reported. Very few events.

1.2 MYOCARDIAL PERFUSION IMAGING

Groutars 2002 (Myocardial perfusion scintigraphy using technetium-99m tetrofosmin with bicycle ergometry)

Population: N=597

From April to December 1996, 610 consecutive patients who were refered for myocardial perfusion scintigraphy were evaluated. Patients with unstable angina or MI within the preceding 6 weeks were excluded. Of the 610 patients, 13 (2%) were lost to follow-up, leaving 597 patients.

The group consisted of 348 men (mean age 60 years, range 27-85 years) and 249 women (mean age 63 years, range 23-84 years). Reasons for performing the perfusion studies included typical NYHA Class I-III angina (54%), non-anginal chest pain (40%), and risk stratification prior to major vascular surgery (6%).

Tests:

Rest thallium-201: BB or CCB were withheld for 48 h and long acting nitrate compounds for 24 h before the study. A weight-adjusted dose of radio-isotope was injected at rest and after 15 min of normal walking and 15 min rest, 201-thallium SPECT imaging was performed.

Exercise electrocardiography: Immediately after rest imaging, a symptom limited exercise test was performed using a calibrated bicycle ergometer in the upright position. The initial external workload was 60 W for 2 min, this being increased by 20 W every 2 min. During exercise and for 5 min after exercise, blood pressure, heart rate, symptoms and electrocardiograms were monitored. At near maximal exercise, 444 MBq (12mCi) of technetium-99m tetrofosmin was injected intravenously and patients were encouraged to continue exercising maximally for one additional minute, after which the workload was gradually reduced.

SPECT imaging: SPECT imaging was performed using a Toshiba triple-detector gamma camera equipped with low energy, high resolution collimators. Image analysis: visual interpretation comprised assessment of short and long axis tomograms each divided in to at least eight slices. Semi quantitative visual analysis of the myocardial scintigrams using a five point scoring system was performed by consensus of two observers who had no knowledge of the clinical history or results of coronary arteriography (0, normal uptake; 1, equivocal; 2, moderate reduction of tracer uptake; 3, severe reduction of tracer uptake; 4, absence of tracer uptake). Three nuclear variables as defined previously by Hachamovitch were used, namely the summed stress score (SSS), the summed rest score (SRS), and the summed difference score (SDS). The SSS was obtained by calculating the sum of the scores of the 20 segments of the stress technetium-tetrofosmin images. An SSS of less than 4 was considered normal, a score between 4 and 13 as mildly to moderate abnormal, and a score greater than 13 as severely abnormal. The SRS was calculated on a similar basis. The SDS was calculated as the sum of the differences between SSS and the SRS for each segment. An SDS score between 2 and 12 was defined as moderate myocardial ischaemia and an SDS score of >12 as severe ischaemia.

Follow-up: 23±9 months

Endpoints: Events were defined as death, caused by any cardiac disorder with underlying coronary artery disease, including sudden death (confirmed by review of death certificate or hospital chart), or non fatal MI (documented by appropriate electrocardiographic and cardiac enzyme changes).

Statistical analysis:

Both univariate and multivariate Cox regression models were used to evaluate the independent and combined effects of predicting cardiac events. In the univariate analysis, all available co-variates were analysed. Values were expressed as HR with 95% CI. A value of $p<0.05$ was considered statistically significant. Cox proportional hazard analysis was applied to determine three distinct statistical models with cardiac death and non fatal MI as a combined endpoint: model A, a clinical model (anginal symptoms, age, gender, prior MI, PTCA or CABG); model B, a clinical and exercise model (model A and post exercise test likelihood of coronary artery disease); model C, a combined clinical, exercise and nuclear model (model B and two nuclear variables, the SSS and abnormal SPECT). A statistically significant increase in global chi-square of the model after addition of the nuclear variables defined incremental prognostic information.

Results:

46 events occurred: 16 cardiac deaths and 30 non fatal MI.

Table X: Groutars 2002 Univariate analysis

Parameters	Events (n=46)	No event (n=55)	HR	95% CI	P
Female	12 (26)	237 (43)	0.424	0.220 to	0.011

				0.820	
Age (yr)	65±9	61±11	1.035	1.006 to 1.068	0.025
Prior MI	25 (54)	168 (30)	2.892	1.618 to 5.168	<0.001
Prior PTCA	17 (37)	89 (16)	3.097	1.702 to 5.637	<0.001
Prior CABG	14 (30)	58 (11)	3.309	1.765 to 6.202	<0.001
Hypercholesterolemia	24 (52)	331 (60)	1.004	0.498 to 2.461	Ns
Smoking	6 (13)	130 (24)	0.513	0.218 to 1.211	Ns
Diabetes mellitus	5 (11)	47 (9)	1.335	0.528 to 3.379	Ns
Hypertension	15 (33)	178 (32)	1.041	0.562 to 1.929	Ns
Type of chest pain					
Indeterminate	3 (7)	118 (21)	1.00		
Atypical angina	5 (11)	123 (22)	1.571	0.410 to 6.574	Ns
Typical angina	34 (74)	281 (51)	4.411	1.364 to 14.42	0.013
Shortness of breath	4 (9)	29 (5)	5.471	1.225 to 24.56	0.024

Concerning the exercise variables, the most predictive value was the post exercise test likelihood of coronary artery disease (HR 1.022, CI 1.009 to 1.035, p=0.001). Also in the subgroup of patients who underwent the bicycle exercise test, the peak heart rate (HR 0.974, CI 0.952 to 0.996, p= 0.021) and the percentage of maximal

heart rate achieved (HR 0.902, CI 0.840 to 0.969, p=0.005) were significant predictors.

Table X: Groutars 2002, Multivariate analysis of nuclear variables

	events (n=46)	No event (n=551)	HR	95% CI	P
Abnormal SPECT (SSS >3)	41 (89)	278 (50)	5.438	1.882 to 15.72	0.002
Summed stress score	28±20	13±17	1.019	1.001 to 1.038	0.035
Summed difference score	12±14	7±11	1.036	1.036	0.110
Severe ischaemia (SDS >12)	15 (33)	96 (17)	0.342	0.342	0.072

Strengths: study sample represents the population of interest. Loss to follow-up is unrelated to key characteristics. The prognostic factor of interest and outcomes of interest is adequately measured in study participants.

Limitations: Composite outcomes used. Few events.

Summary: During the two year follow-up there were 16 cardiac deaths and 30 non fatal MIs. Multivariate analysis was performed by using four different nuclear variables, the SSS, SDS, abnormal SPECT and severe ischaemia. Abnormal SPECT was defined as an SSS greater than 3 and severe ischaemia as SDS greater than 12. Abnormal SPET (HR 5.438, CI 1.882 to 15.72, p=0.002) and SSS (HR 1.019, I 1.001 to 1.038, p=0.035) were significant independent predictors of hard cardiac events.

The Cox hazard proportional hazard analysis was performed using the most predictive clinical variables of the univariate analysis in a clinical model: history of MI, history of PTCA, history of CABG, typical anginal symptoms, age and gender. There was no significant increase in global chi-square after addition of the most predictive exercise variable, the post exercise test likelihood of coronary artery disease, to this model (X^2=45.6 and 47.3, respectively). However, a significant increase in global chi-square occurred with the addition of two nuclear variables (SSS and abnormal SPECT), demonstrating the incremental prognostic information obtained with the addition of these nuclear variables (X^2=70.8; gain in X^2, p<0.001).

Elhendy 2005 (SPECT imaging using technetium-99m tetrofosmin with bicycle ergometry)

Population:

N=455

Selection: The initial study population consisted of 458 consecutive patients referred between Jan 1996 and December 2002 for exercise or dobutamine stress technetium-tetrofosmin SPECT to evaluate typical anginal symptoms. Contraindications for stress testing were unstable angina, uncontrolled heart failure, and severe valvular heart disease. The choice of stress test was based on ability to exercise.

Mean age was 60±10 years. There were 226 men (58% of the patients).

Test: Technetium-tetrofosmin SPECT imaging

Stress test protocol

For 165 patients, an exercise stress test was performed; suing symptom limited upright bicycle ergometry with a stepwise increment of 20 W every minute. For 290 patients, dobutamine-atropine stress testing was performed.

Patients were instructed to discontinue BB at least 24 hours before the stress test, whenever applicable. Other medications were not routinely discontinued.

Technetium-tetrofosmin SPECT imaging: . An intravenous dose of 370 MBq of Technetium tetrofosmin was administered 1 min before termination of the dobutamine or exercise test.

Stress and rest tomographic views were interpreted semi quantitatively by visual analysis by an experienced observer who was unaware of the patient's clinical data.

A reversible perfusion defect was defined as a perfusion defect on stress images that partially or completely resolved at rest in ≥ 2 contiguous segments or slices in the 47 segment model. This was considered diagnostic of myocardial ischaemia. A fixed perfusion defect was defined as a perfusion defect on stress images in 2 or more contiguous segments or slices, which persisted on rest images in the 47 segment model. The impact of extent of perfusion abnormalities on outcome was evaluated by estimating the number of coronary arterial territories with perfusion abnormalities on the stress images, as described above.

Follow-up: 6±1.7 years**.**

Endpoints: Two endpoints were considered: death from any cause, and cardiac death and non fatal MI (defined by cardiac enzyme levels and electrocardiographic changes).

Statistical analysis:

Univariate and multivariate Cox proportional hazard regression models were used to identify independent predictors of events. Parameters considered for multivariate analysis were those with $p<0.05$ in the univariate analysis. Variables were selected in

a stepwise forward manner, with entry and retention set at a significance level of 0.05.

Results:

During a mean follow-up of 6±1.7 years, 93 (20%) patients died. Death was considered cardiac in 46 patients (10%). Non fatal MI occurred in 40 patients (9%), and 152 patients (33%) underwent coronary revascularisation. This was performed early (within 90 days) in 35 and late in 117 patients. The annual mortality rate was 1.5% in patients with normal perfusion and 4.5% in patients with abnormal perfusion. Both reversible and fixed abnormalities were associated with increased risk of death (values not reported). The annual death rate was 5.1% in patients with multivessel distribution of perfusion abnormalities and 3.7% in patients with a single vessel distribution ($p<0.05$). The annual rate of cardiac death or non-fatal MI was 1.2% in patients with normal perfusion and 3.9% in patients with abnormal perfusion (value not reported). Patients with a multivessel distribution of abnormalities had a higher cardiac event rate than patients with a single vessel distribution of abnormalities (4.8% vs. 3.1%, $p<0.05$).

Table X: Predictors of hard cardiac events by Cox models

Parameter	Univariate [RR (95% CI)]	Multivariate [RR (95% CI)]
All cause mortality		
Age	1.05 (1.02 to 1.09)	1.05 (1.03 to 1.08)
Male sex	2.5 (1.5 to 3.1)	2.1 (1.3 to 3.4)
History of heart failure	5.1 (2.7 to 10)	2.7 (1.6 to 4.5)
Diabetes mellitus	2 (1.2 to 3.4)	2.2 (1.4 to 3.5)
Smoking	1.9 (1.2 to 3.1)	1.7 (1.1 to 2.6)
Reversible perfusion defects	2 (1.2 to 3.1)	1.9 (1.1 to 2.8)
Fixed perfusion defects	2.3 (1.3 to 4.1)	2 (1.2 to 3.1)
Cardiac mortality		
Age	1.04 (1.01 to 1.09)	1.04 (1.02 to 1.07)
Male sex	2.5 (1.2 to 3.4)	1.8 (1.2 to 3.8)
History of heart failure	7.3 (3.5 to 15)	4.2 (2.1 to 7)
Diabetes mellitus	2.3 (1.2 to 4.4)	1.7 (1.2 to 3.9)
Abnormal perfusion	2.9 (1.8 to 5.1)	2.5 (1.5 to 3.5)

Cardiac death or non-fatal MI		
Age	1.03 (1.01 to 1.06)	1.03 (1.01 to 1.06)
Male sex	2.2 (1.3 to 3.6)	2.3 (1.3 to 4)
History of heart failure	2.9 (1.7 to 4.9)	2.8 (1.6 to 4.9)
Diabetes mellitus	1.6 (1.1 to 2.8)	1.8 (1.1 to 3.1)
Hypertension	1.7 (1.1 to 2.6)	1.9 (1.2 to 3)
Reversible perfusion defects	2 (1.2 to 3.1)	1.7 (1.1 to 2.4)

Summary: In a multivariate analysis model, independent predictors of death were age (RR 1.05; 95% CI 1.03 to 1.08), male sex (RR , 2.1 (95% CI 1.3 to 3.4); diabetes (RR , 2.2 (95% CI 1.4 to 3.5), history of heart failure (RR 2.7 (95% CI 1.6 to 4.5)); smoking (RR 1.7 (95% CI 1.1 to 2.6); reversible perfusion defects (RR 1.9 (95% CI 1.1 to 2.8); fixed perfusion defects (RR 2 (95% CI 1.2 to 3.1).

Stess technetium-tetrofosmin myocardial perfusion imaging provided independent information for predicting mortality in patients with stable angina. Both reversible and fixed defects were associated with an increased risk of death. Patients with normal perfusion had a lower mortality rate during the follow-up.

Strengths: study sample represents the population of interest. Loss to follow-up is unrelated to key characteristics. Follow-up was complete in 455 patients (99%). The prognostic factor of interest and outcomes of interest is adequately measured in study participants.

Stratmann 1992 (Dypridamole thallium -201 scintigraphy)

Population:

N=373

All patients had stable chest pain suspected of being the result of CAD.

Baseline characteristics of 362 patients followed after dipyridamole thallium studies: mean age: 64±9; male: 327; female: 35; history of old MI: 99; history of congestive cardiac failure: 48;history of diabetes mellitus: 75;history of systemic hypertension: 167;history of peripheral vascular disease: 115;history of cigarette smoking: 124; pre study coronary angiography: 90; CAD present: 87.

Patients referred for dipyridamole testing who were asymptomatic or who had a history of recent (<3 months) MI or unstable angina were excluded from analysis.

All patients were unable or not expected to be able to perform adequate levels of exercise during a treadmill stress test because of lower extremity problems (such as severe peripheral vascular disease or amputation, morbid obesity, or other non cardiac limitations).

Test:

Dypridamole thallium scintigraphy.

All patients underwent testing in the fasting state, with all medications containing theophylline withheld for at least 36 hours before the test.

With the patient in the supine position and under continuous ECG monitoring, dipyridamole (0.56 mg/kg body weight) was given intravenously by continuous infusion over a 4 minute period. Thallium-201 was given 4 minutes after infusion of the dipyridamole. The occurrence of symptoms (including chest pain), arrhythmias, and S changes during the test were recorded.

All studies were reviewed by at least two experienced interpreters who had no knowledge of patients' history or results of any other cardiac testing. Each of the three scans obtained during initial and redistribution imaging was divided in to five segments for analysis. Each segment was evaluated for the presence of a reversible or fixed defect, and both the total number of segments with a perfusion defect and the total number of segments with each type of defect (fixed or reversible) were recorded.

Outcomes: cardiac event (development of unstable angina, occurrence of a nonfatal MI, or death resulting from a primary cardiac cause) and cardiac death.

Mean follow-up: 18±9 months

Statistical analysis:

Statistical analysis of discrete variables was performed with Fisher's exact test. Differences of $p<0.05$ were considered significant. The variables analysed by this method were sex, history of previous MI, congestive heart failure, diabetes mellitus treated with medication, systemic hypertension, peripheral vascular disease, or cigarette smoking, history of coronary angioplasty, angiography, angioplasty, or CABG before or after the dipyridamole study, and presence of chest pain, ECG changes consistent with ischaemia or an abnormal thallium-201 scan (presence of a reversible defect, a fixed defect, or both reversible and fixed defects) with dipyridamole testing. Variables co-related with a cardiac event or with cardiac death alone at a significance level of $p<0.05$ were further analysed by means of stepwise logistic regression.

Results:

Cardiac events occurred in 59 patients during the follow-up period. Unstable angina occurred in 27 patients, non fatal MI in 11, and cardiac death in 21. Death from non cardiac causes (such as malignancy or respiratory failure) occurred in 14 patients.

Univariate analysis:

Of the baseline clinical characteristics evaluated, only a history of previous MI, CABG or congestive heart failure were found to be significantly more frequent in patients with a subsequent cardiac event. Occurrence of a specific cardiac event, cardiac death, was also correlated with these same clinical variables. Only a history of MI (p=0.0007) or peripheral vascular disease (p=0.01) was found to be significantly related to the occurrence of cardiac death. The presence of an abnormal thallium scan (one or more reversible and/or fixed defects) or one with a fixed defect correlated with a significantly increased incidence of subsequent unstable angina or cardiac death but not with non fatal MI. Scans that showed both reversible and fixed defects were associated with an increased incidence of cardiac death. However, the occurrence of a reversible defect in one or more segments was not associated with a significantly increased incidence of cardiac events (p=0.18). This remained true even in patients with scans showing more extensive perfusion defects (i.e, those involving three or more segments, p=0.10).

Multivariable analysis:

Regression analysis showed that a history of previous CABG and the presence of a fixed perfusion defect were the only independent predictors of a subsequent cardiac event. The presence of a fixed perfusion defect and a history of peripheral vascular disease were found to be independent predictors of cardiac death.

Table X: Stratmann 1992, Predictors of cardiac events

All cardiac events	**Chi square**	**P value**
Fixed defect	4.09	0.04
Abnormal scan	2.20	0.13
History of old MI	2.88	0.09
History of peripheral vascular disease	-	-
History of congestive heart failure	2.46	0.11
Pretest CABG	3.87	0.04
Cardiac death only		
Fixed defect	7.04	0.008
Abnormal scan	0.36	0.54
History of old MI	5.46	0.02
History of peripheral vascular disease	8.54	0.004
History of congestive heart failure	-	-
Pre-test CABG	-	-

Summary: During an average follow-up of 18 months, cardiac events occurred in 59 patients-unstable angina in 27, non fatal acute MI in 11 and death from cardiac causes in 21. Stepwise logistic regression showed that a history of CABG before the study and the presence of a fixed perfusion defect were the only variables with independent predictive value for occurrence of a subsequent cardiac event ($p<0.05$).

Strengths: study sample represents the population of interest. Loss to follow-up is unrelated to key characteristics [11/373 lost to follow-up]. The prognostic factor of interest and outcomes of interest are adequately measured in study participants. The statistical analysis was appropriate.

Limitation: short follow-up, combined outcomes reported.

Wiersma 2009 (Myocardial perfusion scintigraphy)

Population:

N=319

This study included 319 patients who underwent a myocardial perfusion scan to establish eligibility for the randomised multicentre MERIDIAN trial (Multicentre trial of Early Revascularisation in patients with diabetes mellitus and mild anginal symptoms).

Patients ≥30 years with mild, stable (≥2 months) angina pectoris (CCS class I-II/IV) and type 2 diabetes mellitus were eligible for screening.

Clinical characteristics of 319 patients: male: 201 (63); age (yrs): 65 (9); CCS II/IV: 130 (41); medical history (%); previous MI: 92 (29); previous PCI: 87 (27); previous CABG: 56 (18); duration of diabetes (yrs) <5 yrs: 119 (38), >10 yrs : 92 (30); insulin: 122 (38); hypertension: 176 (55); smoking: 56 (18); previous smoker: 162 (51); family history: 116 (36); hypercholesterolemia: 201 (63).

Tests: Myocardial Perfusion Scintigraphy

Stress and rest myocardial perfusion scintigraphy (with single photon emission computed tomography (SPECT) was performed with technetium labelled perfusion tracers (tetrofosmin or sesta-MIBI) or thallium-201.

Symptom limited exercise (bicycle or treadmill ergometry) was the preferred stress modality. Pharmacological vasodilatory stress with adenosine or dipyridamole was applied if there was insufficient increase of heart rate (<85% age predicted maximal heart arte) during physical exercise, in the presence of a left bundle branch block, or if the anti anginal medication had not been adequately discontinued beforehand. Dobutamine stress testing was performed in patients with a contra indication for adenosine or dipyridamole.

A local panel of 2-3 nuclear physicians analysed the images using a 17 myocardial segment model. Segments were scored with a 5 point scoring system (0=normal; 1=equivocal; 2=moderate reduction; 3=severe reduction; 4=absent activity). Summed stress score (SSS) and summed rest score (SRS) were obtained by adding the scores of all segments of stress and rest images, respectively. The summed difference score (SDS) was calculated by subtracting the SRS from the SSS. Reversible myocardial perfusion defects, indicative for myocardial ischaemia, were defined as SDS≥3. The MPS outcome for reversible defects was further categorised in to: no ischaemia (SDS<3); moderate ischaemia (sds-3-7) and severe ischaemia (SDS of 8 or higher (SDS≥8). Fixed defects (defects also present at rest) were defined as SRS ≥3. Any perfusion abnormality was defined a SDS ≥3 and/or SRS ≥3.

Outcome: Cardiac event defined as cardiac death or spontaneous, non procedural related, non fatal MI.

Follow-up: 2.2±0.6 years

Statistical analysis:

Cox proportional hazards regression was used to determine independent predictors of cardiac death or non fatal MI. Criterion for entry of variables in to multivariable analysis was set on p≤0.2. The predictive value was expressed as the hazard ratio with corresponding CI. The discriminatory value of this model was calculated by C-index.

Results:

Ten patients were excluded from the analysis because of crescendo angina during MPS (2), inconclusive MPS (2), or withdrawal of consent (6). The remaining 319 patients were eligible for the analysis.

During follow-up 3 /171 patients without reversible defects, 3/83 patients with moderate ischaemia and 8/65 patients with severe ischaemia on MPS had a non fatal MI or died from a cardiac cause. The differences in event rate between patients without and patients with moderate or severe ischaemia were statistically significant (p=0.004).

Table X: Wiersma 2009, Univariable Analysis

Characteristic	Present	Absent	HR (95% CI)
Male gender	9/201	5/118	1.09 (0.36 to 3.25)
CCS II/IV	3/130	11/189	0.39 (0.11 to 1.38)
BMI≥29.9 kg/m2	8/128	6/187	1.71 (0.57 to 5.08)
Age 65 years or older	10/168	4/151	2.08 (0.64 to 6.74)

Previous MI	7/92	7/227	2.94 (0.99 to 8.75)
Previous revascularisation	7/121	7/198	1.63 (0.57 to 4.67)
Aspirin	14/268	0/51	26.53 (0.06 to 11.990)
Statin	11/233	3/86	1.21(0.33 to 4.41)
Insulin	10/122	4/197	4.25 (1.33 to 13.57)
Abnormal rest ECG	11/158	3/161	3.44 (0.95 to 12.50)
MPS: severe ischaemia	8/63	6/256	5.70 (2.00 to 16.60)
Multivariable analysis			
Insulin	11/158	3/161	4.00 (1.25 to 12.75)
MPS: severe ischaemia	8/63	6/256	5.446 (1.89 to 15.71)

Summary: During follow-up (2.2±0.6 years), 14 patients had a cardiac event: 3 in 171 patients without myocardial ischaemia and 11 in 148 patients with myocardial ischaemia. Multivariate analysis identified the presence of severe myocardial ischaemia (SDS ≥8) (HR 5.45, 95% CI 1.89 to 15.71) and insulin use (HR 4.00 95% CI 1.25 to 12.75) as independent predictors of cardiac events.

Strengths: Study sample represents the population of interest. Loss to follow-up is unrelated to key characteristics. The prognostic factor of interest and outcomes of interest is adequately measured in study participants. The statistical analysis was appropriate.

Limitations: Very few events. Hence results should be interpreted with caution. Short follow-up. Combined events.

Stratmann 1994 (Dipyridamole technitiun-99 m sestamibi (MIBI) single photo-emission computed tomography (SPECT))

Population:

N=534

Included patients had stable chest pain consistent with angina pectoris. Patient's referred for testing without a history of chest pain, and those with unstable angina or acute MI ≤ 3 months before testing were excluded from the study.

All included patients were unable or not expected to achieve diagnostic levels of exercise during treadmill testing due to clearly non cardiac limitations such as lower extremity vascular disease, arthritis or amputations, or due to factors such as easy fatigability or deconditioning which may have been at least partly cardiac in origin.

Baseline characteristics of 534 patients: Mean age (yrs): 65±9; Male sex: 519; History of congestive heart failure: 110; History of old MI: 197; History of diabetes mellitus: 113; History of systemic hypertension:316; History of cigarette smoking: 379; History of peripheral vascular disease: 139.

Test:

Dipyridamole technetium-99m sestamibi

Dipyridamole testing was done in the fasting state. MIBI SPECT was performed using a same day, 'rest-stress' protocol.

MIBI myocardial perfusion studies were reviewed by ≥2 experienced observers unaware of clinical data and the results of other tests. 'Stress' images were examined for the presence of myocardial perfusion defects, and compared to the rest images. Defects that were present and unchanged on both stress and rest images were defined as 'fixed'. Stress defects that were absent or less prominent on the rest images were scored as 'reversible'. MIBI studies were characterised as abnormal or normal based on the presence or absence of any kind of perfusion defect. The presence of perfusion defects involving >1 vascular distribution (multi vessel disease) was also noted for each study. Apical segments were excluded from the analysis

Outcomes: Major cardiac events identified and analysed were non fatal acute MI or death due to a primary cardiac cause (cardiac death).

Follow-up: mean 13±5 months

Statistical analysis:

The following clinical variables were analysed: age, gender, history of previous MI, congestive heart failure, diabetes mellitus treated with medication, systemic hypertension, peripheral vascular disease, cigarette smoking, or pre-test coronary revascularisation. The following results of tests were analysed: CAD documented by coronary angiography before or ≤2 months after dipyridamole testing, Q waves on the pre test electrocardiogram consistent with prior MI, and occurrence of dipyridamole-induced chest pain, electrocardiographic changes consistent with ischaemia or MIBI perfusion defects. Variables co-related with a cardiac event at a significance level of $p<0.05$ by univariate analysis were then entered in to stepwise logistic regression models. Relative risk (Cox proportional hazards model) was calculated for variables that were significant by univariate analysis.

Results:

58 patients had a non fatal MI (n=14) or death from a cardiac cause (n=44). Coronary revascularisation, which was not included as an event for the purpose of statistical analysis, was performed ≥6 months after dipyridamole testing in 4 patients. None of these 4 patients had a major cardiac event before revascularisation, and follow-up ended after performance of the procedure.

[Follow-up information was complete in 554 of 574 patients.

Univariable analysis:

Variables associated with increased cardiac risk included a history of congestive heart failure, prior MI or diabetes mellitus, CAD documented by coronary angiography and Q waves on the pre-test electrocardiogram. Dipyridamole induced chest pain and MIBI scintigraphic abnormalities were also associated with increased cardiac risk.

Of the 58 patients who had cardiac events, 55 (95%) had an abnormal scan ($p<0.0000001$ compared to patients with normal scans). Thus, the positive predictive value of an abnormal scan for a cardiac event during the follow-up period (event rate) was 15% (55/355), compared with 2% (3/179) for patients with normal scans. The specific presence of either a reversible or a fixed perfusion defect was also indicative of increased risk, with event rates of 17% (28/162) and 16% (41/262), respectively (both $p<0.01$). Of 69 patients who had both reversible and fixed perfusion defects, 14 had cardiac events (20%, $p<0.05$). Dipyridamole MIBI scans with perfusion defects involving >1 coronary vascular distribution were associated with an event rate of 25% (21/85, $p<0.01$).

Multivariable analysis:

Stepwise logistic regression was used to evaluate the independent predictive value of clinical and test variables. In the first model, the only scintigraphic variable included was the presence of an abnormal MIBI scan. A history of congestive heart failure or diabetes mellitus, Q waves on the pre test electrocardiogram and an abnormal MIBI study were identified as independent predictors in this model. In the second model, the scintigraphic variables entered were specific types of myocardial perfusion defects, either reversible or fixed. Both of these variables retained independent predictive value for a late cardiac event, as did congestive heart failure, Q waves on the pre-test electrocardiogram and dipyridamole induced chest pain.

Table X: Stratmann 1994, Univariate & multivariate analysis

Univariate analysis	**RR (95% CI)**
Abnormal scan	8.4 (2.6 to 26.8)*
Reversible defect	1.9 (1.1 to 3.2) *
Fixed defect	2.4 (1.4 to 4.3) *
Chest pain during test	2 (1.0 to 4) *
History of congestive heart failure	3 (1.8 to 5.1) *

History of diabetes mellitus	2 (1.2 to 3.4) *
CAD by coronary angiography	1.9 (1.1 to 3.1) *
Q waves on pre-test ECG	2.8 (1.6 to 4.8) *
Multivariate analysis - Model I	
Abnormal scan	5.8 (1.8 to 19) *
Reversible defect	-
Fixed defect	-
Chest pain during test	1.8 (0.9 to 3.6)
History of congestive heart failure	1.8 (1.1 to 3.1) *
History of diabetes mellitus	1.8 (1.0 to 3.1)
CAD by coronary angiography	1.3 (0.8 to 2.3)
Q waves on pre-test ECG	1.8 (1.0 to 3.1) *
Multivariate analysis - Model II	
Abnormal scan	-
Reversible defect	2.1 (1.2 to 3.5) *
Fixed defect	1.8 (1.0 to 3.4) *
Chest pain during test	1.7 (0.8 to 3.5)
History of congestive heart failure	2.0 (1.1 to 3.5) *
History of diabetes mellitus	1.9 (1.1 to 3.2) *
CAD by coronary angiography	1.4 (0.8 to 2.3)
Q waves on pre-test ECG	(1.0 to 3.2) *

*P<0.05

Summary: During follow-up (mean 13±5 months), 58 patients had a major cardiac event –non fatal MI (N=14) or cardiac death (n=44). A history of congestive heart failure, diabetes mellitus, and either a reversible or fixed myocardial perfusion defect on MIBI scans were predictors of increased cardiac risk. Cardiac events occurred in 2% of patients with normal MIBI scans, compared with 15% with abnormal scans, 17% with reversible perfusion defects and 16% with fixed defects (all p<0.01).

Strengths: Study sample represents the population of interest. Loss to follow-up is unrelated to key characteristics. Follow-up information was complete in 554 of 574

patients (97%). The prognostic factor of interest and outcomes of interest is adequately measured in study participants. The statistical analysis was appropriate.

Limitation: short follow-up, combined outcomes reported.

Stratmann 1994 (Exercise MIBI imaging)

Population:

N=548

The study population consisted of 548 consecutive patients with stable chest pain consistent with angina pectoris who were referred from March 1991 to September 1992 for exercise testing and MIBI tomographic myocardial perfusion imaging. A total of 22 patients referred for testing who did not have a history of chest pain and those with unstable angina (n=95) or acute MI ≤ 3 months before testing (n=48) were excluded from the study. The presence of any coronary stenosis of ≥50% luminal diameter reduction (as determined in at least two angiographic views) was noted and was considered to represent significant coronary artery disease.

Test:

Exercise MIBI imaging

Exercise testing was done with the patient in the fasting state. MIBI scans were performed using a same day, 'rest-stress' protocol. With the patient at rest, 8mCi of MIBI was injected intravenously. Sixty minutes later, SPECT acquisition was done.

'Stress images' obtained after exercise testing were examined for the presence of perfusion defects and were compared with the 'rest' images. Scans were initially characterised as 'abnormal' or 'normal', based on the presence or absence of any of perfusion defect. Defects that were present and unchanged on both stress and rest images were classified as being 'fixed' in nature. If a defect seen on the stress images was absent or less prominent on the rest inages, it was considered to be 'reversible'.

Outcome: cardiac events (cardiac death or non fatal MI)

Follow-up: Mean follow-up 13±5 months (range 1 to 24 months)

Statistical analysis:

Variables correlated with a cardiac event at a significance level of p≤0.10 by univariate analysis and selected variables with p=0.10 to 0.20 were further analysed using stepwise logistic regression.

Results:

During follow-up 24 patients (9%) had a major cardiac event- non fatal acute MI in 11 and death from a cardiac cause in 13.

Follow-up was completed in 538 of the original 548 patients. Of these 538 patients, 17 had early coronary revascularisation within six months of exercise testing, which might have influenced the prognostic value of the exercise MIBI test compared with patients treated medically. These patients were excluded from further analysis. None of these 17 patients sustained a major cardiac event before coronary revascularisation.

Univariate analysis

A history of congestive heart failure, use of oral or topical nitrates, the presence of angiographic coronary artery disease documented by coronary angiography, and development of exercise induced ischaemic ST depression were all significantly more frequent in patients with cardiac events.

MIBI scintigraphic variables associated with increased cardiac event risk were an abnormal perfusion study ($p<0.0002$) and the presence of a reversible myocardial MIBI perfusion defect ($p<0.005$). Fixed perfusion defects and MIBI scans with both reversible and fixed defects and perfusion defects with a multivessel distribution were not associated with an increased risk of cardiac events by univariate analysis.

Multivariate analysis

In the first regression model, the only scintigraphic variable entered was the presence of an abnormal MIBI scan. In the second model, only the presence of a reversible or perfusion defect was included.

Table X: Stratmann 1994 (Exercise MIBI imaging), Univariate & multivariate analysis

Univariate analysis	**RR (95% CI)**
Abnormal scan	13.8 (1.9 to 102.3)
Reversible defect	3.2 (1.4 to 7.5)
Fixed defect	1.6 (0.7 to 3.5)
Ischaemic ST depression	2.3 (1.0 to 5.3)
History of congestive heart failure	2.1 (0.8 to 5.3)
History of old MI	1.9 (0.8 to 4.2)
history of diabetes mellitus	1.7 (0.6 to 4.6)
Multivariate analysis- Model I	
Abnormal scan	11.9 (1.6 to 89.4)

Reversible defect	-
Fixed defect	-
Ischaemic ST depression	2.2 (0.9 to 5)
History of congestive heart failure	1.6 (0.6 to 4.2)
History of old MI	1.2 (0.5 to 2.8)
history of diabetes mellitus	1.5 (0.6 to 4.1)
Multivariate analysis- Model II	
Abnormal scan	-
Reversible defect	2.9 (1.2 to 7)
Fixed defect	1.4 (0.6 to 3.3)
Ischaemic ST depression	2.0 (0.8 to 4.6)
History of congestive heart failure	1.9 (0.7 to 5.2)
History of old MI	1.3 (0.6 to 3.2)
history of diabetes mellitus	1.6 (0.6 to 4.2)

**In Model I, scintigraphic variable included 'abnormal scan'; In Model II, scintigraphic variables included were 'reversible defect' and 'fixed defect'; 'abnormal scan' was excluded.*

Summary: Major cardiac events occurred in 24 patients. Multivariate models demonstrated that both exercise MIBI perfusion abnormalities (RR 11.9, 95% CI 1.6 to 89.4) and reversible MIBI perfusion defects (RR 2.9, 95% CI, 1.2 to 7.0) had independent predictive value. During 1 year of follow-up, cardiac events occurred in only 0.55 of patients with normal MIBI scans compared with 7% of those with abnormal MIBI scans ($p<0.001$).

Strengths: Study sample represents the population of interest. Follow-up was complete in 538 of the original 548 patients' studies (98%). prognostic factor of interest and outcomes of interest is adequately measured in study participants. The statistical analysis was appropriate.

Limitation: Very few events. Short follow-up. Combined outcomes reported.

Poornima 2004 (SPECT using thallium-201 and treadmill ergometry)

Population:

N=1,461

A total of 3,251 patients referred for evaluation of chest pain or dyspnoea underwent exercise thallium-201 imaging between Jan 1989 and Dec 1991. Of these, 1461 patients (mean age 58.6±11.1 years) were found to have low risk Duke treadmill scores. Exclusion criteria included known cardiomyopathy, valvular heart disease, previous PCI or CABG, recent (within 3 months) MI, or ECG findings that precluded calculation of the Duke treadmill score (e.g. left bundle branch block).

The majority of patients were male. The prevalence of diabetes was low (8.2%) but hypertension and hypercholesterolemia were present in about 45% of patients. The majority had atypical angina (71%).

Tests:

Exercise testing: All patients underwent standard symptom limited treadmill testing using the Bruce, modified Bruce, or Naughton protocol. Near peak exercise, 3 or 4mCi of thallium-201 was injected, and the patient exercised for an additional minute, after the single-photon emission SPECT was initiated.

Perfusion imaging: Stress perfusion images were obtained 10 min after completion of exercise, and redistribution images were obtained 4 h later.

Scintigraphic variables: Nuclear variables were defined using the five point scoring system. A global stress score (GSS) was obtained by adding the scores on all the stress short axis images. A global rest score (GRS) was obtained by adding the scores of all the redistribution short axis images. A global difference score (GDS) was obtained by subtracting GSS from GRS.

Clinical score: A simple five-point scoring system was developed after consideration of 16 clinical and ECG variables. The variables included in the five point scoring were male gender, history of MI (clinical event and Q waves on ECG), diabetes, insulin use, and typical angina.

Outcome: 1) cardiac death, MI, late revascularization 2) cardiac death or non fatal MI.

Follow-up: 7±1 year

Statistical analysis: The association betweenclinical score (CS)and global stress score (GSS) and outcomes was evaluated by Cox proportional hazard analysis on both a univariate and bivariate (each variable adjusted for the other) basis. The GSS was selected prospectively as the single nuclear variable to be included in the analysis.

Results: The total number of events was 211: 30 deaths, 55 non fatal MI and 124 revascularization procedures. Overall, 7 year cardiac mortality was low at 2%. On univariate analysis, both the CS and GSS were predictive of each of the endpoints ($p<0.0001$). The GRS was predictive of each of the endpoints ($p<0.001$). The GDS was predictive of cardiac death and cardiac death/non fatal MI/late revascularisation (both $p<0.001$) but less predictive of cardiac death/non fatal MI ($p=0.08$). On bi-variate (two variable) analysis, the independent predictive power of CS appeared to

be greater than that of GSS. However, the GSS was independently significant for the endpoints of cardiac death and cardiac death/non fatal MI/late revascularisation.

Table X: Poornima 2004 (MPS SPECT) Univariate analysis

Univariate results	**Chi square (X^2) (Individual)**	**p-value**
CS		
Cardiac death	41.9	0.0001
Cardiac death/MI	102.7	0.0001
Cardiac death/MI/ late revascularisation	102.7	0.0001
GSS		
Cardiac death	24.9	0.0001
Cardiac death/MI	14.2	0.0002
Cardiac death/MI/ late revascularisation	65.6	0.0001

Table X: Poornima 2004 (MPS SPECT) Bivariate analysis

Bivariate results	**Chi square (X^2) (Adjusted)**	**p-value**
CS		
Cardiac death	31	0.0001
Cardiac death/MI	40.5	0.0001
Cardiac death/MI/ late revascularisation	73.5	0.0001
GSS		
Cardiac death	7.74	0.005
Cardiac death/MI	2.71	0.10
Cardiac death/MI/ late revascularisation	23.6	0.0001

Summary: The CS and GSS were significant independent predictors of cardiac death. However, in patients with a low CS, 7 year cardiac survival was excellent, regardless of the GSS (99% for normal scans, 99% for mildly abnormal scans, and 99% for severely abnormal scans). In contrast, patients with a high CS had a lower 7

year survival rate (92%), which varied with GSS (94% for normal scans, 94% for mildly abnormal scans, and 84% for severely abnormal scans, p <0.001).

Strengths: Study sample represents the population of interest. Prognostic factor of interest and outcomes of interest is adequately measured in study participants. The statistical analysis was appropriate. Large number of events possibly due to long time follow-up.

Limitation: combined outcome reported.

Vanzetto 1999 (Exercise Treadmill Test (ETT) and T1201 – single photon emission computed tomography (SPECT))

Population:

N=1137

Selection: 1693 patients were referred for exercise stress thallium-201 SPECT. Patients who underwent myocardial revascularisation within 3 months before or after the scintigraphy (n=206) or had previous MI < 3 months before nuclear testing (n=266), as well as patients >75 years (n=39), were excluded. Of the 1182 remaining patients, 45 (3.8%) were lost to follow-up. Consequently, 1137 (96.2%) at 33 month follow-up completed the study.

Test: Exercise Treadmill Test (ETT) and thallium-201 SPECT

Exercise Treadmill Test (ETT): Patients performed a symptom limited bicycle ergometer test using a standard protocol. Patients were asked to discontinue anti-ischaemic drugs at least 48 hours before the test. The exercise tests were classified as 1) positive: horizontal or down sloping ST segment depression of 1 to 2 mm measured 0.08 second after the J point, occurring for a workload >75 W, with or without chest pain; 2) strongly positive: ST segment depression >2 mm at any workload, or >1 mm for a workload ≤75 W, or ST depression post exercise duration >6 minutes 3) negative: when ST segment remained isoelectric and heart rate achieved ≥85% of maximum age predicted heart rate and 4) non diagnostic in all other cases.

Thallium-201 SPECT: Stress-redistribution thallium-201 SPECT was performed according to a standard protocol. The left ventricle was divided in to 6 segments and images were visually analysed by 2 experts. A segment was scored as abnormal in the event of decreased tracer uptake in a surface large enough to be considered significant by the experts. Abnormal segments were defined as reversible (partial or total normalisation on redistribution imaging) or fixed.

Follow-up: 72±18 months

End points: Overall mortality; cardiac mortality (sudden death or death of demonstrated cardiac origin); occurrence of MI (on the basis of characteristic chest pain, ECG changes, and serum creatine kinase level > twice the upper limit of normal); need for myocardial revascularisation > 3 months after SPECT based on occurrence of severe angina, unstable angina or acute MI. Major cardiac events were defined by the occurrence of cardiac death or MI.

Statistical analysis: Univariate and multivariate stepwise analyses using a Cox regression model were performed to compare the prognostic value of clinical, exercise and thallium-201 SPECT data. P value <0.05 was considered statistically significant.

Results: During follow-up (72±18 months [11 days to 8 years]), 88 patients (7.7%) died, 46 (4%) from a cardiac cause and 42 (3.7%) from a non cardiac cause. MI occurred in 57 patients (5%), 7 of whom died from a cardiac cause 8±4 months later. A total of 136 patients (12%) underwent myocardial revascularisation (PTCA, n=63 and/or CABG, n=80]) 24±26 months after inclusion in the study. Major cardiac events and any cardiac event rates were 1.51% and 3.40%/year, respectively.

Univariate predictors of events

Overall mortality: Age >60 years, previous history of MI, Exercise Treadmill Test exercise tolerance and thallium-201 SPECT were predictors of overall mortality. In patients who survived the first 3 years of follow-up, the relationship between the results of the tests and the occurrence of death was maintained for T1201 SPECT (p=0.01) but not for ETT.

Major cardiac events: Gender, previous history of MI, presence of >1 risk factor, Exercise Treadmill Test (ETT) and thallium-201 SPECT were predictors of major cardiac events.

Multivariate predictors of events

Age (p=0.04), Exercise Treadmill Test (ETT) (p=0.03), and thallium-201 SPECT (p=0.003) were independent predictors of overall mortality. Thallium-201 SPECT and Exercise Treadmill Test were independent predictors of cardiac death. Thallium-201 SPECT was also predictive of future MI, whereas Exercise Treadmill Test (ETT)was not.

Table X: Cox Multivariate predictors of cardiac deaths

	Event rate (%)	**Odds ratio**	**95% CI**	**P value**
Age ≤60 years	23/728 (3.2)	-	-	-
Age >60 years	23/409 (5.6%)	1.78	1.02 to 3.11	0.05
No previous MI	22/867 (2.5)	-	-	-
Previous MI	24/270 (8.9)	3.50	2.06 to 5.96	0.006
Negative ETT	16/601 (2.7)	-	-	-

Positive ETT	3/136 (2.2)	0.83	0.25 to 2.80	Ns
Strongly positive ETT	9/127 (7.1)	2.66	1.23 to 5.76	0.02
Non diagnostic ETT	18/273 (6.6)	2.48	1.31 to 4.69	0.006
Normal T1201 SPECT	7/388 (1.8)	-	-	-
1 or 2 abnormal segments on T1201 SPECT	22/554 (4)	2.20	0.97 to 4.98	0.08
≥ 3 abnormal segments on T1201 SPECT	17/195 (8.7)	4.83	2.22 to 9.54	0.001

Table X: Cox Multivariate predictors of Non fatal MI

	Event rate	**Odds ratio**	**95% CI**	**P value**
Absence of risk factors	20/653 (3.1)			
Presence of ≥ 1 risk factor	37/484 (7.6)	2.50	1.50 to 4.17	0.03
No previous MI	30/867 (3.5)	-	-	-
Previous MI	27/270 (10)	2.89	1.78 to 4.69	0.01
Negative Exercise Treadmill Test ETT	38/536 (7.1)	-	-	-
Positive Exercise Treadmill Test (ETT)	11/136 (8.1)	1.14	0.60 to 2.18	ns
Strongly positive	8/127 (6.3)	0.89	0.43 to 1.85	ns

Exercise Treadmill Test (ETT)				
Non diagnostic Exercise Treadmill Test (ETT)	19/273 (6.9)	0.93	1.54 to 1.60	ns
Maximum ST segment depression ≥ 2	15/158 (9.5)	1.34	0.76 to 2.37	ns
Normal T1201 SPECT	6/388 (1.5)	-	-	-
1 or 2 abnormal segments on T1201 SPECT	36/554 (6.5)	4.20	1.93 to 9.14	0.002
≥ 3 abnormal segments on T1201 SPECT	15/195 (7.69)	4.97	2.15 to 11.49	0.004

Strengths- The study sample represented the population of interest. The statistical analysis was appropriate for the design of the study. Univariate and multivariate stepwise analyses using a Cox regression model were performed to compare the prognostic value of clinical, Exercise Treadmill Test (ETT) and thallium-201 SPECT data. The prognostic factors and outcomes of interest were adequately measured.

Weakness: Loss to follow-up was not reported.

Summary: Overall mortality was higher after strongly positive (ST depression > 2 mm, or >1 mm for a workload ≤ 75 W) (2.36%/year) or non diagnostic Exercise Treadmill Test (ETT) (1.63%/year) than after normal (0.85%/year) or positive Exercise Treadmill Test (ETT) (1.37%/year) (p=0.002), and after abnormal SPECT than after normal SPECT (1.60%/year versus 0.68%/year, p=0.001). The major cardiac event rate was 0.88%, 1.59%, 2.10%, and 2.13%/year after normal, positive, strongly positive, and non diagnostic Exercise Treadmill Test (ETT) (p=0.003), and 0.56%, 1.43%, and 2.05%/year in patients with 0,1 to 2, and ≥3 abnormal segments, respectively, on T1201 -SPECT (p<0.002). An abnormal SPECT was predictive of MI (p< 0.001), whereas Exercise Treadmill Test (ETT) was not. In multivariate analysis, SPECT was of incremental prognostic value over clinical and Exercise Treadmill Test (ETT) data for predicting overall mortality and major cardiac events.

Lima 2003 (Pharmacological (dipyridamole) or exercise stress Myocardial Perfusion SPECT with technitium-99 m)

Population:

N=328

Selection of patients: All consecutive patients aged ≥75 years who underwent myocardial perfusion scintigraphy for diagnostic reasons from June 1992 to December 1996. Patients were excluded with a history of MI, CABG, PTCA, with primary cardiomyopathies, severe valve disease or congenital heart disease.

The mean age of the population was 78±3.4 years (75-92 years). The clinical characteristics of 321 patients are: 200 (63.3%) were females, 193 (60.1%) had typical or atypical chest pain, 157 (48.9%) had hypertension, 95 (29.6%) had hypercholesterolemia, 37 (11.5%) had diabetes mellitus, 61.4±27.2% had a Pre test likelihood of CAD.

Tests: Myocardial perfusion SPECT **(**MPS) and exercise or pharmacologic stress tests.

Exercise Treadmill Test (ETT) : A symptom-limited exercise treadmill test was performed with the standard Bruce protocol. An ETT was performed in 160 patients. Of these patients, 51 (31.9%) had ECG changes considered ischaemic and were thus classified as positive, 58 (36.2%) were negative and 51 (31.9%) were inconclusive.

Pharmacologic stress test: This was performed with an intravenous infusion of dipyridamole (0.56mg/kg) over 4 min, under continuous electrocardiographic monitoring.

Myocardial perfusion SPECT (MPS): All patients underwent technetium-sestamibi stress myocardial perfusion scintigraphy. Exercise stress or pharmacologic stress was used as requested by the assistant physician. Image acquisition was performed with a single head camera with a low energy, high resolution collimator. Scans were reported as normal, when normal uptake post-stress and at rest were found or abnormal. When abnormal, defects were classified in to one of three categories: reversible (decreased uptake post stress but normal at rest), fixed (same decreased uptake post stress and at rest) and mixed (decreased uptake post stress with some reversible component at rest). Each of the segments was assigned to one of the three major coronary artery territories. Scans with defects in more than one coronary territory were considered to have extensive defects representing multivessel CAD.

Follow-up: 33.8±15.4 months

Endpoints: Events were cardiac death or MI, or cardiac death, MI or myocardial revascularisation. For statistical analysis, only the first event to occur was analysed.

Statistical analysis: A multivariate analysis was performed using a logistic regression model to determine which variables were independent predictors of hard or total events (hard and soft events).

Results:

During follow-up, 56 patients (17.4%) had cardiac events including 24 cardiac deaths (7.5%) and 11 non fatal MI (3.4%). Revascularization occurred in 21 patients (6.5%), including nine CABG (2.8%) and 12 PTCA (3.7%) procedures. Most interventions occurred up to 4 months after the index MPS. Non cardiac deaths occurred in 19 patients.

Univariate analysis:

Among clinical data, gender and pre scan likelihood of CAD were the only variables with predictive value in the univariate analysis ($p<0.001$). None of the ETT variables could predict this outcome.

Even though pharmacologic stress was not a univariate predictor of hard events, patients with normal scans who underwent dipyridamole had greater hard event rates than patients with normal scans who exercised (0.9% vs. 0.4% per year; $p<0.0001$).

All MPS findings demonstrated significant value for the prediction of cardaic death or MI. During follow-up, major events occurred in 3% of patients with a normal MPS and 32.2% of patients with abnormal studies ($p<0.001$). Partially reversible defects were the most frequently associated with that outcome (40%), followed by fixed defects (34.6%) and reversible defects (26.8%). There was no significant change in the results when soft events were analysed. Myocardial revascularisation occurred in 19.5% of the patients with an abnormal MPS versus 1.7% of those with normal MPS ($p<0.001$). There were no significant differences between the group of patients who underwent revascularisation or not, with the exception of a tendency not to intervene in patients with fixed perfusion defects ($p=0.06$). However, among 14 patients who had early revascularisation, striking differences were found, since all had an abnormal MPS and 13 demonstrated any amount of reversibility.

Multivariate analysis:

Logistic regression analysis using clinical, Exercise Treadmill Test (ETT) and MPS data was used to identify the significant predictors of cardiac events, and separate models for cardiac death, hard events and total events were created. For cardiac death, the MPS result was the most significant variable ($x^2=17.7$, 95% CI: 5.9 to 30.6, $p=0.0001$), followed by LV enlargement ($x^2=10.3$, 95% CI: 2.26 to 46.7, $p=0.0004$).

For hard events, MPS result was also the most predictive variable ($x^2=12.9$, 95% CI: 5.3 to 3.19, $p=0.0001$), followed by male gender ($x^2=3.7$, 95% CI: 1.5 to 8.9, $p=0.0001$) and pharmacologic stress ($x^2=2.8$, 95% CI: 1.15 to 6.4, $p=0.03$).

The independent predictors of total events were an abnormal scan ($x^2=18.7$, 95% CI: 8.9 to 39.6, $p=0.0001$) and male gender with a x^2 of 2.6 (95% CI: 1.3 to 5.2, $p=0.009$). The estimated risk of combined events for a given patient according to the

presence of independent predictors found in the model ranged from 3.2%, in women with normal scans, to 61.8%, in men with abnormal MPS.

Summary: Multivariate analysis revealed that a abnormal scan was the most important independent predictor of hard or total cardiac events. Event rates increased according to myocardial perfusion scintigraphy (MPS) : <1.0% of hard events per year in patients with normal mps versus 14.3% per year in those with abnormal MPS.

Strengths: Study sample represents the population of interest. Loss to follow-up is unrelated to key characteristics. 7 (2.1%) were lost to follow-up. The prognostic factor of interest and outcomes of interest is adequately measured in study participants. The statistical analysis was appropriate.

Limitations: combined outcomes used.

Ambulatory ECG

There were 2 papers that assessed the incremental prognostic value of exercise test and Ambulatory ECG for prediction of adverse cardiac outcomes-(Conti 1997) Forslund 1999.

Forslund 1999 (Ambulatory electrocardiogram)

Population

N=686

This study was based on the patients taking part in the APSIS (Angina Prognosis study in Stockholm) who had 24 hour ambulatory electrocardiographic registrations and exercise tests at baseline (n=678) and after 1 month (n=607).

All patients were with chronic stable angina. Inclusion criteria: Age<70 years and a history of chronic stable angina. Exclusion criteria were MI within the last 3 years, anticipated need for revascularisation within 1 month, significant valvular disease or severe congestive heart failure, other severe diseases, contraindications to either study drug (metoprolol or verapamil) and risk of poor compliance.

Test:

Ambulatory ECG: Ambulatory electrocardiograms were recorded during 24 hours and computer analysed for ST segment depressions and ventricular premature complexes (VPCs) using leads V_2 and V_5 . The channel with the most marked ST segment depression was analysed. The number of episodes with, and the total duration (in minutes/24 hours) of ST segment depression, defined as for the exercise test, were registered. Events had to last ≥ 1 minute and be separated from the next event by ≥ 1 minute.

Exercise tolerance testing: A symptom-limited exercise test was performed on an electrically braked bicycle, starting with 30 W and then 10 W increments every minute. ECG printouts were analysed automatically and manually for ST segment depressions. Significant ischaemia was considered to be present if there was an ST segment depression of at least 1mm (horizontal or down sloping), 80 ms from the J point in at least 2 adjacent leads.

Outcome: CV death, non fatal MI, and revascularisation. CV death was defined as death from acute MI, sudden death, or death from other vascular diseases. The criteria for MI were atypical clinical presentation, a significant increase in cardiac enzymes, and/or development of a new Q wave on the electrocardiogram

Follow-up: Median 40 months (6 to 75 months)

Statistical analysis: To investigate associations between ambulatory ECG variables and events, univariate Cox regression analyses were performed as a first step. In the second step, variables that showed some relation to events were further evaluated with adjustments for known risk factors. Because number of events was low, the number of covariates were limited. Because smoking and history of heart failure did not add prognostic information when included together with other covariates, they were not used.

Results:

During follow-up, 29 patients had CV death, 27 had a nonfatal MI, and 89 underwent revascularisation. Twenty patients had a cerebrovascular event and 4 had nonfatal other vascular events.

686 patients analysed with satisfactory ambulatory ECG at baseline, 678 of whom had performed an evaluable exercise test as well. During ambulatory monitoring, ST segment depression occurred in 395 patients (58%). Both tests showed ST segment depression in 301 patients (44%).

Univariate analysis:

Patients with ST segment depression had a higher risk of CV death (log rank p=0.029) than those without. The risk of CV death +MI showed a trend (p=0.70), and the risk of revascularisation was not significantly increased (p=0.121). However for the composite endpoint (CV death, non fatal MI, and revascularisation), the risk increased significantly (p=0.019).

Multivariate analysis:

The duration of ST segment depression over 24 hours (log transformed) was independently related to CV death, with an odds ratio of 1.23 (CI 1.04 to 1.46, p=0.018). The risk of CV death+ MI increased slightly, with an odds ratio of 1.13 (CI 1.00 to 1.27, p=0.050). The odds ratio for revascularisation was 1.11 (CI 1.01 to 1.22, p=0.035), and that for the composite endpoint 1.11 (CI 1.04 to 1.20, p=0.004).

Prognostic evaluation of ambulatory ischaemia in relation to exercise testing: When related to the results from exercise testing the prognostic information obtained by ambulatory electrocardiography was limited to patients with ST segment depression

≥ 2mm on exercise. Multivariate analyses with maximal ST segment depression during exercise added to the Cox model showed a slight increase in risk of CV death in patients with ST segment depression during the ambulatory electrocardiography (odds ratio 1.19, CI 1.00 to 1.43, p=0.052). There was no independent prognostic impact of ambulatory ischaemia on CV death+ MI or the composite endpoint in the presence of results from exercise testing.

When the treatment given (i.e, metoprolol or verapamil) or treatment effects on ambulatory ischaemia were added to the Cox model, no significant influence on prognosis was detected. Prognosis was not influenced in patients with a 100% reduction of ambulatory ischaemia from baseline to 1 month.

Summary: In a multivariate Cox model including sex, history of previous MI, hypertension, and diabetes, the duration of ST segment depression independently predicted CV death. When exercise testing was included, ambulatory ischaemia carried additional prognostic information only among patients with ST segment depression ≥2 mm during exercise.

Strengths: Study sample represents the population of interest. The prognostic factor of interest and outcomes of interest is adequately measured in study participants. The statistical analysis was appropriate.

Limitation: Loss to follow-up not reported.

Conti 1997 – [Exercise test and Ambulatory ECG]

This paper is based on the ACIP trial

Participants: A total of 558 patients were included in this study.

Of the 558 patients over half reported a history of angina or had stress induced angina, whereas >11% reported angina associated with ischaemic episodes on the 48 hour ambulatory ECG monitoring during activities of daily living (further details not reported).

Tests: Exercise test, Ambulatory ECG

Outcomes: The outcomes assessed were death, MI or hospitalisation for ischaemic event.

Follow-up: The follow-up was for 1 year.

Statistical analysis: Cox regression analysis used. The following baseline variables were considered as potential prognostic factors: number of ambulatory ECG ischaemic episodes; mean heart rate and maximum change in heart rate on baseline ambulatory ECG monitoring; history of revascularisation; history of MI; history of congestive heart failure; family history of coronary artery disease before age 55; diabetes mellitus ; demographic variables (age, gender, race); certain variables related to history and disease (stenosis 50% in 1,2, or 3 vessels); ejection fraction

<50%; history of hypertension; abnormal 12 lead electrocardiogram at rest; and history of smoking. The baseline variables included in a final stepwise model if in addition to treatment assignment they added to a Cox model (p≤0.05). All baseline variables which passed this preliminary screen were then considered in a stepwise Cox regression procedure along with the treatment variables and the angina variable under consideration. Variables in the model each had to have p-value of ≤0.01, as agreed upon by ACIP investigators for secondary analyses of ACIP data. The dependent variable selected for the Cox analyses was death, non fatal MI or hospitalisation for ischaemic event. This variable was chosen because there were a reasonable number of patients presenting with this outcome (n=73) and because subsequent revascularisation in the group assigned to revascularisation was different from the first revascularisation in the medical therapy groups.

Results:

Table X: Cox regression models outcome- Death, MI, Ischaemic event- p value, and relative risk

Variable	p-value	RR; 99% CI
History of angina	0.008	2.00; 1.02 to 39.4 (unadjusted)

Model 1 (=angina history, ischaemia guided therapy, revascularisation strategy –all baseline variables with p<0.05) (n=548)

Variable:	p value;	RR
History of angina	0.01	1.95
Exercise time	0.01	0.89
Ambulatory ECG episodes	0.39	1.03
Duration of ischaemia	0.33	1.00
Ischaemia guided strategy	0.32	0.76
Revascularisation strategy	0.04	0.55

Model 2 (=angina history, ischaemia guided therapy, revascularisation strategy- all baseline variables stepwise)

Variable	p value	RR (99% CI interval)
History of angina	0.008	2.00; 1.02 to 3.94
Exercise time	0.006	0.88; 0.78 to 0.99
Ambulatory ECG episodes	NA	
Duration of ischaemia	NA	
Ischaemia guided strategy	0.32;	0.76
Revascularisation strategy	0.04; 0.55	

The only angina variable significant in Cox regression, once treatment and baseline variables were entered in to the model, was a history of angina in the 6 weeks before randomisation. The baseline variables which passed the screening step of modelling were the total time on exercise treadmill (exercise time), the number of ambulatory ECG episodes at baseline, and duration of ambulatory ECG ischaemia. Once the treatment variables and angina history were put in to the model and a stepwise analysis performed, only the total time on exercise treadmill was significant at the 0.01 level.

Summary: The results indicate that that a history of angina in the 6 weeks before randomisation and a short total time on exercise treadmill at baseline were highly significant independent predictors of adverse events (death, MI or hospitalisation for ischaemic events) within 1 year.

Strengths: The prognostic factor of interest is adequately measured. The outcome of interest is adequately measured. The statistical analysis is appropriate for the design of the study. Cox regression analysis used in the study.

Weakness: small sample.

1.3 Cardiac Syndrome X: Stress echocardiography

<u>Bigi 2002 (Stress Echocardiography)</u>

Population:

N=125

The study population consisted of 125 patients (age 60±10 years old, 60 women) complaining of chest pain potentially suggestive of CAD who had undergone diagnostic coronary angiography with no evidence of more than 50% luminal diameter narrowing in the last month. Patients with significant valvular disease, depressed left ventricular function (ejection fraction <50%), and heart transplantation were excluded. 35 (28%) patients had previous MI at least 6 months before and were taking BB (22 patients), ACE inhibitors (10 patients), aspirin (29 patients) or a combination of these.

Test:

Dobutamine and dipyridamole stress echocardiography (SE) was performed according to standard protocols including atropine co-administration. Computerised assisted analysis of images was used to improve the accuracy of interpretation and reduce intraobserver and interobserver variability. All echocardiograms were analysed by two experienced observers; in case of disagreement, a third observer reviewed the images and a majority decision was achieved. Left ventricular wall motion was semi quantitatively assessed using a 16 segment 4 point (1=normal, 2=hypokinetic, 3=akinetic, 4=dyskinetic) score model. A wall motion score index (WMSI) was calculated by adding the numeric value assigned to each segment and dividing it by the number of visualised segments. Inducible wall motion abnormalities were defined as ‘worsening of wall motion in at least two segments compared with rest or low dose. The test was considered positive in the case of worse wall motion in dysfunctional segments or development of new wall motion abnormalities in normokinetic regions, whereas it was defined as ‘negative’ if no evident change or development of hyperkinetic wall motion was observed.

Pharmacological stress echocardiography was performed in all (77 with dobutamine and 48 with dipyridamole) patients after withdrawing cardio active therapy for at least five half lives.

Follow-up: Mean follow-up 36 months (range 6 to 80).

Outcomes: Target events were cardiac death, non fatal infarction, and unstable angina. Only the worst event was taken in to account for statistical analysis.

Statistical analysis: The ability of clinical (age, sex, diabetes, hypertension, smoking habit, dyslipidemia and previous infarction), resting echocardiography (rest WMSI), and SE (test positivity and stress WMSI) variables to predict outcome was assessed by the Cox proportional hazard model with the use of univariate and stepwise multivariate procedures. The differences in risk were expressed as odds ratio with 95% CI. The Chi-square value was calculated from the log-likelihood ratio. A statistically significant increase in global chi-square of the model after addition of further variables was considered to indicate incremental prognostic value.

Results:

SE was positive in 31 (20 with dobutamine and 11 with dipyridamole) and negative in 94 (57 with dobutamine and 37 with dipyridamole) patients. Target events occurred in

9 patients: 2 cardiac deaths, 5 non fatal MI, and 2 hospitalisations for unstable angina. Furthermore, 2 patients died for non cardiac reasons: 1 for cancer and 1 for cerebrovascular accident. Six of the 9 patients with cardiac events had positive SE.

Univariate predictors of outcome

Univariate predictors of outcome were age and hypertension among the clinical variables, and positive SE and rest and peak WMSI among the echocardiographic variables. However the Cox model selected hypertension and peak WMSI as the only multivariate predictors of outcome.

Table X: Bigi 2002, Univariate predictors of outcome

Variables	Chi-square	Odds ratio	95% CI	P-value
Clinical				
Age	4.7	1.09	1 to 1.18	0.03
sex	2.8	3.80	0.8 to 18	0.09
Previous infarction	2.8	2.9	0.8 to 10	0.09
hypertension	5.2	11.2	1.4 to 89	0.02
Diabetes	0.9	1.4	0.3 to 19	0.40
Hypercholesterolemia	0.04	1.1	0.3 to 4.5	0.83
Echocardiographic				
Positive SE	4.6	3.9	1.1to 13.5	0.03
Rest WMSI	7.0	4.0	1.4to 11.4	0.008
Peak WMSI	9.6	5.8	1.9 to 17.7	0.002

Multivariate predictors of outcome:

Hypertension, positive SE, and peak wall motion score index were multivariate predictors of outcome, but SE provided an 87.5% increase in the global chi-square ($p<0.001$). The event free survival of patients with positive SE was significantly lower compared with those with negative test (Hazard ratio 4.7 95% CI 1.3 to 47)

Table X: Bigi 2002, Multivariate predictors of outcome

Variables	Chi-square	Odds ratio	95% CI	P-value
Clinical				

Hypertension	5.7	13	1.6 to 105	0.01
Echocardiographic				
Positive SE	3.8	3.6	1to 14	0.05
Peak WMSI	8.1	5.0	1.6 to 15	0.004

Strengths:. The statistical analysis was appropriate for the design of the study. Cox proportional hazard model was used in univariate and stepwise multivariate procedures.

Weakness: Loss to follow-up not reported. Small sample size. The study sample did not represent the population of interest, as some of the patients probably had coronary artery disease and may not have 'Syndrome X'

Summary: Nine events occurred: 2 fatal and 5 non fatal infarctions and 2 hospitalisations for unstable angina. Hypertension, positive SE, and peak wall motion score index were multivariate predictors of outcome, but SE provided an 87.5% increase in the global chi-square ($p<0.001$). Patients with positive SE had a significantly lower event free survival compared with those with negative SE.

Evidence Table

Question: What is the clinical/cost effectiveness and safety of cardiac rehabilitation programmes for patients with stable angina?

Study Type	Randomised Controlled Trial

Amarosa-Tupler B;Tapp JT;Carida RV;

Stress management through relaxation and imagery in the treatment of angina pectoris

Ref ID 389 **RID:** 786 1989

QUALITY

A. Selection bias (systematic differences between the comparison groups)

A4 Based on your answers t, in your opinion was selection bias present? If so, what is the likely direction of its effect?:

Unclear/unknown risk

Direction = No description of randomisation or "blinding" described. Groups were comparable at baseline with regard to

B. Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)

B4 Based on your answers to the above, in your opinion was performance bias present? If so, what is the likely direction of its effect?:

Unclear/unknown risk

Direction = Patients were obviously aware of treatment received but no information was given on how or if investigators

C. Attrition bias (systematic differences between the comparison groups with respect to loss of participants)

C4 Based on your answers to the above, in your opinion was attrition bias present? If so, what is the likely direction of its effect?:

High risk of bias

Direction = The patient flow in this trial is badly described. The study reports that n=92 patients were approached and

D. Detection bias (bias in how outcomes are ascertained, diagnosed or verified)

D6 Based on your answers to the above, in your opinion was detection bias present? If so, what is the likely direction of its effect?:

High risk of bias

Direction = Patients had tapes to listen to for 2 weeks and then followed for another 4 wks. Angina improved but incidents had started to return to pre treatment

Overall Study Quality -Strengths and Weaknesses:

This is a poorly described (or badly conducted) trial. The main doubt is about the number of patients who started treatment and who did not complete the study. Although, the study reports on 40 randomised patients (10 in each of the 4 groups) it briefly mentions n=52 patients who did not complete the study and gives reasons, but does not say which treatment they had been assigned to, if any. So, it is not clear how many patients were initially randomised to the groups. If the study is simply poorly reported it could be that all n=52 patients withdrew during the 4 week baseline period before patients were randomised.

DETAILS

# of patients:	n=92 patients were approached. N=52 did not complete the study. N=40 were assigned to n=4 groups (n=10 in each group). This appears to be what the study is
Prevalence (Diagnostic):	
Patient Characteristics	Patients ranged in age from 33 to 81 years (mean=60) and all had diagnosed angina. All subjects were caucasian and 75% had some college training. The groups did not differ in mean age, years education, and years with angina.
Interventions/ Test/ Factor being investigated	Relaxation and imagery delivered by cassette tape.
Comparisons	The cassette tapes were 20 minutes in duration on each side. For all groups the information on one side of the tape was the same. It described angina and explained how pain was caused to the heart due to ischaemia. The information on the other side of the tape varied for each of the four groups. 1) Information only 2) Jacobsons method of Progressive Relaxation 3) a guided visual Imagery description designed specifically for the control of anginal pain. 4) Combination of Relaxation and Imagery.
Length of Study/ Follow-up	2 weeks of treatment (listening to tape) followed by 4 week of recording anginal incidents and pain in diary.
Outcome measures studied	No primary or secondary outcomes specified. Reported number of incidents of angina, pain intensity and medication used for relief.
Results	Number of angina incidents: Data not given but plotted on a line graph. No change in the weekly number of incidents of angina for the group which listened to the tape which contained information. Groups which listened to the tape containing relaxation and/or imagery instructions showed a marked decrease in the weekly number of angina incidents. When the subjects stopped listening to the tapes the incidents of chest pain remained low for 1 or2 weeks, then began to increase. Pain intensity and number of medications: for the three groups with relaxation and/or imagery tapes, the results followed the same pattern as the number of weekly incidents of angina described previously, i.e. a decrease during the tape exposure followed by an increase.
Effect Size	Number of angina incidents: Data not given but plotted on a line graph. No change in the weekly number of incidents of angina for the group which listened to the tape which contained information. Groups which listened to the tape containing relaxation and/or imagery instructions showed a marked decrease in the weekly number of angina incidents. When the subjects stopped listening to the tapes the incidents of chest pain remained low for 1 or2 weeks, then began to increase. Pain intensity and number of medications: for the three groups with relaxation and/or imagery tapes, the results followed the same pattern as the number of weekly incidents of angina described previously, i.e. a decrease during the tape exposure followed by an increase.
Source of funding:	Funds for this research were made available from a training rant to the second author from National Institutes of Heart, Lung and Blood and Psychological health
Does the study answer the question?/Further Comments	Unsure. The study is small (n=10 in each of 4 groups) and has a very short follow-up period of 4 weeks. It would be very useful to know results of study outcomes at even 3 or 6 months post treatment. In addition, it is not clear if only 40 patients were randomised of if there were more. This is because the study is not clear on patient flow through the trial. Therefore the risk of bias in this study is unclear.

Asbury EA;Slattery C;Grant A;Evans L;Barbir M;Collins P;

Cardiac rehabilitation for the treatment of women with chest pain and normal coronary arteries

QUALITY

A. Selection bias (systematic differences between the comparison groups)

A4 Based on your answers t, in your opinion was selection bias present? If so, what is the likely direction of its effect?:

Low risk of bias

Direction =

B. Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)

B4 Based on your answers to the above, in your opinion was performance bias present? If so, what is the likely direction of its effect?:

Low risk of bias

Direction =

C. Attrition bias (systematic differences between the comparison groups with respect to loss of participants)

C4 Based on your answers to the above, in your opinion was attrition bias present? If so, what is the likely direction of its effect?:

Low risk of bias

Direction =

D. Detection bias (bias in how outcomes are ascertained, diagnosed or verified)

D6 Based on your answers to the above, in your opinion was detection bias present? If so, what is the likely direction of its effect?:

Unclear

Direction = The study had an 8 week follow-up period.

Overall Study Quality -Strengths and Weaknesses:

This is a small study (a pilot) designed to assess the impact of a standard 8-week group-based phase III CR exercise programme. The study reports that the programme improves exercise tolerance, quality of life, psychological morbidity, symptom severity, and cardiovascular risk factors. However, it should be noted that there were no between-group differences 8 weeks after intervention.

DETAILS

# of patients: n=64 (n=32 in each group)

Prevalence (Diagnostic):

Patient Characteristics Mean age 58.1+/-9.4 years in the cardiac rehab (CR) programme and 56.4+/- 7.8 years in the control group.

Interventions/ Test/ Factor being investigated CR + symptom monitoring. The CR intervention comprised a standard 8-week group-based phase III CR exercise program: an outpatient cardiovascular exercise program designed to improve aerobic conditioning, functional capacity, muscular strength, endurance, and flexibility.

Comparisons	Symptom monitoring only.
Length of Study/ Follow-up	8 weeks post study end.
Outcome measures studied	No specific outcomes specified as primary or secondary. But a number of variables were specified as primary: psychological morbidity and quality of life. While secondary variables included physiological measurements.
Results	Most of the results reported in this paper are for assessments done at the end of the intervention (8 weeks from study start and for convenience called timepoint 2). However, there are few results for comparisons between the two groups at the follow-up assessment point 3 (8 weeks after the intervention ended). What is reported is "There were no between-group differences 8 weeks after intervention". (Assessment point 3)
Effect Size	Most of the results reported in this paper are for assessments done at the end of the intervention (8 weeks from study start and for convenience called timepoint 2). However, there are few results for comparisons between the two groups at the follow-up assessment point 3 (8 weeks after the intervention ended). What is reported is "There were no between-group differences 8 weeks after intervention". (Assessment point 3)
Source of funding:	No external funding was obtained for the completion of this project.
Does the study answer the question?/Further Comments	Yes. This is a small pilot study. It concludes that improvements were seen between baseline and follow-up in exercise tolerance, quality of life, psychological morbidity, symptom severity and CV risk factors. However, there are no differences found between the two groups in any of these variables 8 weeks after the study ended.

Bundy C;Carroll D;Wallace L;Nagle R;

Psychological treatment of chronic stable angina pectoris

Ref ID 711 **RID:** 864 1994

QUALITY

A. Selection bias (systematic differences between the comparison groups)

A4 Based on your answers t, in your opinion was selection bias present? If so, what is the likely direction of its effect?:

Unclear/unknown risk **Direction =** No description of method of randomisation or of "blinding" reported.

B. Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)

B4 Based on your answers to the above, in your opinion was performance bias present? If so, what is the likely direction of its effect?:

Unclear/unknown risk **Direction =** No description of method of "blinding" of investigators (if any) reported.

C. Attrition bias (systematic differences between the comparison groups with respect to loss of participants)

C4 Based on your answers to the above, in your opinion was attrition bias present? If so, what is the likely direction of its effect?:

Low risk of bias

Direction =

D. Detection bias (bias in how outcomes are ascertained, diagnosed or verified)

D6 Based on your answers to the above, in your opinion was detection bias present? If so, what is the likely direction of its effect?:

Unclear

Direction = No description of "blinding" reported. The follow-up period was short (8 weeks post treatment).

Overall Study Quality -Strengths and Weaknesses:

This is a small study (n=29) which aims to evaluate the effects of Stress Management Training (SMT) compared to routine care (RC) on exercise tolerance, angina symptoms, medication use and anxiety. All patients completed the study and the intervention is well described. Follow-up was relatively short (8 weeks after study end) and the study did not specifiy a primary outcome. It simply reports results for all study outcomes measured. Only exercise tolerance was reported at 8 weeks follow up. The remaining outcomes (medication use, angina symptoms and anxiety) were only reported at baseline and at study end (8 weeks from start of treatment).

DETAILS

# of patients: n=29 (n=14 in Stress Management Training (SMT) and n=15 in routine care (RC))

Prevalence (Diagnostic):

Patient Characteristics

Characteristics of groups at entry

Group	SMT	RC
n	14	15
Male	12	13
Age (years)		
mean	54.4	53.8
SD	8.5	7.6
Range	46-63	46-62
Duration of illness (months)		
mean	18.2	18.6
SD	6.3	5.9
range	12-25	13-24
Number of smokers	4	3
Previous MI	6	7

Interventions/ Test/ Factor being investigated

SMT:group of 6 to 8 , led by experienced clinical psychologist. Weekly session lasted one and a half hours, and full SMT programme took seven weeks. Principle components included: the nature of stress; stress and bodily functioning; problem solving; the interactive nature of thoughts, feelings and behaviour. The programme also included : cognitive control; anger inoculation and control; a rational for how anger is related oto angina; lifestyle and risk factor assessment; liefstyle change and how to maintain behaviour change.

Comparisons

Comparison is between SMT and routine care (RC).

Length of Study/ Follow-up

SMT treatment finished after 8 weeks and patients were followed for a further 8 weeks.

Outcome measures studied

None specified. Study measured exercise tolerance as measured by a symptom limited exercise test. It also measured anginal symptoms, medication use and anxiety.

Results

Exercise tolerance: Mean workload achieved (in Watts) no difference between the two groups. Reading from a line graph results for SMT group at baseline, at treatment end and at 8 weeks follow up mean workload were 85, 90 and 82. For the RC group corresponding values were 88, 74 and 74.

Diary reported frequency of angina: average number of daily attacks

	Baseline			Post treatment		
	Mean	SD	Range	Mean	SD	Range
SMT	6.1	3.3	2.3-12.2	4.3	3.0	0.1-10.2
RC	5.8	3.5	0.8-11.7	7.0	5.7	0.0-16.2

Note: results only presented at study end and not for 8 week follow-up period

Diary reported duration of angina: average number of minutes per attack

	Baseline			Post treatment		
	Mean	SD	Range	Mean	SD	Range
SMT	1.5	0.6	0.3-2.5	1.2	0.5	0.0-2.3
RC	1.7	0.3	1.0-2.1	1.9	0.5	0.9-2.5

Note: results only presented for study end and not for 8 week follow up

Diary reported medication use: average number of GTN tablets/sprays per attack

	Baseline			Post treatment		
	Mean	SD	Range	Mean	SD	Range
SMT	6.1	3.3	2.3-12.2	4.3	3.0	0.1-10.2
RC	5.8	3.5	0.8-11.7	7.0	5.7	0.0-16.2

Note: results only presented for study end and not for 8 week follow up

Effect Size

Exercise tolerance: Mean workload achieved (in Watts) no difference between the two groups. Reading from a line graph results for SMT group at baseline, at treatment end and at 8 weeks follow up mean workload were 85, 90 and 82. For the RC group corresponding values were 88, 74 and 74.

Diary reported frequency of angina: average number of daily attacks

	Baseline			Post treatment		
	Mean	SD	Range	Mean	SD	Range
SMT	6.1	3.3	2.3-12.2	4.3	3.0	0.1-10.2
RC	5.8	3.5	0.8-11.7	7.0	5.7	0.0-16.2

Note: results only presented at study end and not for 8 week follow-up period

Diary reported duration of angina: average number of minutes per attack

	Baseline			Post treatment		
	Mean	SD	Range	Mean	SD	Range
SMT	1.5	0.6	0.3-2.5	1.2	0.5	0.0-2.3
RC	1.7	0.3	1.0-2.1	1.9	0.5	0.9-2.5

Note: results only presented for study end and not for 8 week follow up

Diary reported medication use: average number of GTN tablets/sprays per attack

	Baseline			Post treatment		
	Mean	SD	Range	Mean	SD	Range
SMT	6.1	3.3	2.3-12.2	4.3	3.0	0.1-10.2
RC	5.8	3.5	0.8-11.7	7.0	5.7	0.0-16.2

Note: results only presented for study end and not for 8 week follow up. There was no significant difference between groups with regard to anxiety levels (data not reported).

Source of funding:

Not reported.

Does the study answer the question?/Further Comments

Unsure. This was a small study (n=29) and no primary outcome was specified. Exercise tolerance was not reported in terms of total exercise time but mean workload achieved. The other outcomes measured did not show a difference between groups, although, apart from exercise data, which reported results at 8 weeks follow up, results for the other study outcomes were only reported at study end. This is insufficient time to tell if the SMT programme had an impact on patients well being.

Bundy C;Carroll D;Wallace L;Nagle R;

Stress management and exercise training in chronic stable angina pectoris

Ref ID 968 **RID:** 798 1998 Jan

QUALITY

A. Selection bias (systematic differences between the comparison groups)

A4 Based on your answers t, in your opinion was selection bias present? If so, what is the likely direction of its effect?:

Low risk of bias **Direction =**

B. Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)

B4 Based on your answers to the above, in your opinion was performance bias present? If so, what is the likely direction of its effect?:

Low risk of bias **Direction =** It was not appropriate to blind patients and those administering treatment in this study. However, the study reports

C. Attrition bias (systematic differences between the comparison groups with respect to loss of participants)

C4 Based on your answers to the above, in your opinion was attrition bias present? If so, what is the likely direction of its effect?:

Unclear/unknown risk **Direction =** N=120 patients were randomised but only data for 99 patients was included in the analysis. It is not clear how the

D. Detection bias (bias in how outcomes are ascertained, diagnosed or verified)

D6 Based on your answers to the above, in your opinion was detection bias present? If so, what is the likely direction of its effect?:

Low risk of bias **Direction =**

Overall Study Quality -Strengths and Weaknesses:

This is a relatively small, short term study aimed at assessing stress mgt, exercise training, stress mgt + exercise training combined with a waiting list control group. Patients were male and all had angina. No primary outcome measures were specified.Rather the study measured exercise workload anginal symptoms and glyceryltrinitrate usage.17% of patients were excluded from the analysis because they had only partial outcome data. No description of these patients

was given or the distribution among treatment groups.

DETAILS

# of patients:

n=120 were randomised. 21 were excluded because of incomplete outcome data leaving 99 in the analysis: n=42 in SMT, n=21 in ET group, n=20 in SMT+ET

Prevalence (Diagnostic):

Patient Characteristics

Characteristics of groups at entry for each of the conditions

Condition	SMT	ET	SMT+ET	WLC
Male	36	16	18	14
Female	6	5	2	2
Age (years)				
Mean (SD)	54.5(8.0)	55.5(6.6)	52.1 (8.7)	57.9 (8.3)
Duration of illness (months)				
Mean (SD)	19.4(11.6)	18.1(12.0)	21.6 (11.50)	20.1 (11.2)
Number of smokers	7	1	2	3
Previous MI	31	15	12	9

SMT=stress mgt training, ET = exercise training, WLC = waiting list control.

Interventions/ Test/ Factor being investigated

Stress mgt is compared to exercise training alone and to stress mgt combined with exercise training. Stress mgt: pts met in small groups of 6 to 8 led by an experienced psychologist.Each weekly session lasted one and a half hours and the full programme took seven weeks. It included cognitive control, anger inoculation and relaxation techniques. The exercise training also met in groups over a seven week period. Exercise was undertaken twice a week, with each session lasting 45 minutes. Patients in the combined stress mgt exercise condition undertook both programmes over the course of seven weeks. The waiting list control group received routine care, consisting of regular attendance at an outpatient cardiology clinic.

Comparisons

Comparisons are between stress mgt, exercise training and stress+exercise combined. In addition, these were all compared to waiting list controls.

Length of Study/ Follow-up

15 weeks in total: 7 weeks treatment period followed by 8 weeks follow up.

Outcome measures studied

Primary and secondary outcomes not specified. A symptom limited exercise tolerance test measured workload at baseline, study end and 8 weeks later. Patients recorded diaries related to anginal symptoms and medication usage.

Results

Numbers of patients experiencing ischaemia (1 mm ST-segment depression => 1 minute) and pain dring ETT in each condition and the average workload achieved in watts (SD)

	SMT	ET	SMT+ET	WLC
Ischaemia				
Baseline	28	9	12	8
Study end	24	13	10	10
8 week follow up	22	12	10	10
Pain				
Baseline	37	19	12	13
Study end	30	19	16	15
8 week follow up	33	20	13	13
Workload				
Baseline	95.0(37.0)	98.5(30.0)	100.0(37.9)	104.6(30.7)
Study end	96.3(34.2)	107.7(23.9)	116.3(32.0)	89.2(42.1)

8 week follow up	90.6(37.0)	107.7(27.7)	108.8(35.0)	92.3(36.1)

SMT=stress mgt training, ET = exercise training, WLC = waiting list control.

Average frequency (SD) of angina attacks per day, average duration in minutes of angina (SD), and average pain intensity ratings (SD) for patients in each condition

	SMT	ET	SMT+ET	WLC
Frequency				
Baseline	9.0(4.8)	7.5(4.6)	9.9(6.3)	7.3(4.7)
Study end	7.5(4.6)	8.4(5.2)	6.7(4.7)	8.1(5.7)
8 week follow up	7.4(4.7)	8.2(5.0)	8.0(5.7)	7.4(5.2)
Duration				
Baseline	14.8(8.0)	8.4(6.0)	8.2(7.0)	13.3(5.0)
Study end	11.1(5.2)	7.8(5.1)	6.8(5.1)	12.0(6.6)
8 week follow up	11.0(7.4)	7.7(5.4)	7.0(6.6)	11.4(7.5)
Pain intensity				
Baseline	1.5(0.6)	1.7(0.5)	1.7(0.6)	1.1(0.8)
Study end	1.4(0.4)	1.3(0.5)	1.2(0.5)	1.3(0.6)
8 week follow up	1.4(0.4)	1.4(0.6)	0.7(1.2)	1.2(0.3)

Average number of glyceryltrinitrate tablets/sprays (SD) consumed per angina attack by patients in the different conditions

	Baseline	Study end	8-week follow up
SMT	1.4(0.9)	1.0(0.9)	0.9(0.8)
ET	1.2(1.1)	1.4(1.1)	1.3(1.0)
SMT+ET	1.4(1.0)	1.1(1.1)	0.7(0.8)
WLC	1.0(0.7)	1.0(1.0)	1.2(1.0)

SMT=stress mgt training, ET = exercise training, WLC = waiting list control.

Effect Size

Numbers of patients experiencing ischaemia (1 mm ST-segment depression => 1 minute) and pain dring ETT in each condition and the average workload achieved in watts (SD)

	SMT	ET	SMT+ET	WLC
Ischaemia				
Baseline	28	9	12	8
Study end	24	13	10	10
8 week follow up	22	12	10	10
Pain				
Baseline	37	19	12	13
Study end	30	19	16	15
8 week follow up	33	20	13	13
Workload				
Baseline	95.0(37.0)	98.5(30.0)	100.0(37.9)	104.6(30.7)
Study end	96.3(34.2)	107.7(23.9)	116.3(32.0)	89.2(42.1)
8 week follow up	90.6(37.0)	107.7(27.7)	108.8(35.0)	92.3(36.1)

SMT=stress mgt training, ET = exercise training, WLC = waiting list control.

Average frequency (SD) of angina attacks per day, average duration in minutes of

angina (SD), and average pain intensity ratings (SD) for patients in each condition

	SMT	ET	SMT+ET	WLC
Frequency				
Baseline	9.0(4.8)	7.5(4.6)	9.9(6.3)	7.3(4.7)
Study end	7.5(4.6)	8.4(5.2)	6.7(4.7)	8.1(5.7)
8 week follow up	7.4(4.7)	8.2(5.0)	8.0(5.7)	7.4(5.2)
Duration				
Baseline	14.8(8.0)	8.4(6.0)	8.2(7.0)	13.3(5.0)
Study end	11.1(5.2)	7.8(5.1)	6.8(5.1)	12.0(6.6)
8 week follow up	11.0(7.4)	7.7(5.4)	7.0(6.6)	11.4(7.5)
Pain intensity				
Baseline	1.5(0.6)	1.7(0.5)	1.7(0.6)	1.1(0.8)
Study end	1.4(0.4)	1.3(0.5)	1.2(0.5)	1.3(0.6)
8 week follow up	1.4(0.4)	1.4(0.6)	0.7(1.2)	1.2(0.3)

Average number of glyceryltrinitrate tablets/sprays (SD) consumed per angina attack by patients in the different conditions

	Baseline	Study end	8-week follow up
SMT	1.4(0.9)	1.0(0.9)	0.9(0.8)
ET	1.2(1.1)	1.4(1.1)	1.3(1.0)
SMT+ET	1.4(1.0)	1.1(1.1)	0.7(0.8)
WLC	1.0(0.7)	1.0(1.0)	1.2(1.0)

SMT=stress mgt training, ET = exercise training, WLC = waiting list control.

Source of funding: Not reported.

Does the study answer the question?/Further Comments Yes. The study included men with stable angina and it showed that those who undertook the stress mgt and exercise training fared best. They showed sustained gains in achieved workload, they registered less frequent angina attacks than the exercise only and waiting list controls, and reported reduced reliance on medication.

Cupples ME;McKnight A;

Randomised controlled trial of health promotion in general practice for patients at high cardiovascular risk

Ref ID 9190 **RID:** 820 1994 Oct 15

QUALITY

A. Selection bias (systematic differences between the comparison groups)

A4 Based on your answers t, in your opinion was selection bias present? If so, what is the likely direction of its effect?:

Low risk of bias

Direction =

B. Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)

B4 Based on your answers to the above, in your opinion was performance bias present? If so, what is the likely direction of its effect?:

Low risk of bias

Direction = The main researcher who conducted the reviews at 2 years had not previously been involved with the

C. Attrition bias (systematic differences between the comparison groups with respect to loss of participants)

C4 Based on your answers to the above, in your opinion was attrition bias present? If so, what is the likely direction of its effect?:

Unclear/unknown risk

Direction = There were more patients who died and defaulted in the control group (13%) than in the intervention group

D. Detection bias (bias in how outcomes are ascertained, diagnosed or verified)

D6 Based on your answers to the above, in your opinion was detection bias present? If so, what is the likely direction of its effect?:

Low risk of bias

Direction = The person who conducted patient reviews at study end had not been involved in the study at the beginning. The implication is that this person was

Overall Study Quality -Strengths and Weaknesses:

This publication reports on frequency of physical exercise from a large trial whose main aim originally was to measure reduction in severity of angina in patients who received an education programme for up to 2 years. The frequency of physical exercise outcome reported in this publication was therefore secondary. Although, significant differences were found between the intervention and control groups which showed a benefit from education, the clinical significance of this difference is not reported or discussed.

DETAILS

# of patients: n=688: n=342 randomised to education and n=346 to no education.

Prevalence (Diagnostic):

Patient Characteristics

Characteristics of intervention and control groups at entry to trial

	Intervention group (n=342)	Control group (n=346)
Age (years):		
Mean (SD)	62.7 (7.1)	63.6 (6-8)
Range	38-74	39-74
Sex:		
Male	203	205
Female	139	141
Social class:		

I and II	37	35
III non-manual and manual	157	168
IV and V	148	143
Family history of heart disease:		
Yes	223	231
No	119	115
Previous myocardial infarction:		
Yes	150	159
No	192	187
Electrocardiographic evidence of ischaemia:		
Yes	212	216
No	130	130
No of cigarettes smoked/day:		
None	272	268
1-10	43	44
11-20	21	26
>20	6	8
Severity of angina:		
Severe*	21	18
Not severe	321	328

*Severe angina defined as attacks occurring once or more per day when walking on the level and in sex, sport, housework, or shopping.

Interventions/ Test/ Factor being investigated

Education programme: after the initial interview (questions regarding angina, medication, and lifestyle) patients in the intervention group were given practical relevant advice regarding cardiovascular risk factors. They were reviewed at four monthly intervals and given appropriate health education for two years.

Comparisons

The comparison group had the same intial interview as the intervention group but they received no advice or follow-up visits.

Length of Study/ Follow-up

All patients followed up for two years.

Outcome measures studied

The original study was powered to detect a reduction in severe angina in the study population. Therefore these outcomes reported here are secondary outcomes. They include frequency of physical exercise, dietary habits, smoking cessation, anginal drug use, blood pressure, body mass index, and deaths. It needs to be noted that

Results

Those outcomes relevant to this review question are frequency of physical exercise and deaths.

Frequency of physical exercise in patients with angina at baseline and review after two years. Values are numbers (percentages)

No of episodes/ week	At baseline: Intervention group (n=317)	At baseline: Control group (n=300)	At review: Intervention group (n=317)	At review: Control group (n=300)
0	47 (15)	33 (11)	46 (15)	71 (24)
1-2	57 (18)	50 (17)	31 (10)	58 (19)
3-4	49 (15)	42 (14)	46 (15)	33 (11)
5-6	42 (13)	49 (16)	54 (17)	68 (23)
7-10	59 (19)	64 (21)	93 (29)	53 (18)
>=11	63 (20)	62 (21)	47 (15)	17 (6)

X2 for trend=29.69, df=1; P<0.0001.

Changes in frequency of physical exercise in patients with angina between baseline and review at two years

	No (%) of patients	
	Intervention group	Control group
Increased	108 (34)	63 (21)
No change	120 (38)	74 (25)
Decreased	89 (28)	163 (54)

X2 for trend=35.66, df=1;
P<0.0001.

Deaths.

There were 29 deaths the control group and 13 in the intervention group. The relative odds of death in the control group was 2.32 (95% confidence interval 1.18 to 4.53). Ten of the deaths in the intervention group and 28 in the control group were attributed to cardiovascular causes. The relative odds of death was 2.20 (1.06 to 4.57) after age, sex, history of myocardial infarction, blood pressure, cholesterol, body mass index, smoking status, family history, social class, diabetes, and recent worsening of angina were adjusted for.

Effect Size

Those outcomes relevant to this review question are frequency of physical exercise and
deaths.

Frequency of physical exercise in patients with angina at
baseline and review after two years. Values are numbers (percentages)

No of episodes/ week	At baseline: Intervention group (n=317)	At baseline: Control group (n=300)	At review: Intervention group (n=317)	At review: Control group (n=300)
0	47 (15)	33 (11)	46 (15)	71 (24)
1-2	57 (18)	50 (17)	31 (10)	58 (19)
3-4	49 (15)	42 (14)	46 (15)	33 (11)
5-6	42 (13)	49 (16)	54 (17)	68 (23)
7-10	59 (19)	64 (21)	93 (29)	53 (18)
>=11	63 (20)	62 (21)	47 (15)	17 (6)

X2 for trend=29.69, df=1;
P<0.0001.

Changes in frequency of physical exercise in patients with angina
between baseline and review at two years

	No (%) of patients	
	Intervention group	Control group
Increased	108 (34)	63 (21)
No change	120 (38)	74 (25)
Decreased	89 (28)	163 (54)

X2 for trend=35.66, df=1;
P<0.0001.

Deaths.

There were 29 deaths the control group and 13 in the intervention group. The relative odds of death in the control group was 2.32 (95% confidence interval 1.18 to 4.53). Ten of the deaths in the intervention group and 28 in the control group were attributed to cardiovascular causes. The relative odds of death was 2.20 (1.06 to 4.57) after age, sex, history of myocardial infarction, blood pressure, cholesterol, body mass index, smoking status, family history, social class, diabetes, and recent worsening of angina were adjusted for.

Source of funding: Medical Research Council, UK.

Does the study answer the question?/Further Comments Yes. At two years more of the intervention group (140, 44%) reported taking daily physical exercise than the control group (70, 24%). This study shows that an education programme seems to increase exercise in patients with angina. This is a secondary outcome of the study and the study was not powered to detect differences between groups on this measure. However, the study is large (n=688) and well conducted and the results are useful and important.

Eriksson BE;Tyni L;Svedenhag J;Hallin R;Jensen UK;Jensen UM;Bergman K;Selvé

Physical training in Syndrome X: physical training counteracts deconditioning and pain in Syndrome X

Ref ID 97 **RID:** 776 2000 Nov 1

QUALITY

A. Selection bias (systematic differences between the comparison groups)

A4 Based on your answers t, in your opinion was selection bias present? If so, what is the likely direction of its effect?:

Unclear/unknown risk **Direction =** No description of randomisation method given or any information on 'blinding' of investigators.

B. Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)

B4 Based on your answers to the above, in your opinion was performance bias present? If so, what is the likely direction of its effect?:

Unclear/unknown risk **Direction =** It is unclear whether investigators knew which groups patients were allocated to.

C. Attrition bias (systematic differences between the comparison groups with respect to loss of participants)

C4 Based on your answers to the above, in your opinion was attrition bias present? If so, what is the likely direction of its effect?:

Low risk of bias **Direction =**

D. Detection bias (bias in how outcomes are ascertained, diagnosed or verified)

D6 Based on your answers to the above, in your opinion was detection bias present? If so, what is the likely direction of its effect?:

Unclear **Direction =** Two groups were assessed after 8 weeks(control group and the 8-week exercise group). The third group was assessed after 16 weeks (8 weeks

Overall Study Quality -Strengths and Weaknesses:

This is a very small study (n=26 females) of syndrome X patients with a very short follow-up period (8 to 16 weeks). The study did not specifiy a specific primary outcome. It gave no details of randomisation or concealment of allocation to those conducting the tests at study end.

DETAILS

# of patients:

n=26: n=8 in Group A (body awareness plus exercise training), n=8 in Group B (exercise training only) and n=10 in Group C (control group).

Prevalence (Diagnostic):

Patient Characteristics

Patient Characteristics	Group A (n=7)	Group B (n=7)	Group C (n=10)
Age (yrs)	59+/-5	55+/-9	53+/-10
Weight (kg)	72+/-6	68+/-6	74+/- 9
History of angina (months)	44+/-38	42+/-39	44+/-36
Functional class (CCS)	II (7)	II (7)	II (10)
Beta-blockers	2	2	3
Calcium antagonists	3	2	4
Nitroglycerine	5	5	8

Interventions/ Test/ Factor being investigated

Group A had body awareness training plus physical exercise, Group B had only physical exercise, and Group C had neither. The main intervention of interest was the physical exercise. Physical training was performed as outpatient activity in hospital settings and was supervised by a physical therapist. Body-awareness training consisted of body and mind relaxationperformed twice a week for eight weeks. Exercise training was performed on a cycle ergometer three times a week for eight weeks. Training time was 30 min and the intensity was 50% of peak work rate determined at onset of the study.

Comparisons

The comparison was between physical exercise and normal daily activities. In addition, a comparison was conducted between those who had just physical exercise and those who had physical exercise plus body awareness.

Length of Study/ Follow-up

Two groups were assessed after 8 weeks(control group and the 8-week exercise group). The third group was assessed after 16 weeks (8 weeks body awareness plus 8 weeks exercise).

Outcome measures studied

No primary outcome specified. Outcomes included in the study were: exercise capacity, hormonal analysis, adenosine sensitivity test, endothelial and nonendothelial vascular function. Only exercise capacity and pain (quality of life proxy) are relevant to the review question and are reported in results. Maximal exercise capacity was assessed by a symptom-limited exercise test on a cycle ergometer. Exercise tests started at 30 W and stepwise increments of 10 W every minute were used (W not defined). Time to pain onset was given in minutes and maximal pain measured according to the Borg Category Ratio Scale (instrument not described further).

Results

Exercise Capacity and Pain

	Group A (Relaxation and Exercise Training)	Group B (Exercise Training)	Group C (Ordinary Life Only)
Peak work (W) baseline	91± 15	97±8	92±15
Peak work (W) after relaxation	89± 11		
Peak work (W) after exercise training	124±19	127±14	95± 9
p value (training effect)	0.0018	0.0008	ns

Pain onset (min) baseline
3±2 4±1 3± 1
Pain onset (min) relaxation 3±2
Pain onset (min) after exercise training 6±3
6±1 3±1
p value (training effect) 0.04
0.01 ns

Max pain (Borg CR-10 baseline
4±1 3±1 4± 1
Max pain (Borg CR-10) after relaxation 4±1
Max pain (Borg CR-10) after exercise training 4±1
3±1 4± 1
p value (training effect)
ns ns ns

Effect Size

Exercise Capacity and Pain

	Group A	Group B	Group C
	(Relaxation and Exercise Training)	(Exercise Training)	(Ordinary Life Only)
Peak work (W) baseline	91± 15	97±8	92±15
Peak work (W) after relaxation	89± 11		
Peak work (W) after exercise training	124±19	127±14	95± 9
p value (training effect)	0.0018	0.0008	ns

Pain onset (min) baseline
3±2 4±1 3± 1
Pain onset (min) relaxation 3±2
Pain onset (min) after exercise training 6±3
6±1 3±1
p value (training effect) 0.04
0.01 ns

Max pain (Borg CR-10 baseline
4±1 3±1 4± 1
Max pain (Borg CR-10) after relaxation 4±1
Max pain (Borg CR-10) after exercise training 4±1
3±1 4± 1
p value (training effect)
ns ns ns

Source of funding:

Not reported.

Does the study answer the question?/Further Comments

Yes. The study shows that physical training in syndrome X results in an increased exercise capacity with lesser anginal pain. However, this is a small study with short follow up and includes only females.

Gallacher JEJ;Hopkinson CA;Bennett P;Burr ML;Elwood PC;

Effect of stress management on angina

Ref ID 749 **RID:** 865 1997 Jul

QUALITY

A. Selection bias (systematic differences between the comparison groups)

A4 Based on your answers t, in your opinion was selection bias present? If so, what is the likely direction of its effect?:

Low risk of bias

Direction = Randomisation method was well described. Blinding was not described but relevant study results are based on

B. Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)

B4 Based on your answers to the above, in your opinion was performance bias present? If so, what is the likely direction of its effect?:

Low risk of bias

Direction =

C. Attrition bias (systematic differences between the comparison groups with respect to loss of participants)

C4 Based on your answers to the above, in your opinion was attrition bias present? If so, what is the likely direction of its effect?:

Unclear/unknown risk

Direction = More outcome data was missing for the stress mgt group but reasons for this are not reported, either in total or

D. Detection bias (bias in how outcomes are ascertained, diagnosed or verified)

D6 Based on your answers to the above, in your opinion was detection bias present? If so, what is the likely direction of its effect?:

Unclear

Direction = For the primary outcome there are more data available for the control group than for the stress mgt group. If the missing subjects' data showed

Overall Study Quality -Strengths and Weaknesses:

This is a large (n=452), well conducted study which assessed the effect of a minimal stress management programme (3 x 1 hour sessions, with tapes and manual provided) for the treatment of angina in a primary care setting. There was a statistically significant decrease in frequency of chest pain at rest in the SMP group compared to those in the control group. Analysis however, was performed on data for only 70% of patients in the SMP group and 80% of those in the control group.

DETAILS

# of patients: n=452 (n=227 in SMG and n=225 in control group)

Prevalence (Diagnostic):

Patient Characteristics Comparison of baseline cardiovascular risk factors, Baseline stress scores, and chest pain frequencies were similar between the two groups. No data reported.

Interventions/ Test/ Factor being investigated A stress management programme consisting of 3 one-hour sessions over a period of six weeks. Patients were also asked to practice relaxation with the aid of cassette tapes and read a course "manual" at home. The study did not describe the type of health professional who delivered the sessions.

Comparisons

The comparison is between the stress management programme and no psychological intervention.

Length of Study/ Follow-up

6 months post intervention.

Outcome measures studied

The primary endpoint in the analysis was the frequency of chest pain occurring at rest. Secondary endpoints were : frequency of chest pain on exertion; and stress score. The Derogatis Stress Profile (DSP) is a 78 item self report Likert scaled questionnaire covering 11 areas of possible stress. In addition the DSP provides a subjective stress score. Here the respondent is asked to mark their perceived level of stress along a continuous line with the send points "Totally free from stress" and "Extremely highly stressed".

Results

Change in frequency of chest pain at six months between men instructed in stress management and men in the non-intervention group

Frequency of chest pain (days per fortnight)

Difference	Stress management (n=158)		No intervention (n=179)		
	Mean	(SD)	Mean	(SD)	
At rest					
Baseline	2.18	3.28	2.06	2.91	0.12
6 months	1.83	2.92	2.42	3.19	-0.59
Change	-0.35	2.54	+0.36	2.87	-0.71
t=2.41(p<0.02)					
On exertion					
Baseline	3.62	3.83	3.68	3.95	-0.06
6 months	3.42	3.71	3.96	3.86	-0.54
Change	-0.20	3.43	+0.28	3.33	-0.48
t=1.28, n.s.					

n.s. = not significant.

Change in Derogatis Stress Profile (DSP) score at six months in stress management and non-intervention

(n=194) Difference	Changes in DSP scores Stress management (n=184)		No intervention	
	Mean	(SD)	Mean	(SD)
Total DSP score 2.77 (p<0.005)	-18.2	41.9	-6.7	34.7
Subjective stress score 2.15 (p<0.05)	-9.0	21.8	-4.2	22.2

Effect Size

Change in frequency of chest pain at six months between men instructed in stress management and men in the non-intervention group

Frequency of chest pain (days per fortnight)

Difference	Stress management (n=158)		No intervention (n=179)		
	Mean	(SD)	Mean	(SD)	
At rest					
Baseline	2.18	3.28	2.06	2.91	0.12
6 months	1.83	2.92	2.42	3.19	-0.59
Change	-0.35	2.54	+0.36	2.87	-0.71
t=2.41(p<0.02)					
On exertion					
Baseline	3.62	3.83	3.68	3.95	-0.06
6 months	3.42	3.71	3.96	3.86	-0.54
Change	-0.20	3.43	+0.28	3.33	-0.48

t=1.28, n.s.

n.s. = not significant.

Change in Derogatis Stress Profile (DSP) score at six months in stress management and non-intervention

(n=194)	Difference	Changes in DSP scores: Stress management (n=184) Mean	(SD)	No intervention Mean	(SD)
Total DSP score	2.77 (p<0.005)	-18.2	41.9	-6.7	34.7
Subjective stress score	2.15 (p<0.05)	-9.0	21.8	-4.2	22.2

Source of funding:

Not reported.

Does the study answer the question?/Further Comments

Yes. This is a relatively large study with a 6 month follow up. It concludes that a minimal stress management programme decreases the frequency of chest pain (at rest) in those taking part in the programme compared to those not receiving the programme. The difference between the two groups was 0.71 days per fortnight. That is, the stress management group had 0.71 fewer days chest pain per fortnight than the control group. It should be noted that data were available for only 70% of those participating in the stress management programme and 80% in the control group.

Hambrecht R;Walther C;Mobius WS;Gielen S;Linke A;Conradi K;Erbs S;Kluge R;Kendziorra K;Sabri O;Sick P;Schuler G;

Percutaneous coronary angioplasty compared with exercise training in patients with stable coronary artery disease: a randomized trial

Ref ID 9023 **RID:** 878 2004 Mar 23

QUALITY

A. Selection bias (systematic differences between the comparison groups)

A4 Based on your answers t, in your opinion was selection bias present? If so, what is the likely direction of its effect?:

Low risk of bias **Direction =**

B. Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)

B4 Based on your answers to the above, in your opinion was performance bias present? If so, what is the likely direction of its effect?:

Low risk of bias **Direction =**

C. Attrition bias (systematic differences between the comparison groups with respect to loss of participants)

C4 Based on your answers to the above, in your opinion was attrition bias present? If so, what is the likely direction of its effect?:

Low risk of bias

Direction =

D. Detection bias (bias in how outcomes are ascertained, diagnosed or verified)

D6 Based on your answers to the above, in your opinion was detection bias present? If so, what is the likely direction of its effect?:

Low risk of bias

Direction =

Overall Study Quality -Strengths and Weaknesses:

Strengths: Randomised control trial (with allocation concealment), intention to treat analysis, authors performed a power analysis.
Weaknesses: No 'usual care' control group. Even though the authors reported high compliance (70±2%) with the exercise regime it is not clear how that was evaluated (whether that was attendance at the weekly group training or self reported daily exercise or both)

DETAILS

# of patients: n=101 (n=50 PCI and n=51 exercise)

Prevalence (Diagnostic):

Patient Characteristics

	Exercise (n=51)	PCI (n=50)β
Age years (±SE)	62±1	60±1
Current smoking No. of patients (%)	9 (18)	8 (16)
Diabetes mellitus No. of patients (%)	12(23)	11(22)
Myocardial infarction no. of episodes*	26(52)	20(39)
CCS classification of angina No. of patients (%):		
Class I	21(41)	15(30)
Class II	27(53)	33(66)
Class III	3(6)	6(12)
Current medication No. of patients (%):		
ACE inhibitiors / AT1-receptor antagonists	38(74)	44(88)
β-HMG-CoA reductase inhibitors	36(72)	40(80)
β-Receptor antagonists	45(88)	43(86)
Acetylsalicylic acid	50(98)	49(98)
Nature of coronary artery disease, No. of patients (%):		
Single vessel	29(57)	30(60)
Double vessel	13(26)	14(28)
Tripel vessel	9(18)	6(12)
Location of target lesion, No. of patients (%):		
Left anterior descending CA	11(22)	10(20)
Left circumflex CA	22(43)	25(50)
Right CA	18(35)	16(32)

*Myocardial infarction did not occur within 2 months before the screening visit

Inclusion criteria: Eligible patients had class I to III angina pectoris with documented myocardial ischemia during stress ECG and / or 99mTc scienigraphy.
Exclusion criteria: Acute coronary syndromes or recent myocardial infarction (<2 months), left main coronary artery stenosis >25% or high-grade proximal left anterior descending artery stenosis, reduced left ventricular function (ejection fraction <40%), significant valvular heart disease, insulin-dependent diabetes mellitus, smoking, and occupational, orthopaedic, and other conditions that

	precluded regular exercise. Patients after previous CABG or PCI within the last 12 months were also excluded. Only patients living within a 25-km radius of the research institution were recruited.
Interventions/ Test/ Factor being investigated	intervention – stent angioplasty. Exercise training program: During the first 2 weeks patients exercised in the hospital 6 tiems per day for 10 minutes on a bicycle ergometer at 70% of the symptom-limited maximal hear rate. After discharge from hospital patients were asked to exercise on their bicycle ergometer close to the target heart rate for 20 minutes per day and to participate in one 60-minute group training session of aerobic exercise per week.
Comparisons	Exercise vs. PCI
Length of Study/ Follow-up	1 year
Outcome measures studied	Clinical symptoms: angina-ree exercise capacity, myocardial perfusion; clinical end points: death of cardia cause, stroke, CABG, angioplasty, acute myocardial infarction and worsening angina with objective evidence resulting in hospitalisation).
Results	
Effect Size	Clinical events:

	Exercise (n=51)	PCI (n=50)
Total number of patients with event:		
Death of cardiac causes	0	0
Cerebrovascular accident	2	3
Revascularisation	3	10
Hospitalisation and coronary angiography owing to worsening angina:	1	7

Source of funding:	supported by an unconditional scientific grant from Aventis Germany
Does the study answer the question?/Further Comments	No, not exactly, only with regards to exercise as treatment rather than rehabilitation. Furthermore I lack of a 'usual care' group makes the interpretation difficult. In patients with stable CAS and an angiographically documented stenosis amenable for PTCA, a 12-month exercise training program resulted in a higher event-free survival rate than with standard PCI intervention.

Jiang X;Sit JW;Wong TKS;

A nurse-led cardiac rehabilitation programme improves health behaviours and cardiac physiological risk parameters: evidence from Chengdu, China

Ref ID 652 **RID:** 797 2007 Oct

QUALITY

A. Selection bias (systematic differences between the comparison groups)

A4 Based on your answers t, in your opinion was selection bias present? If so, what is the likely direction of its effect?:

Unclear/unknown risk

Direction = The study does not report on concealment methods for investigators.

B. Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)

B4 Based on your answers to the above, in your opinion was performance bias present? If so, what is the likely direction of its effect?:

Unclear/unknown risk

Direction = No description of routine care was given or even if it included advice on diet, exercise and smoking cessation.

C. Attrition bias (systematic differences between the comparison groups with respect to loss of participants)

C4 Based on your answers to the above, in your opinion was attrition bias present? If so, what is the likely direction of its effect?:

Unclear/unknown risk

Direction = More patients dropped out in the control group but analysis was done on an intention-to-treat basis.

D. Detection bias (bias in how outcomes are ascertained, diagnosed or verified)

D6 Based on your answers to the above, in your opinion was detection bias present? If so, what is the likely direction of its effect?:

Unclear

Direction = No information in the study about "blinding" of investigators. Whether it was done or how it was done.

Overall Study Quality -Strengths and Weaknesses:

This is a relatively short term study of patients (n=167) with angina who underwent a 12 week rehabilitation course and who were assessed at 6 months for smoking cessation, exercise, and physiological risk factors. Very little information is given about whether investigators were "blinded" to patients' allocation to intervention or control group. Most of the outcomes measured in the study were not relevant to the review question (10) for which this study was included.

DETAILS

# of patients:

n=167 (n=83 in intervention group(rehabilitation programme) and n=84 in control group (routine care)).

Prevalence (Diagnostic):

Patient Characteristics

Baseline characteristics

	Intervention (n=83)(%)	Control (n= 84)(%)
Gender		
Male	57 (68.67)	62 (73.81)
Female	26 (31.33)	22 (26.19)
Age	62.11 (7.44)*	61.37 (7.61)*
Diagnoses		
Angina pectoris	56 (67.47)	58 (69.05)
Myocardial infarction	27 (32.53)	26 (30.95)
Family history of		

coronary heart disease		
Yes	3 (3.61)	10 (11.90)
No	80 (96.39)	74 (88.09)
Smoker		
Yes	33 (39.76)	38 (45.24)
No	50 (60.24)	46 (54.76)
Hypertension		
Yes	61 (73.49)	51 (60.71)
No	22 (26.51)	33 (39.29)

Interventions/ Test/ Factor being investigated

The intervention is a cardiac rehabilitation programme. The cardiac rehabilitation programme of this study was a 12-week hospital-initiated home-based multifaceted cardiac rehabilitation intervention designed for enhancing cardiac self-management for recovery and secondary prevention during the transition from hospital to home. The design and delivery of the programme were based on the cardiac rehabilitation and secondary prevention guidelines established by the American Heart Association. Programme was started in hospital and maintained to 12 weeks after discharge. It was led by an experienced cardiac nurse and the major elements were: setting daily goals for walking, smoking cessation, diet adherence and medication adherence; setting goals for reducing risk factors; keeping a diaryto track progress; and encouraging family members to support the programme.

Comparisons

The control group received "routine care" but this is not described.

Length of Study/ Follow-up

The final patient assessments were conducted after 6 months.

Outcome measures studied

Primary and secondary outcomes were not specified. Outcomes included: smoking cessation, walking performance, diet adherence, medication adherence and cardiac physiological risk factors.The outcome relevant to review question 10 was walking performance. The Jenkins Activity Checklist for Walking (Jenkins 1989) was used. There are 16 activities on the scale, ranging from walking from bed to bathroom to walking 6.5 km. The answer format is dichotomous. Subjects were required to indicate whether they had performed each activity in the previous 24-hour period. For scoring, the number of 'yes' responses was summed to provide an activity total score, ranging from 0 to 16. The reported content validity index of the scale is 0.92, the reliability coefficient alpha values were 0.93–0.96 among myocardial infarction patients.

Results

Compared with baseline, the intervention group demonstrated a significantly greater increase in the mean scores of Jenkins Activity Checklist for Walking.

	Baseline		Six months		Net change			
	Intervention (n = 83)	Control (n= 84)	Intervention (n= 83)	Control (n=84)	Intervention (n= 83)	Control (n=84)	U	p
Walking Performance	2.78 (1.61)	2.68(1.50)	10.63 (2.13)	8.62 (2.98)	7.85(3.41)	5.94(3.94)	3.13	0.002

U=Whitney U test.

Effect Size

Jenkins Activity Checklist for Walking.

	Baseline		Six months		Net change			
	Intervention (n = 83)	Control (n= 84)	Intervention (n= 83)	Control (n=84)	Intervention (n= 83)	Control (n=84)	U	p
Walking Performance	2.78 (1.61)	2.68(1.50)	10.63 (2.13)	8.62 (2.98)	7.85(3.41)	5.94(3.94)	3.13	0.002

U=Whitney U test.

Source of funding: Not reported.

Does the study answer the question?/Further Comments This study shows that a cardiac rehabilitation programme improves walking performance at 6 months compared to normal care. It is not clear how clinically significant the difference between the two groups is. It would be interesting to see if the difference was maintained at 1 year or longer.

Lewin RJ;Cay EL;Todd I;Soryal I;Goodfield N;Bloomfield P;Elton R;

The Angina Management Programme: A rehabilitation treatment

Ref ID 9184 **RID:** 814 1995

QUALITY

A. Selection bias (systematic differences between the comparison groups)

A4 Based on your answers t, in your opinion was selection bias present? If so, what is the likely direction of its effect?:

Low risk of bias **Direction =**

B. Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)

B4 Based on your answers to the above, in your opinion was performance bias present? If so, what is the likely direction of its effect?:

Low risk of bias **Direction =** For investigator measured outcome such as the exercise tolerance test, results were analysed by a doctor not

C. Attrition bias (systematic differences between the comparison groups with respect to loss of participants)

C4 Based on your answers to the above, in your opinion was attrition bias present? If so, what is the likely direction of its effect?:

Low risk of bias **Direction =**

D. Detection bias (bias in how outcomes are ascertained, diagnosed or verified)

D6 Based on your answers to the above, in your opinion was detection bias present? If so, what is the likely direction of its effect?:

Low risk of bias **Direction =** The study had an unusual design in that the control phase of the study was only 8 weeks (treated patients versus waiting list controls). At 4

Overall Study Quality -Strengths and Weaknesses: This paper reports summary results of 5 small (n=16) trials which took place over 2 years. Each trial was exactly the same design. In total n=77 patients were randomised to the Angina Management Programme (AMP) or to Waiting List Controls (WLC) for 8 weeks. After 8 weeks of being in the WLC group patients went on to the AMP for 8 weeks. Further assessments were carried out for all

patients at 4 months and 1 year. However, at the latter two timepoints all patients had had treatment with AMP. Therefore, the only relevant results are for the initial 8 week controlled phase of the study. That is, there was no long term control group.

DETAILS

# of patients:

n=77 (n=39 in the AMP group and n=38 in the WLC group)

Prevalence (Diagnostic):

Patient Characteristics

Baseline data by group

	AMP group (n=39)		Waiting list controls (n=38)	
	Mean	SD	Mean	SD
Male/Female	30/9		29/9	
Age (years)	59	7	57	7
History of angina (months)	55	57	52	52
Family history CAD/none	23/16		27/10*	
No. of previous Mis 0/1/2/3	24/8/6/1		24/11/3	
Number of smokers/non-smokers	7/32		7/31	
Episodes angina per week	15.4	11.7	17.6	17.0
Disability (Sickness Impact Profile)	20.3	12.4	21.6	13.5
Resting heart rate	60.9	13.0	64.9	9.6
Time of treadmill	402	219	373	221

Interventions/ Test/ Factor being investigated

For the Angina Management Programme (AMP) patients attended the hospital for two mornings per week for eight weeks. The AMP included the following elements: Exercise - consisted of 10 movements designed to improve general fitness and flexibility. Number of repetitions increased as patients felt fitter up until "somewhat hard"; Stress management - using relaxation, breathing re-training, bio-feedback, yoga exercises and behaviour modification; Psychological status - a self help rehab programme designed to reverse beliefts known to predict poor psychological recovery from MI; Behavioural change - help to return to appropriate but abandoned activities using goal setting and pacing; and education - extensive information about coronary artery disease.

Comparisons

Comparisons are between the AMP and patients on the waiting list for AMP.

Length of Study/ Follow-up

8 weeks (which is the length of treatment)

Outcome measures studied

No primary or secondary outcomes specified. Study outcomes included: frequency and severity of angina episodes (diary) ; disability (Sickness Impact Profile questionnaire); and exercise tolerance test (treadmill and ECG. Terminated at patient request due to pain or fatigue or decrease in systolic BP >10mm).

Results

Summary statistics for five measurements in the 65 patients who completed the controlled phase 8-week period.

Mean (SD) at baseline and post-treatment or post-waiting period for highly skewed outcomes.

	Treatment group		Waiting list control group	
	N=34		n=31	
	Baseline	Post treatment	Baseline	Post-waiting
Episodes angina	15.2 (11.3)	4.5 (5.7)	18.1 (17.4)	16.6 (17.8)
Severity of angina	31.0 (18.6)	21.2 (21.8)	30.9 (19.3)	32.9 (24.6)
Duration of angina	22.0 (26.1)	16.3 (23.8)	19.6 (22.3)	26.0 (39.7)
Use of GTN	19.4 (39.6)	5.4 (13.0)	18.2 (25.5)	17.7 (28.1)
Disability	19.6 (10.9)	6.8 (6.3)	22.1 (14.2)	19.5 (12.9)

No data were presented for exercise tolerance test in the table, but in a bar chart. Reading data from that figure the change score in time on treadmill for the treatment group was approx +225 seconds compared to a change of approx +40 seconds for the control group at 8 weeks.

Effect Size

Summary statistics for five measurements in the 65 patients who completed the controlled phase 8-week period.

Mean (SD) at baseline and post-treatment or post-waiting period for highly skewed outcomes.

	Treatment group		Waiting list control group	
	N=34		n=31	
	Baseline	Post treatment	Baseline	Post-waiting
Episodes angina	15.2 (11.3)	4.5 (5.7)	18.1 (17.4)	16.6 (17.8)
Severity of angina	31.0 (18.6)	21.2 (21.8)	30.9 (19.3)	32.9 (24.6)
Duration of angina	22.0 (26.1)	16.3 (23.8)	19.6 (22.3)	26.0 (39.7)
Use of GTN	19.4 (39.6)	5.4 (13.0)	18.2 (25.5)	17.7 (28.1)
Disability	19.6 (10.9)	6.8 (6.3)	22.1 (14.2)	19.5 (12.9)

No data were presented for exercise tolerance test in the table, but in a bar chart. Reading data from that figure the change score in time on treadmill for the treatment group was approx +225 seconds compared to a change of approx +40 seconds for the control group at 8 weeks.

Source of funding:

British Heart Foundation

Does the study answer the question?/Further Comments

Yes. For almost all patients, the 8 week outpatient treatment resulted in significant improvements in the frequency of angina, the use of nitrates, disability and time on the treadmill. Statistically significant treatemnt effects were demonstrated within each of the five controlled trials.

Lewin RJ;Furze G;Robinson J;Griffith K;Wiseman S;Pye M;Boyle R;

A randomised controlled trial of a self-management plan for patients with newly diagnosed angina

Ref ID 9191 **RID:** 821 2002

QUALITY

A. Selection bias (systematic differences between the comparison groups)

A4 Based on your answers t, in your opinion was selection bias present? If so, what is the likely direction of its effect?:

Low risk of bias

Direction =

B. Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)

B4 Based on your answers to the above, in your opinion was performance bias present? If so, what is the likely direction of its effect?:

Low risk of bias

Direction = Baseline and follow-up measures were collected, scored, and entered into the computer by

C. Attrition bias (systematic differences between the comparison groups with respect to loss of participants)

C4 Based on your answers to the above, in your opinion was attrition bias present? If so, what is the likely direction of its effect?:

Low risk of bias

Direction =

D. Detection bias (bias in how outcomes are ascertained, diagnosed or verified)

D6 Based on your answers to the above, in your opinion was detection bias present? If so, what is the likely direction of its effect?:

Low risk of bias

Direction =

Overall Study Quality -Strengths and Weaknesses:

This was a relatively large (n=142), well conducted study which compared psychological adjustment in patients with newly diagnosed angina who took part in the Anginal Plan and those who took part in an education programme. Primary and secondary outcomes were clearly specified. The study had 80% power to detect a difference of 0.5 units on the Hospital Anxiety and Depression Scale. . However, the study acknowledges that the mean reduction in anxiety and depression is slight, even though for some patients it was profound. Follow up was 6 months so the study was not capable of determing if the observed beneftis continue beyond this time.

DETAILS

# of patients:

N=142 (n=68 in Angina Plan and n=74 in Educational Prog.)

Prevalence (Diagnostic):

Patient Characteristics

Demographic and medical variables at baseline. All comparisons are non-significant, P>0.05.

Demographic variables	Angina Plan patients	Educational session patients
Mean age in years on entry to the study (SD)	66.74 (9.37)	67.64 (9.01)
Number (% group) of men	39 (57)	46 (62)
Number (% group) married	51	

(75) 49 (66)
Number (% group) in classes 3m, 4 and 5 [Registrar General Social Class] 25
(37) 25 (34)
Mean number of years in full-time education 10.98
(2.12) 10.95 (2)
Illness measures
Mean number of episodes of angina a week 7.55
(10.11) 6.29 (8.87)
Canadian angina class: number (% group)
1 29
(43) 27 (36)
2 31
(46) 40 (54)
3 8
(12) 7 (9)
4
0 0
NYHA Cardiac Failure class: number (%) scoring >1 28
(41) 37 (50)
Number (%) with positive exercise test 27
(53) 23 (47)
Mean number of minutes (SD) on treadmill 5.09
(2.26) 5.04 (2.17)
History of acute events
Number (%) previously referred to cardiology 30
(44) 28 (38)
Number (%) with previous myocardial infarction 16
(24) 25 (34)
Number (%) with previous angiogram 9
(13) 16 (22)
Number (%) with previous PTCA 7
(10) 5 (7)
Cardiac risk markers
Number (%) with recorded hypertension 29
(43) 36 (49)
Mean (SD) systolic blood pressure 144
(25.92) 141 (23.53)
Number (%) with recorded diabetes 5
(7) 11 (15)
Number (%) with cholesterol >5.2 at some time 57
(84) 57 (77)
Number (%) with family history in near relative 29
(43) 42 (57)
Number (%) of current or previous smokers 49
(72) 52 (70)
Mean (SD) body-mass index 26.4
(3.77) 27.66 (4.25)

Interventions/ Test/ Factor being investigated

The Anginal Plan

'The Angina Plan' consisted of a 70-page, patient-held 'work-book' and an audio-taped relaxation programme which was introduced to the patient during a 30 to 40-minute structured interview. Before commencing, the nurse asked the patient to complete a questionnaire designed to establish if he or she had any of the common misconceptions about angina. Any misconceptions were discussed with the patient to correct their understanding of the illness and to explain how such beliefs can lead to undue invalidism. The nurse then worked with the patient to identify all of his or her personal risk factors for coronary heart disease in the normal manner. A method of gradually and systematically reducing these and increasing activity levels, 'goal setting and pacing' that we have developed in previous research with angina patients, was used to negotiate gradual return to abandoned activities or to increase the patients' capacity for that activity. The same method was used to introduce lifestyle change; improved diet and walking. Patients were asked to practice relaxation, using the audio cassette, for 20 minutes each day. The nurse contacted the patient with a brief phone call at the end of weeks 1, 4, 8, and 12. Any success with the goals the patients had set was rewarded with praise and encouragement and they were asked if they wished to extend the goal. The Plan also contained written information about the

role of frightening thoughts and misconceptions in triggering adrenaline release and anxiety and how this can result in poor coping strategies (such as the 'overactivity-rest cycle'), as well as an explanation of the symptoms of hyperventilation and panic. Standard advice on risk factors, medication, and what to do in the event of a suspected heart attack were also included.
Educational sessions
The nurse identified the patients' risk factors for coronary heart disease from the research clinic
measurements and a personal history and discussed ways in which each of them could be reduced.
Patients were invited to ask questions about each risk factor and about angina or heart disease in
general. They were also encouraged to discuss how it had affected their lives. Any questions they had
were answered in an honest and factual manner by the nurse. If she did not know the answer at the time
then she found it later and telephoned or wrote to them. Every patient was given a package of written
information, designed for patients with coronary heart disease and angina and produced by authoritative
sources, including the British Heart Foundation, the Chest Heart and Stroke Association, and the Family
Heart Association.

Comparisons

Comparisons are made between the Angina Plan and the Education Programme.

Length of Study/ Follow-up

6 months.

Outcome measures studied

The principle outcome measures were anxiety and depression from the Hospital Anxiety and Depression Scale
(HADS).Additional outcome measures included an angina diary kept by the patient for one week for recording the frequency of episodes of angina and the number of short-acting glyceryl trinitrate (GTN) pills or 'puffs' of sub-lingual spray taken each day. Patients rated each episode of angina for severity using a scale from 1 to 100, with 100 being 'worst possible
pain' and the duration of the episode in minutes.
A disease-specific health-related quality-of-life measure,
the Seattle Angina Questionnaire,20 was completed.

Results

Change scores for psychological and quality of life measures. Intention-to-treat analysis of covariance.

	Angina Plan: mean change in score (SD)	Educational session: mean change in score (SD)	Significance level (P-value)
Hospital Anxiety and Depression (HAD) Scale			
Anxiety	-1.03 (2.61)	0.00 (3.07)	0.052
Depression	-0.48 (1.89)	0.41 (2.10)	0.013
Angina diary			
Angina attacks per week	-2.98 (5.54)	-0.41 (5.97)	0.016
Number GTN per week	-4.19 (11.48)	0.59 (9.81)	0.018
Mean pain score	-1.69 (14.78)	-3.48 (17.35)	0.56
Mean duration of event	-9.21 (34.87)	-6.78 (22.98)	0.69
Seattle Angina Questionnaire			
Physical limitation	8.42 (16.07)	-1.43 (14.24)	<0.001
Anginal stability	8.73 (31.48)	4.17 (29.93)	0.40
Angina frequency	5.71 (23.54)	4.24 (24.06)	0.72
Treatment satisfaction	0.81 (16.82)	2.75	

(13.52) 0.50
Disease perception 7.8 (14.35) 4.29
(16.94) 0.21

Effect Size

Change scores for psychological and quality of life measures. Intention-to-treat analysis of covariance.

	Angina Plan: mean change in score (SD)	Educational session: mean change in score (SD)	Significance level (P-value)
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Treatment satisfaction	0.81 (16.82)	2.75 (13.52)	0.50
Disease perception	7.8 (14.35)	4.29 (16.94)	0.21

Source of funding:

Pfizer

Does the study answer the question?/Further Comments

Yes. This is a large, well conducted RCT which shows that the Angina Plan appears to improve the psychological, symptomatic, and functional status of patients newly diagnosed with angina.

Malmborg RO;Isacsson SO;Kallivroussis G;

The effect of beta blockade and-or physical training in patients with angina pectoris

Ref ID 9189 **RID:** 819 1974 Mar

QUALITY

A. Selection bias (systematic differences between the comparison groups)

A4 Based on your answers t, in your opinion was selection bias present? If so, what is the likely direction of its effect?:

Low risk of bias

Direction =

B. Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)

B4 Based on your answers to the above, in your opinion was performance bias present? If so, what is the likely direction of its effect?:

Low risk of bias

Direction = Patients were blind to the drug/placebo they took in addition to exercise or no exercise.

C. Attrition bias (systematic differences between the comparison groups with respect to loss of participants)

C4 Based on your answers to the above, in your opinion was attrition bias present? If so, what is the likely direction of its effect?:

Low risk of bias

Direction =

D. Detection bias (bias in how outcomes are ascertained, diagnosed or verified)

D6 Based on your answers to the above, in your opinion was detection bias present? If so, what is the likely direction of its effect?:

Unclear

Direction = Although investigators were blind to allocation of drug/placebo it is not clear if they were blind to allocation to exercise/no exercise training.

Overall Study Quality -Strengths and Weaknesses:

This is a small pilot study (n=29 with n=8 maximum in the 4 groups). It did not specify a primary outcome and did not perform a power calculation. It assessed the effect of beta blockade and/or physical training after 4 months of therapy. It appears to be otherwise well conducted (patients and investigators kept blind to placebo/drug allocation and good description of outcomes measured.).

DETAILS

# of patients:

n=29: n=8 in Group I (Placebo), n=8 in Group II (Placebo + training), n=7 in Group III (Beta blocker), and n=6 in Group IV (Beta blocker + training)

Prevalence (Diagnostic):

Patient Characteristics

Baseline characteristics

Patients	n	Age	Duration of Symptoms Months	Diastolic BP	Max work Capacity kpm/min	Anginal attacks per week	Nitroglycerin consumption tabl/week
Group I Placebo	8	55±4.8	46±31	84±10	600±200	4.0±3.9	5.8±6.8
Group II	8	52±5.6	42±39	86±5	394±111	12.3±8.4	

	11.7±16.6 Placebo + Training					
	Group III	7	57±1.9	66±66	83±7	364±191	7.4±9.0 4.7±6.9 Beta-blocker
	Group IV	6	58±1.9	63±61	83±7	300±134	12.5±11.7 12.6±11.5 BB + training

Interventions/ Test/ Factor being investigated

Physical training + beta blockade. Physical training comprised interval work on a bike, during 3 mins at approx 70% of maximal working capacity pulse rate followed by 2 minutes of rest, for altogether 30 mins twice weekly. BB was prindolol 5 mg tid.

Comparisons

The comparison is between physical training + BB with physical training alone and BB alone.

Length of Study/ Follow-up

Patients are followed for 4 months from start of treatment.

Outcome measures studied

No primary or secondary outcomes specified. Outcomes included exercise tolerance test (Wahlund kpm/min with initial work load 150kpm/min. Increased by 150kpm every sixth minute), anginal attacks per week and nitroglycerin tablets per week (using a diary).

Results

Change in variables at 4 months

Patients	Change in % working capacity	Change in % anginal attacks per week	Change % in nitroglycerin/week
Group I Placebo	+19±53	-49±66	0±135
Group II Placebo + Training	+15±21	-24±50	+4±54
Group III Beta-blocker	+48±41	-85±21	-73±32
Group IV BB + training	+42±49	-44±50	-15±115

Effect Size

Change in variables at 4 months

Patients	Change in % working capacity	Change in % anginal attacks per week	Change % in nitroglycerin/week
Group I Placebo	+19±53	-49±66	0±135
Group II Placebo + Training	+15±21	-24±50	+4±54

	Group III 73±32 Beta-blocker	+48±41	-85±21	-
	Group IV 15±115 BB + training	+42±49	-44±50	-

Source of funding: Not reported.

Does the study answer the question?/Further Comments Yes. This was only a pilot study but it showed that BB was effective, increasing the maximal working capacity and reducing parameters such as number of anginal attacks and nitroglycerin consumption. Physical training alone gave no significant improvements but when combined with BB there was a trend toward better results than with BB alone.

Manchanda SC;Narang R;Reddy KS;Sachdeva U;Prabhakaran D;Dharmanand S;Rajani M;Bijlani R;

Retardation of coronary atherosclerosis with yoga lifestyle intervention

Ref ID 94 **RID:** 775 2000 Jul

QUALITY

A. Selection bias (systematic differences between the comparison groups)

A4 Based on your answers t, in your opinion was selection bias present? If so, what is the likely direction of its effect?:

Unclear/unknown risk **Direction =**

B. Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)

B4 Based on your answers to the above, in your opinion was performance bias present? If so, what is the likely direction of its effect?:

Low risk of bias **Direction =**

C. Attrition bias (systematic differences between the comparison groups with respect to loss of participants)

C4 Based on your answers to the above, in your opinion was attrition bias present? If so, what is the likely direction of its effect?:

Low risk of bias **Direction =**

D. Detection bias (bias in how outcomes are ascertained, diagnosed or verified)

D6 Based on your answers to the above, in your opinion was detection bias present? If so, what is the likely direction of its effect?:

low risk

Direction =

Overall Study Quality -Strengths and Weaknesses:

Strengths: prospective randomised ; no attrition ; independent observers blinded to treatment allocation ; good compliance

Weaknesses: small sample size ; randomisation and allocation concealment methods unclear ; blinding not possible due to nature of intervention ; groups significantly different at baseline in number of anginal episodes and exercise duration

DETAILS

# of patients:

N=42 (n=21 control ;n=21 yoga intervention group)

Prevalence (Diagnostic):

Patient Characteristics

42 men (mean age 51 ±9.5, range 32-72)
Inclusion: men with chronic stable angina and angiographically proven CAD
Exclusion: patients with recent (within last 6 months) MI or unstable angina

Baseline characteristics:

Parameter	Yoga	Control	p values
Age	51±9	52±10	NS
Diabetic	29%	24%	NS
Smokers	19%	24%	NS
Previous MI	33%	29%	NS
Previous CABG	10%	5%	NS
Anginal episodes/wk	6.71±2.95	4.10 ±2.14	0.002
Weight (kg)	72.1 ±12.5	72.81±9.84	NS
Exercise duration (sec)	349±147	430±119.29	0.056
ST segment depression during exercise (mm)	2.62±0.62	2.23±0.53	0.044
Mean lesion severity (%diameter stenosis)	62.4±14.5	59.7±17.7	NS

Interventions/ Test/ Factor being investigated

The active group was treated with a user-friendly program consisting of yoga, control of risk factors, diet control and moderate aerobic exercise. After inclusion patients and their spousesspent 4 days at a yoga residential centre where they underwent training in various yoga lifestyle techniques. Subsequently they carried out the yogic exercises at home for an average of 90 minutes daily. The yoga intervention consisted of health rejuvenating exercises, breathing exercises, yogic postures for stretch relaxation, relaxation exercises, meditation, reflection and contemplation, stress management, dietary control and moderate aerobic exercises. Patients visited yoga centre every fortnight for monitoring and evaluation.
The control group was managed by conventional methods (ie risk factor control and American Heart Association step I diet)

Comparisons

yoga intervention lifestyle vs conventional methods

Length of Study/ Follow-up

1 year

Outcome measures studied

anginal episodes/week ; exercise duration ; body weight ;revascularisation ; lesion severity

Results

Results
Revascularisation procedures: CABG and PTCA were markedly reduced in the yoga group compared to controls. Only 1 in the yoga group needed revascularisation (PTCA) against 8 in the control group (2 PTCA and 6 CABG) (RR 5.45 p=0.001)/ No mortality was observed in either group at 1 year follow up

At 1 year

Parameter yoga control p value (yoga vs control)
Anginal episodes/wk 2.1 ±2.7 ; 5.4 ±2.3 ; 0.0001
Weight 66±8 ; 72±9.7 ; 0.005
Exercise duration 413±132 ; 374±151 ; 0.0007
ST segment depression during exercise test 1.8±0.8 ; 2.7±0.6 ; 0.0001
Mean lesion severity (% diameter stenosis) 60.9±16 ; 68.4±16 ; <0.0001

Effect Size

Source of funding:

Supported in part by a grant from the Central Research Institute of Yoga, Ministry of Health, Government of India

Does the study answer the question?/Further Comments

At one year, the yoga groups showed significant reduction in number of anginal episodes per week, improved exercise capacity and decrease in body weight. Revascularisation procedures (coronary angioplasty or bypass surgery) were less frequently required in the yoga group (one vs eight patients RR 5.45 p=0.01). Coronary angiography repeated at one year showed that significantly more lesions regressed (20% vs 2%) and less lesions progressed (5% vs 37%) in the yoga group (chi square=24.9 p<0.0001)
Conclusions: yoga lifestyle interventions retard progression and increases regression of coronary atherosclerosis in patients with severe coronary artery disease. It also improves symptomatic status, functional class and risk factor profile

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O'Neill C;Normand C;Cupples M;McKnight A;

A comparison of three measures of perceived distress: results from a study of angina patients in general practice in Northern Ireland

Ref ID 9181 **RID:** 811 1996 Apr

QUALITY

A. Selection bias (systematic differences between the comparison groups)

A4 Based on your answers t, in your opinion was selection bias present? If so, what is the likely direction of its effect?:

Low risk of bias **Direction =**

B. Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)

B4 Based on your answers to the above, in your opinion was performance bias present? If so, what is the likely direction of its effect?:

Low risk of bias **Direction =** The main researcher who conducted the reviews at 2 years had not previously been involved with the

C. Attrition bias (systematic differences between the comparison groups with respect to loss of participants)

C4 Based on your answers to the above, in your opinion was attrition bias present? If so, what is the likely direction of its effect?:

Low risk of bias **Direction =**

D. Detection bias (bias in how outcomes are ascertained, diagnosed or verified)

D6 Based on your answers to the above, in your opinion was detection bias present? If so, what is the likely direction of its effect?:

Low risk of bias

Direction = The person who conducted patient reviews at study end had not been involved in the study at the beginning. The implication is that this person was

Overall Study Quality -Strengths and Weaknesses:

This publication reports on QoL data from a trial whose main aim originally was to measure reduction in severity of angina in patients who received an education programme for up to 2 years. The QoL outcomes reported in this publication were therefore secondary. Although, significant differences were found between the intervention and control groups which showed a benefit from education, the clinical significance of this difference is not reported or discussed. Approximately 60% of patients in each group had outcome data for analysis of QoL changes at study end.

DETAILS

# of patients:

n=688: n=342 randomised to education and n=346 to no education.

Prevalence (Diagnostic):

Patient Characteristics

Characteristics of intervention and control groups at entry to trial

	Intervention group (n=342)	Control group (n=346)
Age (years):		
Mean (SD)	62.7 (7.1)	63.6 (6-8)
Range	38-74	39-74
Sex:		
Male	203	205
Female	139	141
Social class:		
I and II	37	35
III non-manual and manual	157	168
IV and V	148	143
Family history of heart disease:		
Yes	223	231
No	119	115
Previous myocardial infarction:		
Yes	150	159
No	192	187
Electrocardiographic evidence of ischaemia:		
Yes	212	216
No	130	130
No of cigarettes smoked/day:		
None	272	268
1-10	43	44
11-20	21	26
>20	6	8
Severity of angina:		
Severe*	21	18
Not severe	321	328

*Severe angina defined as attacks occurring once or more per day when walking on the level and in sex, sport, housework, or shopping.

Interventions/ Test/ Factor being investigated

Education programme: after the initial interview (questions regarding angina, medication, and lifestyle) patients in the intervention group were given practical relevant advice regarding cardiovascular risk factors. They were reviewed at four monthly intervals and given appropriate health education for two years.

Comparisons

The comparison group had the same intial interview as the intervention group but they received no advice or follow-up visits.

Length of Study/ Follow-up

All patients followed up for two years.

Outcome measures studied

The original study was powered to detect a reduction in severe angina in the study population. Therefore the quality of life outcomes reported in this study are secondary outcomes. They are the Nottingham health Profile(NHP) and the Simple Categorical Scale (SCS). The Nottingham Health Profile is intended for primary health care, to provide a brief indication of a patient's perceived emotional, social and physical health problems. It gives a range of possible scores from zero (no problems at all) to 100 (presence of all problems within a dimension). Here, a higher aggregate score, weighted or unweighted, is interpreted as being associated with greater distress/illness. The study also used a simple categorical scale (SCS). This offered the respondent five possible descriptions of their health status ranging from poor= 1 to very good= 5 with which they could agree.

Results

Changes in health status for control and intervention groups

Profile aspect	Intervention mean diff	Control mean diff	MWW	Prob
Physical mobility	-1.49	-6.19	-2.9357	0.0015
Social isolation	+ 1.42	-3.01	-1.7412	0.0408
Emotional reaction	-0.79	-1.91	-0.6434	0.2600
Energy	-3.88	-6.52	-0.9741	0.165
Sleep	-1.67	-0.10	-0.8637	0.1938
Pain	-1.23	-2.70	-0.1018	0.4594
Total	-7.64	-20.43	-1.5069	0.0659
SCS	-0.211	-0.01	-2.3154	0.0206

N=221 for intervention group and 212 for control group.
MWW=Mann-Whitney-Wilcoxon sum of ranks test.

Effect Size

Changes in health status for control and intervention groups

Profile aspect	Intervention mean diff	Control mean diff	MWW	Prob
Physical mobility	-1.49	-6.19	-2.9357	0.0015
Social isolation	+ 1.42	-3.01	-1.7412	0.0408
Emotional reaction	-0.79	-1.91	-0.6434	0.2600
Energy	-3.88	-6.52	-0.9741	0.165
Sleep	-1.67	-0.10	-0.8637	0.1938
Pain	-1.23	-2.70	-0.1018	0.4594
Total	-7.64	-20.43	-1.5069	0.0659
SCS	-0.211	-0.01	-2.3154	0.0206

N=221 for intervention group and 212 for control group.
MWW=Mann-Whitney-Wilcoxon sum of ranks test.

Source of funding:

Medical Research Council UK.

Does the study answer the question?/Further Comments

Yes. The intervention group showed a statistically significant improvement in health relative to the control group in
terms of physical mobility and social isolation using the NHP. In terms of overall wellbeing, both the NHP and SCS results showed the intervention group had experienced statistically significant improvements in health relative to the control group.

This study was not powered to detect differences in quality of life between the intervention and control groups. Quality of life (QoL) is a secondary outcome. In the intervention group QoL data were available for 64% of patients and for 61% of patients in the control group. However, this is a relatively large study (n=688) and the results are useful and important.

Ornish D;Scherwitz LW;Billings JH;Brown SE;Gould KL;Merritt TA;Sparler S;Armstrong WT;Ports TA;Kirkeeide RL;Hogeboom C;Brand RJ;

Intensive lifestyle changes for reversal of coronary heart disease

Ref ID 120 **RID:** 777 1998 Dec 16

QUALITY

A. Selection bias (systematic differences between the comparison groups)

A4 Based on your answers t, in your opinion was selection bias present? If so, what is the likely direction of its effect?:

Direction =

B. Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)

B4 Based on your answers to the above, in your opinion was performance bias present? If so, what is the likely direction of its effect?:

Direction =

C. Attrition bias (systematic differences between the comparison groups with respect to loss of participants)

C4 Based on your answers to the above, in your opinion was attrition bias present? If so, what is the likely direction of its effect?:

Direction =

D. Detection bias (bias in how outcomes are ascertained, diagnosed or verified)

D6 Based on your answers to the above, in your opinion was detection bias present? If so, what is the likely direction of its effect?:

Direction =

Overall Study Quality -Strengths and Weaknesses:

DETAILS

# of patients:

Prevalence (Diagnostic):

Patient Characteristics

Interventions/ Test/ Factor being investigated

Comparisons

Length of Study/ Follow-up

Outcome measures studied

Results

Effect Size

Source of funding:

Does the study answer the question?/Further Comments

Potts SG;Lewin R;Fox KA;Johnstone EC;

Group psychological treatment for chest pain with normal coronary arteries

Ref ID 9348 **RID:** 892 1999 Feb

QUALITY

A. Selection bias (systematic differences between the comparison groups)

A4 Based on your answers t, in your opinion was selection bias present? If so, what is the likely direction of its effect?:

Unclear/unknown risk **Direction =**

B. Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)

B4 Based on your answers to the above, in your opinion was performance bias present? If so, what is the likely direction of its effect?:

Low risk of bias **Direction =**

C. Attrition bias (systematic differences between the comparison groups with respect to loss of participants)

C4 Based on your answers to the above, in your opinion was attrition bias present? If so, what is the likely direction of its effect?:

High risk of bias

Direction =

D. Detection bias (bias in how outcomes are ascertained, diagnosed or verified)

D6 Based on your answers to the above, in your opinion was detection bias present? If so, what is the likely direction of its effect?:

Unclear risk of bias

Direction =

Overall Study Quality -Strengths and Weaknesses:

Strengths – Randomised, baseline characteristics reported, n=4 lost to follow-up
Weakness – allocation concealment not reported, ITT not reported.

DETAILS

# of patients:

N=60 (n=34 immediate treatment and n=26 waiting control)

Prevalence (Diagnostic):

Patient Characteristics

Baseline characteristics-
The treatment and control groups did not differ as to age (mean 52.8 years (SD 8.6) vs. 55.4 (7.7) respectively, NS) or sex (59% and 63% female, respectively, NS). Nor did they differ on baseline variables of chest pain episode severity, frequency, duration of nitrate use, or any of the psychological or functional measures.

Inclusion criteria- aged 18-70 yrs , recent (within the last year) coronary angiography for the investigation of chest pain revealed coronary arteries which were either normal or <50% stenosed, chest pain continuing at twice weekly after angiography, despite reassurance by the cardiology team.
Exclusion criteria- past history of MI or serious concurrent physical or psychiatric illness.

Interventions/ Test/ Factor being investigated

Intervention - Psychological treatment package consisting of education, relaxation, breathing training, graded exposure to activity and exercise, and the use of thought diaries to record and challenging automatic thoughts about heart disease. Groups met weekly for 4 weeks, then every 2 weeks for a further 4 weeks. Each session lasted 2 hours, with a short break. Subjects were asked to practice various exercises at home between sessions, and to report their progress at the beginning of subsequent sessions. Treatment was broadly behavioural in orientation, based on a manual developed via an initial pilot group, and was supplemented by written material given to subjects at each session.

Comparisons

Control group assigned to a waiting period before being reassessed and then entering treatment.

Length of Study/ Follow-up

6 months

Outcome measures studied

Outcomes- Exercise duration (min), duration of pain, severity of pain, questionnaires- Nottingham Health Profile, Hospital Anxiety and Depression scale, Sickness Impact Profile.

Results

Effect Size	Results- Changes in treatment versus changes on waiting list control- Outcome- Treatment group (n=32) vs. Control group (n=24) Chest pain Episodes/week: -3 vs. 0; p=0.01 Duration (min): -1.6 vs. -0.5; NS Severity (1-100): -5.9 vs. 0.8; NS **HAD anxiety: -1.5 vs.0; p=0.05 HAD depression: -2 vs. 0; p=0.05 NHP problem scores Energy: -24 vs.0; p=0.01 Pain: 5 vs.0; p=0.05 Emotion: 0 vs.0; NS Sleep: 0 vs.0; p=NS Special isolation: 0 vs.0; NS Mobility: 0 vs. 0; NS SIP disability: -6.5 vs. 1.4; p=0.05 Exercise duration (min): β 1.3 vs. 0.1; p=0.5 *All above values are medians, negative values indicating reductions. **Hospital anxiety Depression scale (HAD)-A 14 item inventory covering non somatic symptoms of anxiety and depression, intended for use in medical populations. It yields separate scores for anxiety and depression, with cut offs indicating caseness above 11. Sickness Impact Profile (SIP) – A 136 item inventory yielding measures of the impact of illness on various domains of everyday life, as well as an overall disability score. Nottingham Health Profile (NHP) – A 24 item inventory quantifying the impairments due to illness in six areas.
Source of funding:	The study was funded by the Cohen Bequest and the Scottish Office, Home & Health Department
Does the study answer the question?/Further Comments	Yes. Treatment significantly reduced chest pain episodes (p<0.01). There were significant improvements in anxiety and depression scores (p<0.05), disability rating (p<0.0001) and exercise tolerance (p<0.05).

Schuler G;Hambrecht R;Schlierf G;Niebauer J;Hauer K;Neumann J;Hoberg E;Drinkmann A;Bacher F;Grunze M;.;

Regular physical exercise and low-fat diet. Effects on progression of coronary artery disease

Ref ID 9192 **RID:** 822 1992 Jul

QUALITY

A. Selection bias (systematic differences between the comparison groups)

A4 Based on your answers t, in your opinion was selection bias present? If so, what is the likely direction of its effect?:

Low risk of bias

Direction =

B. Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)

B4 Based on your answers to the above, in your opinion was performance bias present? If so, what is the likely direction of its effect?:

Low risk of bias

Direction =

C. Attrition bias (systematic differences between the comparison groups with respect to loss of participants)

C4 Based on your answers to the above, in your opinion was attrition bias present? If so, what is the likely direction of its effect?:

High risk of bias

Direction = More patients did not complete treatment in the intervention group than in the control group. There were

D. Detection bias (bias in how outcomes are ascertained, diagnosed or verified)

D6 Based on your answers to the above, in your opinion was detection bias present? If so, what is the likely direction of its effect?:

Unclear.

Direction = The study examined effect of exercise on myocardial perfusion. It did not specify what changes would constitute a clinical improvement.

Overall Study Quality -Strengths and Weaknesses:

This was a study of n=113 men with angina. Only compliant and responsive subjects were selected for this study, so results are likely to be better than those which would be found in a general population of patients with angina. Patients were randomised using proper methods. Technicians conducting tests were kept blind to treatment, but the study gives very little information on how many other investigators were blind to the patient's allocated treatment group. More patients dropped out of the study before treatment was complete in the exercise group (29% vs. 9% in the control group). No allowance was made for this in analysis of final dataset. Therefore, the health benefits gained in the exercise group will be an overestimate.

DETAILS

# of patients:

n=113: n=57 in the intervention group (exercise) and n=56 in the control group (normal care).

Prevalence (Diagnostic):

Patient Characteristics

	Intervention	Control
No. of randomized patients	56	57
Age (years)	52.8±5.8	54.2+7.7
Previous AMI (No.) (%)	31(60)	40(70)
LVEF (%)	57±9	55±8
Body mass index (kg/M2)	26.7±2.5	26.4±2.2
Cholesterol (mmol/l)	6.05±1.00	6.09±1.03
HDL (mmol/l)	0.92±0.24	0.91±+0.18

LDL (mmol/l)	4.24±0.69	4.25±0.85
Triglycerides (mmol/1)	1.97±0.81	2.16±1.24
Resting heart rate (1/min)	74+11	76±12
Resting systolic blood pressure (mm Hg)	128±19	128±21
Tl perfusion defect	44±440	42±370

AMI, acute myocardial infarction; LVEF, left ventricular ejection fraction; HDL, high density lipoproteins; LDL, low density lipoproteins.
No significant difference between groups was detected for any variable (Mann-Whitney rank sum test, X2 analysis).

Interventions/ Test/ Factor being investigated

Regular physical exercise and low-fat diet. Patients in the intervention group had 3 weeks of instruction on how to lower fat in their diet. They were asked to exercise daily at home on a cycle ergometer for a minimum of 30 mins and at close to their target heart rates. Also expected to participate in at least two group trainings session of 60 mins each week. Anti anginal drugs allowed at these times. Info sessions throughout the year on diet and exercise. Control group simply given information at start of trial about importance of low fat diet and exercise. Neither group took lipid-lowering medications.

Comparisons

Intervention is being compared with usual care.

Length of Study/ Follow-up

12 months

Outcome measures studied

The study did not explicitly specify primary and secondary outcomes. In the introduction its stated aim was to assess the effects of the intervention on myocardial perfusion and progression of coronary atherosclerosis. Other outcomes measured were dietary changes, metabolic variables (e.g. BMI and cholesterol levels) and hemodynamic variables (e.g. heart rate and blood pressure), blood rheology,and psychological changes. Descriptive statistics were presented on deaths, drop outs and cardiac arrests.It did not report on improvement in angina symptoms.

Results

Study results relevant to question 10 (deaths, non-fatal myocardial infarction, and psychological
changes).

In the exercise group there were 2/56 deaths (both cardiac arrest) compared to 1/57 in the control group (from cancer). In the intervention group there were no reported non-fatal myocardial infarctions compared to one patient who suffered a non-fatal myocardial infarction and two patients had angioplasty for evolving myocardial infarction. There was no difference between groups in the degree of depression at 12 months. A significant change was detected in the intervention group on one of the health locus-ofcontrol scales: Patients' personal-external orientation
decreased from 22.8+/-5.4 to 20.8+/-5.2 ($p<0.05$); at the same time, the control group's tended to increase
(21.9+/-6.5 versus 23.2±6.0,$p>0.30$), resulting in a significant interaction effect ($p<0.05$).

Effect Size

Source of funding:

Supported by a grant from Bundesministerium fir Forschung und Technologie, Bonn, FRG

Does the study answer the question?/Further Comments

Unsure. There are very few outcomes in this study which are of relevance to the review question. Some data are reported for number of deaths and cardiac arrests but these were not specified outcomes. They were simply described as part of patient disposition descriptions for the intervention and control groups. In addition, there were a high number of patients dropping out of the exercise group. For 29% of this group no outcome data were available. If they all dropped out because of ill health or death then the benefits from exercise as reported in this study will be overestimated.

Todd IC;Ballantyne D;

Antianginal efficacy of exercise training: a comparison with beta blockade

Ref ID 601 **RID:** 794 1990

QUALITY

A. Selection bias (systematic differences between the comparison groups)

A4 Based on your answers t, in your opinion was selection bias present? If so, what is the likely direction of its effect?:

Unclear/unknown risk

Direction = The two groups were different at baseline. The overall trend was for the exercise group to be less fit. Given that

B. Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)

B4 Based on your answers to the above, in your opinion was performance bias present? If so, what is the likely direction of its effect?:

Unclear/unknown risk

Direction = The risk of bias is unclear. The study did not report any methods of blinding investigators or clinicians.

C. Attrition bias (systematic differences between the comparison groups with respect to loss of participants)

C4 Based on your answers to the above, in your opinion was attrition bias present? If so, what is the likely direction of its effect?:

Low risk of bias

Direction =

D. Detection bias (bias in how outcomes are ascertained, diagnosed or verified)

D6 Based on your answers to the above, in your opinion was detection bias present? If so, what is the likely direction of its effect?:

Unclear

Direction = No information was given about blinding investigators to patient group allocation so the risk of detection bias is unknown.

Overall Study Quality -Strengths and Weaknesses:

The study aimed to compare the effectiveness of B-blockers and the effectiveness of exercise in improving exercise tolerance in patients with angina at 1 year. The study was small (n=20 in the exercise group and n=20 in the control group) and no power calculations were performed to determine the appropriate sample size. No information was reported for methods of randomisation, or concealment of allocation to investigators. Although exercise tolerance was the main outcome and a number of variables were measured, the preferred outcome (for this review question) of total exercise time was not measured.

DETAILS

# of patients:

n=40 (n=20 in the exercise group and n=20 in the control group). All study patients were given atenolol for 2 weeks and then atenolol was stopped 4 wks before they

Prevalence (Diagnostic):

Patient Characteristics

The mean age for the exercise group was 53 (range 45-60) with a mean duration of angina of 20-0 months, while the mean age for the controls was 51 (range 37- 60) with a mean duration of angina of 12-7 months. There was a low overall incidence of smoking although many patients were former smokers, most having stopped since diagnosis. Randomisation produced groups whose baseline measurements differed statistically in only one respect. The mean (SD) maximum ST depression for the control group (1.5 (0.8) mm) was significantly less than that for the exercise group (1.9 (0.9) mm). Quite large variations in other variables were, however, not statistically significant. Most notable among these differences was the time to 1 mm ST depression, which was twice as long in the controls as in the exercise group. The overall trend was for the exercise group to be less fit, as judged by resting and submaximal heart rate, and to have more severe disease, judged by maximum heart rate and double product, maximum ST depression, and double product ST threshold.

Interventions/ Test/ Factor being investigated

The intervention is a one-year intensive exercise training programme. The training group undertook the Canadian Airforce Programme for Physical Fitness. It is a brief (11 minutes) daily exercise programme of five callisthenic type exercises.Exercise levels increase in intensity each week to achieve a progressive increase in physical fitness.

Comparisons

The main comparison is between the exercise training programme (n=20) and B-blockers (same patients) with regard to exercise tolerance. In addition, a further comparison is made between the exercise training programme patients and those who did not receive the exercise programme. Instead patients in the control group were informed that mild exercise could be beneficial and were advised on diet and smoking habits.

Length of Study/ Follow-up

Results of exercise testing were performed for all study patients after 2 weeks of atenolol treatment and before they were randomised to exercise/control. Exercise testing was done on patients in the exercise group and in the control group at 1 year.

Outcome measures studied

The study did not specify any primary or secondary outcomes. Instead, the study examined three broad groups of variables: (a) those which reflect "fitness"-that is resting and submaximal heart rates; (b) those which reflect disease severity-that is maximum heart rate, maximum double product (heart rate x systolic pressure), maximum ST depression, and double product ST threshold (double product at which 1 mm of horizontal or downsloping ST depression was first recorded); and (c) those that reflect a combination of fitness and disease severity-that is treadmill time, estimated workload, and time to 1 mm ST depression.

Results

Effect of training and atenolol on variables of treadmill performance

	Exercise group			Control group	
	Baseline	Atenolol	One year	Baseline	Oneyear
	N=17	n=17	n=17	n=17	n=17
	mean(SD)	mean(SD)	mean(SD)		
RestingHR	81(12)	64(8)	76(10)	74(10)	75(9)
Stage I HR	111(19)	88(11)	98(15)	106(16)	102(10)
Stage II HR	116(19)	93(13)	103(16)	110(18)	106(10)
Max HR	128(17)	109(12)	138(21)	136(22)	134(24)
Max DP	219(55)	164(44)	244(67)	259(74)	248(74)
DP ST threshold	183(51)	143(43)	205(64)	227(75)	206(60)
Max ST depression	1.9(0.9)*	1.6(1.0)	1.6(1.2)	1.5(0.8)*	1.4(0.8)

Time to 1 mm ST dep
374(369)** 749(439) 881(668) 719(560)
715(580)
Log time to 1 mm ST dep
2.37(0.44) - -
2.68(0.46) -
Treadmill time(s) 741(356) 974(430) 1272(514)
1006(504) 1010(546)
Workload (METS) 6.3 (1.9) 7.6(2.2) 9.5(2.9) 7.8
(2.8) 8.0(3.1)
DP, double product; HR, heart rate. *p < 0.05. **Non-normal data by "goodness of fit" test.

Effect Size

Effect of training and atenolol on variables of treadmill performance

	Exercise group			Control group
	Baseline	Atenolol	One year	Baseline
Oneyear				
	N=17	n=17	n=17	n=17
n=17				
	mean(SD)	mean(SD)	mean(SD)	
mean(SD) mean(SD)				
RestingHR	81(12)	64(8)	76(10)	
74(10) 75(9)				
Stage I HR	111(19)	88(11)	98(15)	106(16)
102(10)				
Stage II HR	116(19)	93(13)	103(16)	110(18)
106(10)				
Max HR	128(17)	109(12)	138(21)	
136(22) 134(24)				
Max DP	219(55)	164(44)	244(67)	
259(74) 248(74)				
DP ST threshold	183(51)	143(43)	205(64)	
227(75) 206(60)				
Max ST depression	1.9(0.9)*	1.6(1.0)	1.6(1.2)	1.5(0.8)*
1.4(0.8)				
Time to 1 mm ST dep				
	374(369)**	749(439)	881(668)	719(560)
715(580)				
Log time to 1 mm ST dep				
	2.37(0.44)	-	-	
2.68(0.46) -				
Treadmill time(s)	741(356)	974(430)	1272(514)	
1006(504) 1010(546)				
Workload (METS)	6.3 (1.9)	7.6(2.2)	9.5(2.9)	7.8
(2.8) 8.0(3.1)				

DP, double product; HR, heart rate. *p < 0.05. **Non-normal data by "goodness of fit" test.

Source of funding:

Not reported.

Does the study answer the question?/Further Comments

Although this is an RCT the main comparison of interest in the study is between two treatments (atenolol and exercise training programme) both of which were received by the same group of patients. Before patients were randomised to exercise or control groups they all received atenolol and were assessed for exercise tolerance. After 4 weeks of no treatment they were then randomised to exercise or control. Results are presented then for 3 patient groups: a) those in the exercise group who received atenolol b) those in the exercise group after 1 year intensive exercise training and c) those in the control group.

Tyni-Lenne R;Stryjan S;Eriksson B;Berglund M;Sylven C;

Beneficial therapeutic effects of physical training and relaxation therapy in women with coronary syndrome X

Ref ID 9178 **RID:** 808 2002

QUALITY

A. Selection bias (systematic differences between the comparison groups)

A4 Based on your answers t, in your opinion was selection bias present? If so, what is the likely direction of its effect?:

Low risk of bias

Direction = Randomisation and concealment methods were not clear. But the outcomes were objective measures and

B. Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)

B4 Based on your answers to the above, in your opinion was performance bias present? If so, what is the likely direction of its effect?:

Low risk of bias

Direction = The study states clearly that this was a single blind study but gives no information on how investigators were

C. Attrition bias (systematic differences between the comparison groups with respect to loss of participants)

C4 Based on your answers to the above, in your opinion was attrition bias present? If so, what is the likely direction of its effect?:

Low risk of bias

Direction =

D. Detection bias (bias in how outcomes are ascertained, diagnosed or verified)

D6 Based on your answers to the above, in your opinion was detection bias present? If so, what is the likely direction of its effect?:

Unclear.

Direction = The study was relatively short (8 weeks) but length of follow-up was the same for all three groups.

Overall Study Quality -Strengths and Weaknesses:

This is a small study (n=24) which compares physiotherapy led exercise and relaxation training with controls who have no training. It shows that there are benefits from exercise and relaxation training using objective measures. However, it is more an exploratory study given that it is relatively small study, with a very short follow-up (8 weeks) and no primary outcome was specified.

DETAILS

# of patients: n=24 (n=8 in each of the three groups). One subject dropped out of each of the three groups before study end.

Prevalence (Diagnostic):

Patient Characteristics Baseline characteristics of study patients

	Exercise training	Relaxation training	Non-training

	A (n = 7)	B (n = 7)	C (n = 7)
Age (years)	55 (±9)	59 (±5)	55 (±8)
Weight (kg)	68 (±6)	72 (±6)	73 (±8)
History of angina (months)	42 (±39)	44 (±38)	43 (±34)
Smoking status			
smoker	0	0	0
previous smoker	4	1	2
non-smoker	3	6	5

Data presented are mean values (± SD) and number of patients.

Interventions/ Test/ Factor being investigated

Training programmes were carried out as an outpatient activity in a group under the supervision of a physical therapist. Group A carried on with endurance training on a cycle ergometer three times a week for eight weeks at the intensity of 50% of the peak work rate achieved in VO2max test. The training time was 30 minutes. Group B performed relaxation
training twice a week for eight weeks. Relaxation training consisted of a modified Jacobson's approach (Jacobson, 1978) and autogenous training (Gruden, 1999) for one hour at a time. Group C engaged only in their normal daily activities.

Comparisons

Comparisons are made between all of the groups.

Length of Study/ Follow-up

8 week follow-up period.

Outcome measures studied

No primary or secondary outcomes were specified. Outcomes included exercise capacity, a six-minute walk test and quality of life.Peak exercise capacity was assessed by a symptom-limited exercise test on a cycle ergometer with continuous respiratory gas analyses. Starting at 30 W, stepwise increments of 10 W every minute were used
(A° ström and Jonsson, 1976).A standardized six-minute walk test was used to assess functional exercise capacity
related to daily activities (Gyatt, 1987;Lipkin et al., 1986). Two trials were performed and the second test was recorded.
Subjects walked as long a distance as possible during six minutes on the pre-marked 70-m
walkway.

For quality of life, self-reported data on subjects' general coping capacity were collected by use of the Sense of Coherence (SOC) questionnaire (Antonovsky, 1993).Higher SOC scores are indicative of better coping capacity.Self-reported data on dysfunctional stress reactions were collected using a Swedish version of the Stress and Crisis
Inventory (SCI-93) questionnaire (Nyström and Nyström, 1996). SCI-93 questionnaire quantifies perceived psychological, muscular and autonomous symptoms. This questionnaire consists of 28 items on a sixpoint
scale. The Swedish version of the instrument has shown good validity and reliability, and lower scores are indicative of
lower symptom experience. Data on the perceived health-related quality of life were further collected by means of the Sickness Impact Profile (SIP) questionnaire (Bergner et al., 1981). This extensive instrument includes 136 questions assessing a range of physical activities and psychological features (Turk and Okifuji, 1999). The validity and reliability of this instrument have been tested in a normal population and in patients with a variety of chronic diseases.
Lower SIP scores are indicative of a better quality of life.

Results

Exercise capacity

			p Value		
			Before versus	After versus	Within-group
	non-training	relaxation			
Peak work rate (W)					
Physical training (A)	97 (±5)	127 (±14)	<0.002	<0.002	<0.0001
Relaxation (B)	91 (±15)	89 (±11)			

NS			NS		–
Non-training (C)			93 (±16)		94 (±10)
NS			–		–

Data presented are mean value (± SD).
W=watt.

Six minute walking

			p Value		
			Before	After	Within-group
			versus	versus	
non-training	relaxation	Distance walked (m)			
Physical training (A)			555 (±47)		587 (±49)
<0.006			<0.003		<0.0004
Relaxation (B)			573 (±54)		565 (±47)
NS			NS		–
Non-training ©			576 (±64)		545 (±46)
NS			–		
–					

Quality of life

			p Value		
			Before	After	Within-group
			versus	versus	
non-training	relaxation	Sense of Coherence (score)			
Physical training (A)			148 (135–162)		155 (128–166)
NS			NS		NS
Relaxation (B)			144 (127–161)		140 (130–164)
NS			NS		–
Non-training (C)			146 (116–187)		144 (126–185)
NS			–		–
Stress Crisis Inventory (score)					
Physical training (A)			33 (19–80)		26 (8–62)
<0.02			<0.006		NS
Relaxation (B)			44 (31–83)		43 (22–65)
NS			<0.04		–
Non-training (C)			44 (12–45)		40 (16–57)
NS			–		–
Sickness Impact Profile (score)					
Physical training (A)			7 (2–23)		4 (1–9)
<0.02			<0.02		NS
Relaxation (B)			9 (2–20)		9 (2–15)
<0.03			<0.009		–
Non-training (C)			6 (1–22)		9 (2–23)
NS			–		–

Data presented are median and (range).

Effect Size

Exercise capacity

			p Value		
			Before	After	Within-group
			versus	versus	
non-training	relaxation				
Peak work rate (W)					
Physical training (A)			97 (±5)		127 (±14)
<0.002			<0.002		<0.0001
Relaxation (B)			91 (±15)		89 (±11)
NS			NS		–
Non-training (C)			93 (±16)		94 (±10)
NS			–		–

Data presented are mean value (± SD).

W=watt.

Six minute walking

				p Value	
		Before	After	Within-group	
		versus	versus		
non-training	relaxation	Distance walked (m)			
Physical training (A)		555 (±47)	587 (±49)	<0.006	<0.003
<0.0004					
Relaxation (B)		573 (±54)	565 (±47)	NS	NS
–					
Non-training ©		576 (±64)	545 (±46)	NS	–
–					

Quality of life

				p Value	
		Before	After	Within-group	
		versus	versus		
non-training	relaxation	Sense of Coherence (score)			
Physical training (A)		148 (135–162)	155 (128–166)	NS	NS
NS					
Relaxation (B)		144 (127–161)	140 (130–164)	NS	NS
–					
Non-training (C)		146 (116–187)	144 (126–185)	NS	–
–					
Stress Crisis Inventory (score)					
Physical training (A)		33 (19–80)	26 (8–62)	<0.02	<0.006
NS					
Relaxation (B)		44 (31–83)	43 (22–65)	NS	<0.04
–					
Non-training (C)		44 (12–45)	40 (16–57)	NS	–
–					
Sickness Impact Profile (score)					
Physical training (A)		7 (2–23)	4 (1–9)	<0.02	<0.02
NS					
Relaxation (B)		9 (2–20)	9 (2–15)	<0.03	<0.009
–					
Non-training (C)		6 (1–22)	9 (2–23)	NS	–
–					

Data presented are median and (range).

Source of funding: Not reported.

Does the study answer the question?/Further Comments Yes. The study shows that after 8 weeks female patients with syndrome X benefit from physical training in terms of exercise capacity and quality of life and from relaxation therapy in terms of quality of life.

Zetta S;Smith K;Jones M;Allcoat P;Sullivan F;

Evaluating the Angina Plan in Patients Admitted to Hospital with Angina: A Randomized Controlled Trial

QUALITY

A. Selection bias (systematic differences between the comparison groups)

A4 Based on your answers t, in your opinion was selection bias present? If so, what is the likely direction of its effect?:

Low risk of bias

Direction =

B. Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)

B4 Based on your answers to the above, in your opinion was performance bias present? If so, what is the likely direction of its effect?:

Low risk of bias

Direction =

C. Attrition bias (systematic differences between the comparison groups with respect to loss of participants)

C4 Based on your answers to the above, in your opinion was attrition bias present? If so, what is the likely direction of its effect?:

Low risk of bias

Direction =

D. Detection bias (bias in how outcomes are ascertained, diagnosed or verified)

D6 Based on your answers to the above, in your opinion was detection bias present? If so, what is the likely direction of its effect?:

Low risk of bias

Direction =

Overall Study Quality -Strengths and Weaknesses:

Strengths – Random allocations were computer generated, allocated to permuted fixed blocks of 20 and stratified for site. The researcher was blinded to group allocation throughout the trial. ITT reported.
Weakness - none

DETAILS

# of patients:

N=218 (n=109- standard care) (n=109 Angina Plan)

Prevalence (Diagnostic):

Patient Characteristics

Baseline characteristics:
Variable: Standard care (n=109) ; Angina Plan
Mean age (SD): 65.94 (9.96); 64.8 (10.04)
Number of males: 71 (65%); 78 (72%)
Females: 38 (35%); 31 (28%)
Presence of CHD and/or angina: 87 (80%); 94 (86%)
Previous diagnosis of unstable angina: 51 (47%); 57 (52%)
Previous MI: 48 (44%); 50 (46%)
Procedure performed in the past
PTCA: 21 (19%); 25 (23%)
CABG: 20 (18%); 22 (20%)

	Presence of peripheral vascular disease: 9 (8%); 6(6%) Previous cerebro vascular event: 11 (10%); 12 (11%) Diabetes: 24 (22%); 18 (17%) Family history of CHD: 78 (72%); 67 (62%) Hypertension diagnosis: 70 (64%); 59 (54%) Inclusion criteria: Patients who are living in the hospital catchment area; able to speak, read and understand English; either sex; aged 18 or over; definite angina based on clinical history, a positive exercise tolerance test, negative cardio-specific enzyme measurement or past coronary angiography. Exclusion criteria: Patients who have current symptoms of psychosis or dementia; life threatening co-morbidities, or a concurrent illness (es) preventing participation based on clinical opinion; patients who are unable to comply with the trial procedure; patients who are currently attending Cardiac rehabilitation for a previous cardiac event.
Interventions/ Test/ Factor being investigated	Angina Plan – During a 45 minute in-hospital consultation the AP nurse completed an assessment and initiated the AP intervention, which was then facilitated over the next 12 weeks. The patients' cardiac misconceptions were identified using the brief questionnaire within the AP pack at the start of the consultation to allow the nurse to proactively target and correct these misconceptions. Individual cardiovascular risk was assessed and advice on risk factor modification given. Participants received the AP, which included a patient-held 'work-book' and an audio taped relaxation and information programme. The work-book provided information on angina and its management, cardiovascular risk, relaxation, exercise and goal setting and pacing techniques. Over the following 12 weeks a method of 'goal setting and pacing' based on the principles of CBT was used by the AP facilitator introduce lifestyle changes and support recovery during telephone follow-up at weeks 1,4, 8 and 12 for all participants in the AP group.
Comparisons	Standard care – A minimal intervention by nurses during their admission which identified patients risk factors , provided advice on their condition and risk factor reduction where possible depending on staff workload and skill mix.
Length of Study/ Follow-up	6 months
Outcome measures studied	Anxiety (HAD scale) was the primary outcome measure. The other outcomes were knowledge and misconceptions (Angina Beliefs questionnaire), cardio vascular symptoms (Seattle angina questionnaire and the Cardiovascular Limitations and Symptoms Profile (CLASP).
Results	
Effect Size	Results: Outcomes: Standard care vs. Angina Plan group Misconceptions/knowledge: 26.43 (6.81) vs. 22.15 (7.38) HADS* anxiety: 2.41 (0.95) vs. 2.16 (1.08) HADS depression: 2.15 (0.86) vs. 2.00 (0.93) CLASP* angina: 8.22 (2.56) vs. 8.77 (2.85) CLASP SOB: 8.51 (3.15) vs. 8.33 (2.90) CLASP ankle swelling: 5.17 (2.34) vs. 6.26 (2.22) CLASP tiredness: 6.76 (1.68) vs. 6.57 (1.88) CLASP mobility: 9.25 (3.35) vs. 9.07 (3.30) CLASP social/leisure: 4.67 (1.53) vs. 4.39 (1.52) CLASP concerns: 2.29 (0.44) vs. 2.24 (0.44) CLASP sex: 6.81 (3.32) vs. 6 (3.15) SAQ exertional capacity: 59.39 (23.77) vs. 63.51 (26.16) SAQ* anginal frequency: 70.81 (28.35) vs. 70.32 (27.92) SAQ disease perception: 66.21 (23.73) vs. 71.77 (23.93) SF-36 physical function: 55.66 (28.13) vs. 57.96 (28.33) SF-36 energy and vitality: 48.51 (22.93) vs. 50.45 (23.59) SF-36 pain: 59.47 (28.58) vs. 61.43 (28.27) SF-36 GH perception: 50.53 (23.45) vs. 53.01 (24.79) SF-36 change in health: 49.21 (26.01) vs. 49.41 (24.76) SEIQol-DW Qol score: 73.36 (16.76) vs. 73.55 (15.19)

*Hospital Anxiety and Depression scale (HADS): 14 item tool with 2, seven item subscales to measure anxiety and depression within a non psychiatric population. A score from 0 to 3 for each item generated a total score (range 0 to 21 for each sub scale. Scores between 8 and 10 indicate borderline presence of anxiety or depression and those above suggest that these states may be present.
Knowledge and misconceptions were assessed using the 14 item York Angina Beliefs Questionairre. This uses a Likert scale response format ranging 'strongly agree' to 'strongly disagree'. Items targeted the cause, physiology and coping with angina. Summation and transformation of the item scores generated a scale total ranging from 0-56 with higher numbers indicating more misconceptions.
The Seattle Angina Questionnaire is a disease specific health related quality of life measure comprised of a 19 item questionnaire measuring five dimensions of coronary artery disease: physical limitation, angina stability, anginal frequency, treatment satisfaction and disease perception. Each dimension is scored separately on a 0-100 scale with higher scores indicating better functioning.
The Cardiovascular Limitations and Symptoms Profile (CLASP) measures nine physical and functional dimensions, including four symptom subscales (angina, shortness of breath, tiredness, ankle swelling) and five subscales focusing on functional limitations (mobility, social life and leisure activities, activities within the home, concerns and worries, sexual activity). Each of the nine subscales is scored separately to calculate a specific measure of impairment.
Quality of life was measured using two instruments. The Short Form 36 Health Survey (SF-36) is a 36 item questionnaire assessing general health and QoL. The 8 dimensions of SF-36 (physical functioning, role limitations caused by emotional problems, bodily pain, social functioning, mental health, role limitations caused by emotional problems, vitality-energy/fatigue and general health perception) generates scores on each dimension between 0 and 100, with higher scores representing better health status. The second the Schedule for the Evaluation of Individual Quality of Life –Direct Weighting (SEIQol-DW) is an interview based tool specifically designed for the assessment of individual quality of life. Using the SEIQoL-DW participants define five areas that comprise their individual 'quality' of life. These items are rated in terms of level of importance. An overall score ranging from 0-100 is then calculated with higher scores reflecting better quality of life. The SEIQoL-DW is totally subjective and patient centred and provides a relatively unique measure of quality of life.

Source of funding:

The study was supported by a grant provided by the Chief Scientist Office.

Does the study answer the question?/Further Comments

Yes. Angina Plan reported increased knowledge, less misconceptions, an increase in self-reported exercise, less functional limitation, and improvements in general health perceptions and social and leisure activities compared to those receiving standard care. There was no significant difference in between-group change scores for anxiety or depression.

Evidence Table

Question: What is the clinical /cost effectiveness of angina specific interventions to modify lifestyle/CVD risk factors to reduce symptoms, morbidity and mortality and improve quality of life in angina patients?

Study Type	Randomised Controlled Trial

Anderson TW;

Vitamin E in angina pectoris

Ref ID 15907 **RID:** 1164 1974 Feb 16

QUALITY

A. Selection bias (systematic differences between the comparison groups)

A4 Based on your answers t, in your opinion was selection bias present? If so, what is the likely direction of its effect?:

Unclear/unknown risk **Direction =**

B. Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)

B4 Based on your answers to the above, in your opinion was performance bias present? If so, what is the likely direction of its effect?:

Unclear/unknown risk **Direction =**

C. Attrition bias (systematic differences between the comparison groups with respect to loss of participants)

C4 Based on your answers to the above, in your opinion was attrition bias present? If so, what is the likely direction of its effect?:

Unclear/unknown risk **Direction =**

D. Detection bias (bias in how outcomes are ascertained, diagnosed or verified)

D6 Based on your answers to the above, in your opinion was detection bias present? If so, what is the likely direction of its effect?:

Unclear risk of bias **Direction =**

Overall Study Quality -Strengths and Weaknesses:

Strengths- Randomised. Double blind. 33/40 completed 9 full weeks of records. In 5 cases (3 vitamin and 2 placebo) only 8 weeks of records could be used because one record card was incomplete or missing, in one (vitamin group) only 7 weeks of records were available, and one other patient (vitamin) withdrew from the study after 7 weeks because of persistent diarrhoea.
Limitations- allocation concealment not reported. Randomisation was not carried out properly, patients randomised after giving the intervention. Baseline characteristics not well reported. Only subjective data available. Blinding process unclear. ITT not reported.

DETAILS

# of patients:	N=40 (vitamin E (n=20); Placebo (n=20))(n=36 included in the analysis)
Prevalence (Diagnostic):	
Patient Characteristics	Variable: vitamin E (n=20); Placebo (n=20) Age (mean) yrs: 58.4 (57.7); 63.6 (63.2) Duration of angina (yrs): 6.0 (5.8); 5.2 (5.1) Nitroglycerin consumption per week: 20.4 (22.8); 11.0 (10.4) Inclusion criteria:: Physicians were asked to recruit patients whose angina was reasonably stable, who had had no major change in health status (such as acute MI) or a change in usual medications for at least 3 months, and who could be depended on to take their test capsules regularly and keep adequate records. Note: of the 40 patients, four patients had already demonstrated themselves to be 'non reactors' and they were therefore excluded from the main analysis. The remaining 36 were then equally divided between Vitamin and Placebo.
Interventions/ Test/ Factor being investigated	Vitamin E capsules (3200 IU per day). The form of vitamin E used in this study was the succinate. The treatment was for 9 weeks.
Comparisons	placebo tablets.
Length of Study/ Follow-up	At the end of 9 week treatment.
Outcome measures studied	improvement in angina, NTG consumption, change in pain
Results	
Effect Size	Angina symptoms: Change in symptoms: Vitamin (n=20) vs. Placebo (n=20) Much improved: 1 vs. 0 Improved: 4 vs. 3 Slightly improved: 0 vs. 2 No change: 13 vs. 12 Slightly worse: 0 vs. 1 Nitroglycerin consumption was higher in the vitamin group from the start, and the mean weekly intake rose from 18.7 in the first week to 23.5 in the last week. In the placebo patients the corresponding figures were 10.9 and 6.4 (standard deviations not reported). The authors report that the interpretation of these changes was made difficult by the fact that they were due largely to one or two patients in each group who had a large initial intake and showed great variation. One patient in the vitamin group had an average weekly consumption of 180 nitroglycerin tablets- more than the entire placebo group combined. Most patients in each group showed little change in the nitroglycerin consumption during the trial. Most of the patients also showed little change in pain or activity scores at the end of the trial compared to the beginning. The change in activity scores was more favourable to the vitamin group, but the difference between the groups was not statistically significant. (actual values not reported).
Source of funding:	Webber pharmaceuticals supplied vitamin and placebo capsules
Does the study answer the question?/Further Comments	Yes. There was no statistically significant difference between fish oil and control group for improvement in angina, NTG consumption, and change in pain at the end of 9 week treatment.

Aucamp AK;Schoeman HS;Coetzee JH;

Pilot trial to determine the efficacy of a low dose of fish oil in the treatment of angina pectoris in the geriatric patient

Ref ID 415 **RID:** 1167 1993 Sep

QUALITY

A. Selection bias (systematic differences between the comparison groups)

A4 Based on your answers t, in your opinion was selection bias present? If so, what is the likely direction of its effect?:

Unclear/unknown risk **Direction =**

B. Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)

B4 Based on your answers to the above, in your opinion was performance bias present? If so, what is the likely direction of its effect?:

Unclear/unknown risk **Direction =**

C. Attrition bias (systematic differences between the comparison groups with respect to loss of participants)

C4 Based on your answers to the above, in your opinion was attrition bias present? If so, what is the likely direction of its effect?:

Unclear/unknown risk **Direction =**

D. Detection bias (bias in how outcomes are ascertained, diagnosed or verified)

D6 Based on your answers to the above, in your opinion was detection bias present? If so, what is the likely direction of its effect?:

Unclear risk of bias **Direction =**

Overall Study Quality -Strengths and Weaknesses:

Strengths- Placebo controlled cross-over trial. Single blind. 23 patients completed the trial: 11 patients taking placebo in phase 1(group A) and 12 patients taking the active fish oil in phase 1 (group B). Very little baseline characteristics reported. Limitations- Very little detail provided regarding baseline characteristics of patients. No ITT reported. Poorly reported trial.

DETAILS

# of patients: N=28 (cross over trial)

Prevalence (Diagnostic):

Patient Characteristics	28 patients, average age 74.5 years, with the diagnoses of stable angina pectoris, entered the trial. All patients received placebo capsules during a 2 week pre-trial period, and were then randomised to 12 weeks active (or placebo) capsules (phase 1), then placebo capsules during a 4 week wash out period, and lastly placebo (or active) treatment for 12 weeks (phase 2)
Interventions/ Test/ Factor being investigated	Fish oil capsules for 12 weeks. 12 fish oil capsules of 500 mg each taken after meals. 4 week wash out period between treatments. Patients were instructed to continue with existing vasodilator therapy.
Comparisons	Placebo for 12 weeks. 12 olive oil capsules (placebo) taken after meals.
Length of Study/ Follow-up	At the end of the trial.
Outcome measures studied	no. of anginal attacks per 30 days, average severity per attack per day, average duration of an attack per patient , average number of sublingual tablets taken per 30 days.
Results	
Effect Size	Group A (placebo in phase 1 and fish oil capsules in phase 2) Outcome: Placebo vs. fish oil Number of anginal attacks per 30 days: 22.1 (31.1) vs. 11.2 (18.2) Duration of attack (min): 2.2 (0.8) vs. 2.1 (1.3) Intensity of pain: 3.5 (1.5) vs. 3.8 (2.8) Number of sublingual tablets consumed: 17 (16.8) vs. 8.8 (12.5) Group A: The average no. of attacks per 30 days with fish oil capsule differed significantly from that with placebo ($p<0.02$). The mean duration of attacks per patient, using fish oil capsules or placebo did not differ significantly. The mean intensity of pain per attack per patient, using fish oil capsules or placebo did not differ significantly. The mean no. of sublingual tablets consumed by patients on fish oil capsules differed significantly from those taking placebo. Group B (Fish oil capsules in phase 1 and placebo in phase 2) Outcome: Fish oil capsules vs. Placebo Number of anginal attacks per 30 days: 12.9 (13.7) vs. 14.7 (22.4) Duration of attack (min): 1.8 (0.5) vs. 1.6 (0.8) Intensity of pain: 2.5 (1.2) vs. 2.4 (1.6) Number of sublingual tablets consumed: 17 (22.5) vs. 20.1 (34.0) Group B: None of the parameters monitored differed significantly when treatments with fish oil are compared with placebo. Note: No. of participants completing the trial only reported for Phase 1 patients but not phase 2.
Source of funding:	not reported
Does the study answer the question?/Further Comments	Yes. The results indicated a significant reduction in the number of anginal attacks, as well as a significant reduction in the consumption of sublingual isosorbide dinitrate tablets.

Burr ML;Ashfield-Watt PA;Dunstan FD;Fehily AM;Breay P;Ashton T;Zotos PC;Haboubi NA;Elwood PC;

Lack of benefit of dietary advice to men with angina: results of a controlled trial

Ref ID 15912 **RID:** 1157 2003 Feb

QUALITY

A. Selection bias (systematic differences between the comparison groups)

A4 Based on your answers t, in your opinion was selection bias present? If so, what is the likely direction of its effect?:

Unclear/unknown risk

Direction =

B. Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)

B4 Based on your answers to the above, in your opinion was performance bias present? If so, what is the likely direction of its effect?:

Unclear/unknown risk

Direction =

C. Attrition bias (systematic differences between the comparison groups with respect to loss of participants)

C4 Based on your answers to the above, in your opinion was attrition bias present? If so, what is the likely direction of its effect?:

High risk of bias

Direction =

D. Detection bias (bias in how outcomes are ascertained, diagnosed or verified)

D6 Based on your answers to the above, in your opinion was detection bias present? If so, what is the likely direction of its effect?:

Unclear risk of bias

Direction =

Overall Study Quality -Strengths and Weaknesses:

Strengths-Randomised. Baseline characteristics reported,
Limitations-Loss to follow-up not reported. ITT not reported. Allocation concealment not reported.

DETAILS

# of patients:

N= 3114 (n=764 in the fish advice group, n=779 in the fruit advice group, n=807 fish+fruit advice group, n=764 in sensible eating group)

Prevalence (Diagnostic):

Patient Characteristics

Inclusion: Men under 70 years of age with stable angina. General practitioners in south Wales were asked to identify patients for whom they prescribed nitrates (as tablets, sprays or patches) or other treatment for angina.
The following subjects were excluded from the trial: men who denied ever having exertional chest pain or discomfort (except for men who never hurried whose pain was brought on by stress); men awaiting CABG; men who already ate oily fish twice a week; men who could not tolerate oily fish or fish oil; men who appeared to be unsuitable on other grounds (eg other serious illness, likelihood of moving out of the area).

A dietician randomly assigned the subjects to 4 groups, using prepared envelopes

to be advised to eat: Oily fish; fruit and vegetables; combination of these two; 'sensible ating' -non specific advice.

Baseline characteristics:
Variables: Fish advice group; Fruit advice group; Fish+Fruit; sensible eating
No. of subjects: 764; 779; 807; 764
Mean age (yrs): 61; 61; 61.1; 61.2
Percentage with history of
Heart attack: 49.6; 48.3; 49.8; 52.2
Hypertension: 49; 45.8; 48.1; 49.1
Diabetes: 11.3; 11.6; 13.7; 13.1
Percentage on BB: 42.5; 41.6; 42.4; 39.5

The baseline characteristics were broadly similar in the groups; those allocated to sensible eating were slightly more likely than the others to give a history of a heart attack, and slightly less likely to be taking a BB, while the fruit group had a lower prevalence of a history of hypertension than the rest.

Interventions/ Test/ Factor being investigated

1) To eat at least two portions of oily fish each week, or to take up to 3 g of fish oil as a partial or total substitute. Fish oil capsules were supplied to men who were advised to eat fish but found it unpalatable; for part of the trial, the fish group was sub randomised to receive either fish advice or capsules. 2)To eat four to five portions of fruits and vegetables and drink at least one glass of natural orange juice daily, and also increase the intake of oats, so as to obtain a higher intake of vitamin C and at least 8g of soluble fibre from all sources everyday. 3) A combination of both these forms of advice. 4) 'Sensible eating'- non-specific advice that did not include either of the above interventions.

Comparisons

All comparisons in the above section.

Length of Study/ Follow-up

Mortality ascertained after 3 to 9 years

Outcome measures studied

Death, cardiac death

Results

Effect Size

Outcome: Fish (n=764) vs. Fruit (n=779) vs. Fish+fruit (n=807) vs. sensible eating (n=764)
Total number of deaths: 141 vs. 133 vs. 142 vs. 142 vs. 109
Number of cardiac death: 94 vs. 72 vs. 86 vs. 67
Number of sudden deaths: 42 vs. 30 vs. 31 vs. 17
Mortality of subjects advised about fish and fruit: adjusted hazard ratio (HR) *

The subjects not given any specific advice had the lowest mortality from all causes, cardiac death and sudden death, while the group advised only about fish or fish oil had the highest mortality.

Outcome: Fish advice vs. Fruit advice
All deaths: 1.15 (0.96 to 1.36) p=0.13 vs. 1.12 (0.94 to 1.34) p=0.20
Cardiac deaths: 1.26 (1.00 to 1.58) p=0.04 vs. 1.00 (0.80 to 1.25) p=1
Sudden deaths: 1.54 (1.06 to 2.23) p=0.02 vs. 1.01 (0.70 to 1.46)
*Hazard ratios adjusted for age, smoking, previous MI, history of high blood pressure, BMI, serum cholesterol, medication, and fruit advice (for fish) and fish advice (for fruit)
The above table shows that those given fish advice had a significantly higher mortality from cardiac and sudden death; fruit advice appeared to have no effect in either direction.

In order to attempt to explain the unexpected excess mortality associated with fish advice, subgroup analyses were carried out. The apparently adverse e effect of fish advice was confine d to the second phase of the trial (data not shown), when a much higher proportion of participants were given fish capsules than in the first phase. During this phase some of the participants in the fish advice group were sub randomised to receive fish oil capsules, so survival analysis was carried out to examine the effect on those sub randomised to capsules rather than to dietary fish advice.

Survival analysis of subjects advised on dietary fish or fish oil: n umber (HR* 95% CI)
Outcome: dietary fish (n=1109) vs. Fish oilcapsules (n=462)
All death: n=198 (HR 1.13 (0.94 to 1.37) p=0.20 vs. n=85 (HR 1.19 (0.92 to 1.54) p=0.19
Cardiac death: n=121 (HR 1.20 (0.93 to 1.53) p=0.16 vs. n=59 (HR 1.45 (1.05 to 1.99) p=0.02
Sudden death: n=49 (HR 1.43 (0.95 to 2.15) p=0.08 vs. n=24 (HR 1.84 (1.11 to 3.05); p=0.01
*hazard ratios adjusted for age, smoking, previous MI, history of high blood pressure, diabetes, BMI, serum cholesterol, medication and fruit advice.

The hazard ratios for each mortality category were higher in the fish oil capsules than in the dietary fish group. The possibility was considered that dietary fish or fish oil could adversely interact with drugs commonly given for heart disease. Hazard ratios of cardiac deaths were calculated in relation to fish advice, with subjects classified in to those receiving and those not receiving various types of drugs at recruitment in to the trial. No evidence was found of any adverse interactions; treatment with BB showed a significant favourable interaction with fish advice.

Source of funding:

British Heart Foundation, Seven seas Ltd, Novex Pharma Ltd and The Fish Foundation

Does the study answer the question?/Further Comments

The subjects not given any specific advice had the lowest mortality from all causes, cardiac death and sudden death, while the group advised only about fish or fish oil had the highest mortality. There was no evidence that it was due to interaction with medication. The authors state that this could arise from risk compensation or some other effect on patients or doctors behaviour.

Gillilan RE;Mondell B;Warbasse JR;

Quantitative evaluation of vitamin E in the treatment of angina pectoris

Ref ID 15914 **RID:** 1166 1977 Apr

QUALITY

A. Selection bias (systematic differences between the comparison groups)

A4 Based on your answers t, in your opinion was selection bias present? If so, what is the likely direction of its effect?:

Unclear/unknown risk **Direction =**

B. Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)

B4 Based on your answers to the above, in your opinion was performance bias present? If so, what is the likely direction of its effect?:

Unclear/unknown risk **Direction =**

C. Attrition bias (systematic differences between the comparison groups with respect to loss of participants)

C4 Based on your answers to the above, in your opinion was attrition bias present? If so, what is the likely direction of its effect?:

Unclear/unknown risk

Direction =

D. Detection bias (bias in how outcomes are ascertained, diagnosed or verified)

D6 Based on your answers to the above, in your opinion was detection bias present? If so, what is the likely direction of its effect?:

High risk of bias

Direction =

Overall Study Quality -Strengths and Weaknesses:

Strengths- Double blind cross over study. Blinding of outcome assessors.
Weakness- Baseline comparison between groups not reported. Method of randomisation and allocation concealment not reported. No ITT reported. 4 patients died during the study, 48 patients completed the study.

DETAILS

# of patients:

N=52 (cross over study)

Prevalence (Diagnostic):

Patient Characteristics

Mean age, 57 years.

The patients had typical, stable, effort related angina pectoris. All patients had Q wave ECG evidence of previous MI as defined by Minnesota criteria (25 patients) and/or positive coronary arteriograms as defined by 75% obstruction of at least one major coronary artery (31 patients).

26 patients received vitamin E during the first 6 month treatment phase; the remaining 22 patients received vitamin E during the second 6 month treatment phase. The mean duration of double blind therapy was 189±15 days of vitamin E and 192±13.3 days of placebo. In addition, all patients received 2 months of placebo therapy known only to the cardiologist (single-blind, during which time patients continued to keep diaries) following each 6 month double blind treatment phase.

Interventions/ Test/ Factor being investigated

Vitamin E in the form of d-alpha-tocopherol succinate, 400 I.U. per capsule. Duration of treatment for 6 months.
No antianginal agents other than nitroglycerin were taken by the subjects for the duration of the study. Patients were advised to continue the same habits of physical activity, diet, and smoking throughout the study. Patients avoided the use of multivitamins as well as mineral oil and iron preparations which may interfere with absorption of vitamin E.
Drug adherence was followed by capsule count and a urine fluorescence test that was performed by a technician who reported the fluorescence results to the investigators only at the completion of the project, in order that the study might remain 'blind' to the investigators.

Comparisons

Placebo capsule containing 2.5 mg of riboflavin (for purposes of urine fluorescence test to judge drug adherence).

Length of Study/ Follow-up

At the end of 6 months treatment phase

Outcome measures studied	Anginal attacks per week, number of nitroglycerin tablets per week, Exercise treadmill test, cardiac death, hospitalisation.
Results	
Effect Size	Outcome: Vitamin E (n=48) vs. Placebo (n=48) Duration of treadmill (min): 5.48±1.69 vs. 5.30±1.60 ST depression (mm): 2.4±1.45 vs. 2.4±1.34 Angina pains (per week): 7.3±12.6 vs. 6.7±10.5* Nitroglycerin per week: 7.6±12.1 vs. 7.7±14.2 Cardiac death (no. of patients): 2 vs. 2** Hospitalisation (no. of admissions): 5 vs. 6 *** *No patient became angina free during vitamin E therapy. **4 patients died during the study, two of which occurred suddenly at home (apparently cardiac deaths) and two of which occurred during hospitalisation for recurrent MI (established at autopsy). **3 patients hospitalised because of acute MI or the development of unstable angina in 8 patients. Side effects: No deleterious side effects were observed resulting from the use of Vitamin E during the study. There were slightly more complaints of mild gastrointestinal disturbances during placebo phase (6%) than during vitamin E phase (4%). No exacerbation of hypertension, congestive heart failure, or skeletal-muscular complaints could be attributed to vitamin E therapy.
Source of funding:	Wilson and Wolfer Pharmaceutical manufacturers and Distributors, Detriot, Mich.
Does the study answer the question?/Further Comments	Yes. There was no significant difference s between Vitamin E and placebo for ETT parameters, anginal attack, NTG consumption, cardiac death, and hospitalisation.

Salachas A;Papadopoulos C;Sakadamis G;Styliadis J;Voudris V;Oakley D;Saynor R;

Effects of a low-dose fish oil concentrate on angina, exercise tolerance time, serum triglycerides, and platelet function

Ref ID 403 **RID:** 1163 1994 Dec

QUALITY

A. Selection bias (systematic differences between the comparison groups)

A4 Based on your answers t, in your opinion was selection bias present? If so, what is the likely direction of its effect?:

Unclear/unknown risk

Direction =

B. Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)

B4 Based on your answers to the above, in your opinion was performance bias present? If so, what is the likely direction of its effect?:

Unclear/unknown risk

Direction =

C. Attrition bias (systematic differences between the comparison groups with respect to loss of participants)

C4 Based on your answers to the above, in your opinion was attrition bias present? If so, what is the likely direction of its effect?:

High risk of bias

Direction =

D. Detection bias (bias in how outcomes are ascertained, diagnosed or verified)

D6 Based on your answers to the above, in your opinion was detection bias present? If so, what is the likely direction of its effect?:

Low risk of bias

Direction =

Overall Study Quality -Strengths and Weaknesses:

Strengths- Randomised . Double blind.
Weakness-Allocation concealment not reported. Numbers lost to follow-up not reported. No ITT reported. Baseline comparison between groups not made.

DETAILS

# of patients:

N=39 (n=20 fish oil group and n= 19 control group) [Participants who completed the trial].

Prevalence (Diagnostic):

Patient Characteristics

Population: 39 patients (37 men and 2 women) mean age 54 years with CAD, were recruited to take part in the trial. 32 patients had undergone coronary angiography that revealed significant CAD. The 7 other patients had exercise-induced ischemia. 19 patients had previous MI and 10 had previous CABG.

Before entering the trial patients fulfilled the following criteria: 1) 1 year history of stable angina. 2) Ability to recognise promptly the anginal attack and have it recorded in a special diary card provided for the trial. 3) At least 6 anginal episodes in the 2 week run-in period before entering the trial so that potential reduction of the number of anginal episodes could be easily assessed.

All patients continued with their antianginal medication provided the dose regimen was not altered. Sublingual use of nitroglycerin was not permitted for prophylactic purpose. Dietary habits were not changed during the trial.
Exclusion criteria: 1) patients with MI more recent than 3 months. 2) Patients who during the trial underwent coronary angiography or were subjected to CABG. 3)

	Patients already taking aspirin or non steroidal anti inflammatory agents. 4.) Non compliant patients. Selection of patients: 50 patients initially entered the trial and were divided in to 2 groups. In the fish oil group, 5 patients had to be excluded-3 because they underwent coronary angiography and only 2 because of poor compliance. In the placebo group, 6 patients had to be excluded – 3 because of non compliance and 3 underwent coronary angiography. Therefore 20 patients taking fish oil and 19 taking olive oil completed the trial.
Interventions/ Test/ Factor being investigated	5 capsules of fish oil twice daily containing 1.8 g eicosapentaenoic acid and 1.2 docosahexanoic acid . 5 weeks of treatment
Comparisons	5 capsules of olive oil twice daily. The olive oil capsules were visually indistinguishable and also contained peppermint oil to disguise the taste.
Length of Study/ Follow-up	At the end of 12 weeks treatment.
Outcome measures studied	Number of anginal episodes, GTN consumption, exercise tolerance time (ETT).
Results	
Effect Size	Outcome: Fish oil (n=20) vs. control (olive oil) (n=19) Anginal episodes per week: 8.36±103.6 vs. 11.36±51.7 GTN consumption per week: 10.43±15.07 vs. 12.42±12.61 Exercsie duration (min): 10.096±5.16 vs. 9.1094±4.38
Source of funding:	Fish oil by Seven Seas Healthcare Ltd.
Does the study answer the question?/Further Comments	Yes. Then number of anginal attacks was significantly reduced in the fish oil group but not the control group. GTN consumption was significantly reduced in the fish oil group but there was no significant change in the control group. ETT increased significantly in the fish oil group but there was a smaller but insignificant increase in the control group.

Evidence Table

Question: What is the clinical/cost effectiveness of (angina specific) specialised pain interventions in patients with stable angina?

Study Type	Randomised Controlled Trial

Arora RR;Chou TM;Jain D;Fleishman B;Crawford L;McKiernan T;Nesto R;Ferrans CE;Keller S;

Effects of enhanced external counterpulsation on Health-Related Quality of Life continue 12 months after treatment: a substudy of the Multicenter Study of Enhanced External Counterpulsation

Ref ID 9401 **RID:** 1108 2002 Jan

QUALITY

A. Selection bias (systematic differences between the comparison groups)

A4 Based on your answers t, in your opinion was selection bias present? If so, what is the likely direction of its effect?:

Low risk of bias **Direction =**

B. Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)

B4 Based on your answers to the above, in your opinion was performance bias present? If so, what is the likely direction of its effect?:

High risk of bias **Direction =**

C. Attrition bias (systematic differences between the comparison groups with respect to loss of participants)

C4 Based on your answers to the above, in your opinion was attrition bias present? If so, what is the likely direction of its effect?:

High risk of bias **Direction =**

D. Detection bias (bias in how outcomes are ascertained, diagnosed or verified)

D6 Based on your answers to the above, in your opinion was detection bias present? If so, what is the likely direction of its effect?:

High risk of bias **Direction =**

Overall Study Quality -Strengths and Weaknesses:

Strengths- Multicentre randomised study. Baseline characteristics reported. Allocation concealment reported. N=137 received treatment, 71 patients (54%) completed questions for the primary HRQOL parameters at baseline, end of treatment, and 1 year follow-up..[therefore there is a high risk that this sample is not representative of the study population]
Weakness- Data not well reported. [No values for HQOL].N=137 received treatment, 71 patients (54%) completed questions for the primary HRQOL parameters at baseline, end of treatment, and 1 year follow-up..[therefore there is a high risk that this sample is not representative of the study population]
*this is The Multicenter study of enhanced external counterpulsation (MUST)-EECP trial conducted at 7 medical centres in the US.

DETAILS

# of patients:	N=139 (n=EECP 72, n=inactive counterpulsation n= 67) all male. Data available for n=71 (36 in EECP and n=35 inactive CP)
Prevalence (Diagnostic):	
Patient Characteristics	see Ref ID 9404
Interventions/ Test/ Factor being investigated	EECP
Comparisons	Inactive CP
Length of Study/ Follow-up	At end of treatment and 1 year after treatment
Outcome measures studied	Health related quality of life (HQOL). Four primary outcomes for the analysis: the physical functioning, bodily pain and social functioning subscales of the SF-36, and QOL score.
Results	
Effect Size	Baseline to end of treatment Both EECP and inactive CP groups reported significant improvements in physical functioning, bodily pain, and cardiac specific health and functioning from baseline to end of treatment. The size of the improvement in HQOL parameters was always larger for the EECP than for inactive CP; however, this difference was only statistically significant for one of the four primary parameters: social functioning. Those in the EECP group reported a substantially greater increase in their abilities to participate in social activities with family and friends than did those in the inactive CP, who, on average, reported a decrease in social activity. [Values not reported] Baseline to 1 year follow-up At 1 year follow-up , the EECP group maintained statistically significant improvements in HQOL across all primary HQOL parameters, where as the inactive CP group only maintained a significant improvement in the physical functioning scale. At 1 year follow-up, improvements for the EECP group were significantly greater than those for the inactive CP group on 3 of 4 primary parameters: bodily pain, social functioning, and cardiac specific health and functioning [no values reported] *36 item Short-Form Health Survey (SF-36) and the cardiac version of the Quality of Life Index (QIL) used for measuring HQOL. The SF-36 comprises 36 items that yield 8 multi item scales that measure physical functioning, work role disability due to emotional problems, bodily pain, general health perceptions, vitality, social functioning, work role disability due to emotional problems, mental health, and a single item evaluation of change in health. The QIL is in 2 parts: Part 1 measures satisfaction with various aspects of life as they are impacted by the respondent's cardiac health. Part 2: Measures the importance of these same aspects of life to the respondent personally.
Source of funding:	SEE Ref ID 9404
Does the study answer the question?/Further Comments	Yes. At baseline both groups had similar HQOL. At 12 month follow-up, improvements for the EECP were significantly greater than those for the inactive CP group on three of four primary parameters: bodily pain, social functioning and cardiac specific health and functioning.

Arora RR;Chou TM;Jain D;Fleishman B;Crawford L;McKiernan T;Nesto RW;

The multicenter study of enhanced external counterpulsation (MUST-EECP): effect of EECP on exercise-induced myocardial ischemia and anginal episodes

Ref ID 9404 **RID:** 1133 1999 Jun

QUALITY

A. Selection bias (systematic differences between the comparison groups)

A4 Based on your answers t, in your opinion was selection bias present? If so, what is the likely direction of its effect?:

Low risk of bias **Direction =**

B. Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)

B4 Based on your answers to the above, in your opinion was performance bias present? If so, what is the likely direction of its effect?:

Unclear/unknown risk **Direction =**

C. Attrition bias (systematic differences between the comparison groups with respect to loss of participants)

C4 Based on your answers to the above, in your opinion was attrition bias present? If so, what is the likely direction of its effect?:

Low risk of bias **Direction =**

D. Detection bias (bias in how outcomes are ascertained, diagnosed or verified)

D6 Based on your answers to the above, in your opinion was detection bias present? If so, what is the likely direction of its effect?:

High risk of bias **Direction =**

Overall Study Quality -Strengths and Weaknesses:

Strengths- Multicentre randomised study. Baseline characteristics reported.The EECP group and inactive CP group were not balanced at baseline, the patients in the EECP group had significantly longer duration of angina and higher proportion of patients with previous MI. Allocation concealment reported. 2 /139 withdrew prior to first treatment. 1/66 in inactive CP and 12/71 in EECP lost to follow-up[more drop out from the EECP than the control group] . No data reported on long term outcomes especially cardiac mortality. Completed trial: N = 124: EECP,n= 59; Inactive CP ,n=65. ITT analysis used.(but not for all outcomes). ITT was not reported for ST segment depression and exercise duration which was the oputcome the trial was powered to detect. This may overestimate the treatment effect.

Weakness- Data not well reported. No data reported on long term outcomes especially cardiac mortality.
*this is The Multicenter study of enhanced external counterpulsation

(MUST)-EECP trial conducted at 7 medical centres in the US.

DETAILS

# of patients:

N = 139 (n=EECP 72, n=inactive counterpulsation 67) all male.

Prevalence (Diagnostic):

Patient Characteristics

Baseline characteristics:
Characteristics: no EECP (n=66); EECP (n=71)
Age (mean ±SD): 62±9; 64±9; p<0.1
Male: 58 (87.9%); 61 (85.9%); <0.8
CCS
Class I: 17 (25.8%); 19 (26.8%)
Class II: 34 (51.5%); 35 (49.3%)
Class III: 15 (22.7%); 17 (23.9%)
Angina years (mean±SD): 4.5±4.06; 8.56±7.88; P<0.01
Previous MI: 27 (40.9%); 40 (56.3%); P<0.05
Previous CABG: 25 (37.9%); 33 (46.5%);p>0.3
Previous PTCA: 22 (33.3%); 27 (38%);P>0.5
Nitrates: 54 (81.8%); 56 (78.9%)
Acetalylslicylic acid: 60 (90.9%); 32 (87.3%)
CCB: 36 (54.5%); 44 (62%)
BB: 51 (77.3%); 50 (70.4%)
Lipid lowering agents: 33 (50%); 44 (62%)

Inclusion criteria: 21 to 81 years; CCS I, II or III; have symptoms consistent with CCS class I,II, or III; have documented evidence of CAD; ETT positive for ischaemia
Exclusion criteria: MI or CABG in the preceding 3 months; cardiac catheterization in preceding 2 weeks; unstable angina; overt congestive heart failure or a left ventricular ejection fraction ≤ 30%; significant valvular heart disease; BP > 180/100 Hg; permanent pacemaker or implantable defibrillator; non-bypassed left main stenosis > 50%; sever symptomatic peripheral vascular disease, history of varicosities, deep vein thrombosis, phlebitis or stasis ulcer, warfarin use with International Normalised Ratio >2.0, atrial fibrillation or frequent ventricular premature beats that would interfere with EECP triggering or baseline electrocardiographic abnormalities that would interfere with interpretation of exercise ECG; pregnant women or of childbearing potential; inability to undergo treadmill testing.

Interventions/ Test/ Factor being investigated

EECCP (Enhanced external counterpulsation) 35 hours of (once or twice/day) of active counterpulsation over a 4 to 7-week period. Nitroglycerin (NTG) medication was permitted as and when required.

Comparisons

Inactive counterpulsation (CP). 35 hour sessions (once or twice/day) of CP over a 4 to 7-week period.

Length of Study/ Follow-up

3 days after follow-up for angina pain counts, one week after treatment for exercise duration.

Outcome measures studied

Exercise test, Anginal pain counts , Nitroglycerin use.

Results

Effect Size

Exercise duration
Exercise duration was 426±20 sec at baseline and 470±20 sec post treatment in the EECP group. In the inactive-CP group, exercise duration was 432±22 sec at baseline and 464±22 sec post treatment. There was no significant difference between groups in change in exercise duration from baseline to post treatment (adjusted mean: EECP :42±11 sec vs. Inactive CP: 26±12 sec; p>0.3).
Time to ≥ 1mm ST segment depression was 337±18 sec at baseline and 379 ±18

sec post treatment in the EECP group. In the inactive CP group, time to ≥1 mm ST segment depression was 326±21 sec at baseline and 330±20 sec post-treatment. There was a significant difference between groups in the change in time to exercise induced ischemia from baseline to post treatment (adjusted mean: EECP: 37±11 vs. inactive CP:-4±12 sec; p=0.01

*Duration of exercise was measured from initiation to the beginning of recovery. Time to ST segment depression: exercise initiation to horizontal/down sloping ST depression ≥ 1 mm, 80ms after the J point persisting for three beats.

Anginal pain counts

In the intention-to-treat analysis, angina counts were 0.76 ± 0.15 at baseline and 0.55 ± 0.27 post-treatment in the EECP group. In the inactive-CP group, angina counts were 0.76 ± 0.13 at baseline and 0.77 ± 0.2 post-treatment. The difference between groups in the change in angina counts from baseline to post-treatment showed a trend to statistical significance (adjusted mean EECP: 20.11 ± 0.21 versus inactive CP: 0.13 ± 0.22; P < 0.09). In patients who completed 34 sessions, angina counts were 0.72 ± 0.14 at baseline and 0.57 ± 0.38 post-treatment in the EECP group. In the inactive-CP group, angina counts were 0.77 ± 0.14 at baseline and 0.76 ± 0.22 post-treatment. The difference between groups in the change in angina counts from baseline was statistically significant (adjusted mean EECP: -0.033 ± 0.27 versus inactive CP: 0.15 ± 0.27; P < 0.035). A similar number of patients in each group showed a 0% to 25% level of improvement, but more patients reported a > 50% improvement in angina frequency, and fewer worsened in the EECP group compared with the inactive-CP group (P < 0.05).

*The average frequency of angina episodes per day (angina counts) was computed by dividing the total number of angina episodes reported at three successive treatmnet sessions by the number of days in which the sessions took place.

Nitroglycerin usage

In the intention-to-treat analysis, nitroglycerin usage was 0.47 ± 0.13 at baseline and 0.19 ± 0.07 post-treatment in the EECP group. In the inactive-CP group, nitroglycerin usage was 0.51 ± 0.15 at baseline and 0.45 ± 0.19 post-treatment. The difference between groups in change in nitroglycerin usage from baseline to post-treatment was not significant (adjusted mean EECP: 20.32 ± 0.12 versus inactive CP: 20.10 ± 0.12; P < 0.1). In patients who completed 34 sessions, nitroglycerin usage was 0.39 ± 0.11 at baseline and 0.12 ± 0.04 post-treatment in the active-CP group. In the inactive-CP group, nitroglycerin usage was 0.56 ± 0.17 at baseline and 0.43 ± 0.21 post-treatment. The difference between groups in this parameter from baseline to post-treatment was not significant (adjusted mean: EECP: 20.32 ± 0.15 versus inactive CP: 20.19 ± 0.14; P < 0.1).

Adverse events

Adverse events (AE): Inactive CP (n=66) vs. EECP (n=71)
Patients with AE: 17 (25.8%)) vs. 39 (54.9%) ;p<0.001
Adverse events- non device related:
Viral syndrome: 0 vs. 1; p>0.5
Anxiety: 0 vs. 2p=0.5
Tinnitus: 1 vs. 3; p>0.5
GI disturbances: 1 vs. 1; p>0.5
Headache: 0 vs. 1: p>0.5
Blood pressure change: 1 vs. 1: >0.5
Epitaxis: 0 vs. 2: p=0.5
Angina: 1 vs. 1: p>0.5
Other chest pain: 3 vs. 7 : p=0.3
A/V arrhythmia: 3 vs.9: p>0.2
Heart rate change (sinusal): 3 vs.0: p=0.1
Respiratory: 2 vs. 4: p>0.5
Total: 15 vs. 33:p<0.005
Adverse events (device related)
Paresthesia: 1 vs. 2: p>0.5
Edema, swelling: 0 vs. 2: p=0.5
Skin, abrasion, bruise, blister: 2 vs. 13: p=0.005
Pain (legs, back): 7 vs. 20: p=0.01
Total: 10 vs. 37:p<0.001

Both groups reported a relatively high incidence of adverse events related to the

device. More patients in the EECP group reported adverse vents than in the inactive CP: 39 (55%) of the treated group reported adverse events compared to 17 (26%) in the control group (P = 0.001). Ten of the 25 events reported by the 17 patients in the control group were considered device-related, involving the skin, lower legs or back. Thirty-seven of the 70 events reported by the 39 patients in the treated group were considered device-related. The remaining complaints in each group were considered minor and not directly related to treatment. Leg discomfort was reported in 11.6 ± 22.7% of sham sessions and 4.9 ± 18.7% of enhanced external counterpulsation (EECP) sessions (P = 0.06). Although 47 of the 95 events reported by both groups combined were considered device-related, only five patients withdrew from the study due to leg complaints (e.g. pain, abrasion).

Source of funding: grant from Vasomedical Inc., Westbury, New York

Does the study answer the question?/Further Comments Yes. Exercise duration increased in both groups, but the between-group difference was not significant (p>0.3). Time to ≥1 mm ST segment depression increased significantly from baseline in EECP compared with inactive CP (p=0.01). More EECP patients saw a decrease and fewer experienced an increase in angina episodes as compared with inactive CP patients (p<0.05). Nitroglycerin use decreased in EECP but did not change in the inactive CP group. The between group difference was not significant (p>0.7).

Ballegaard S;Jensen G;Pedersen F;Nissen VH;

Acupuncture in severe, stable angina pectoris: a randomized trial

Ref ID 9409 **RID:** 1123 1986

QUALITY

A. Selection bias (systematic differences between the comparison groups)

A4 Based on your answers t, in your opinion was selection bias present? If so, what is the likely direction of its effect?:

Unclear/unknown risk **Direction =**

B. Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)

B4 Based on your answers to the above, in your opinion was performance bias present? If so, what is the likely direction of its effect?:

Low risk of bias **Direction =**

C. Attrition bias (systematic differences between the comparison groups with respect to loss of participants)

C4 Based on your answers to the above, in your opinion was attrition bias present? If so, what is the likely direction of its effect?:

Low risk of bias **Direction =**

D. Detection bias (bias in how outcomes are ascertained, diagnosed or verified)

D6 Based on your answers to the above, in your opinion was detection bias present? If so, what is the likely direction of its effect?:

High risk of bias

Direction =

Overall Study Quality -Strengths and Weaknesses:

Strengths- Randomised. All patients completed the trial. Baseline characteristics reported. The subjects and the doctor in charge of the exercise test were blinded and the global evaluation was carried out by the other authors on a blind basis as well.
Weakness- Method of randomisation not reported. Allocation concealment not reported. No blinding (not possible due to the kind of intervention)

DETAILS

# of patients:

N=26 (n=13 in active acupuncture and n=13 in sham acupuncture)

Prevalence (Diagnostic):

Patient Characteristics

Twenty six patients with stable, medically resistant, exercise provoked angina pectoris (functional class II-1V NYHA) entered the trial. They were all waiting for aortocoronary bypass surgery, had no previous heart surgery, no other competing cause of chest pain, no previous MI within the last 6 months, no valvular heart disease, no sever heart failure, no arterial hypertension WHO group II and III, and no previous acupuncture treatment.

No significant difference was detected between the two groups with regard to age, sex, prior MI, extension of coronary artery disease, left ventricular function, exercise test variables, anginal attack rate and nitroglycerin consumption at randomisation.

Baseline characteristics:
Characteristics: genuine acupuncture; sham acupuncture
No. of patients completing treatment: 13; 13
Male: female: 12:1; 11; 2
Median age (year) (range): 54 (40-70); 58 (38-66)
Extension of atherosclerosis 1:2:3 vessel disease: 1:7:5; 0:2:11
Prior MI: 8; 9
Left ventricular function
Ejection fraction≤40%: 1; 2
Ejection fraction>40%: 12; 11
Medical treatment
BB: 9; 9
CCB: 11; 12

Selection of patients: The patients were selected among 56 consecutive patients with a positive evaluation with regard to aortocoronary bypass surgery. Eleven of the patients were excluded because of long travelling distance, seven refused participation, seven underwent acute operation, two had previous acupuncture treatment, one developed unstable angina pectoris, one severe heart failure and died.

The anti anginal drug treatment given to the patients at the entry of the trial was regarded as optimal and remained unchanged during the study. The patients were told not to change habits concerning daily exercise and smoking.

Interventions/ Test/ Factor being investigated

Active acupuncture.
During the treatment period all patients received seven treatments in the supine position. Active treatment: acupuncture was given at points Pericardium 6, stomach 36 and urinary bladder 14 bilaterally. The acupoints were identified according to traditional anatomical locations. The needles used were Chinese stainless steel, 30 gauge and 1.5 inches long. After obtaining needle sensation (or

	the arrival of 'QI') the needles were left in place for 20 mins. No electrical or mechanical stimulation of the needles was given. To increase the patients confidence that they were receiving the correct acupuncture treatment, the acupuncturist employed an electrically resistant measurement device, which was adjusted to beep over both active and sham acupoints. He then explained to the patient that the beep indicated the exact location of the acupoint and would then confirm the accuracy required for correct needling technique. The treatment was carried out in the hospital on an outpatient basis.
Comparisons	Sham acupuncture. The needles were inserted through the skin in points within the same spinal segments as the acupoints, but outside the Chinese meridian system and were not trigger points. In all aspects both genuine and sham acupuncture treatments were identical.
Length of Study/ Follow-up	Immediately after the 9 week treatment period.
Outcome measures studied	Exercise tests variables (Exercise tolerance, difference in pressure rate product between rest and maximum exercise, maximal PRP during exercise, maximum ST depression and length of time maximum ST depression); anginal attacks, activity at the time of the pain attack and nitroglycerin consumption (from diaries); subjective global evaluation by the patient at the end of the trial : improvement of general well-being after treatment /no improvement of general well-being after treatment.
Results	
Effect Size	Exercise variables Variable: Active acupuncture vs. sham acupuncture Exercsie tolerance (Wmin): 550 (150 to 1300) vs. 256 (100 to 1700) Time to maximal ST depression (min): 2 (0 to 7.5) vs. 2 (0 to 4.5) Size of maximal ST depression (mm): 1 (0 to 3) vs. 1 (0 to 2) Maximal PRP (mmHgmin-1): 24.640 vs. 13.530 ** Delta PRP (mmHgmin-1): 12.580 vs. 6.592** *Delta PRP is expressed as median, other values as median and range. Delta indicates difference between exercise and rest values. **p<0.005 Comparison of anti-anginal effects of active and sham acupuncture evaluated from patient's diary (median and range) Variable: active acupuncture vs. sham acupuncture No. of anginal attacks per 3 weeks: 55 (8 to 168) vs. 66 (41 to 149) Nitroglycerin consumption (0.25 mg tablets per 3 weeks): 39 (1 to 193) vs. 30 (0 to 152) Six of the 12 patients in the active treatment group and one of 12 patients in the sham treatment group reported improvement in general well being after treatment (p=0.10). No complications or adverse effects were observed. The study period consisted of: 3 weeks of pre treatment control; after randomisation 3 weeks of treatment, during which the patients received either active or sham acupuncture, and 3 weeks of post treatment control.
Source of funding:	Danish Medical Research Council, the Arvind Nilsson Foundation, Ib Henriksen Foundation, the Einar and Meta Thorsen Foundation, Augustinus Foundation
Does the study answer the question?/Further Comments	Yes. Compared to patients receiving sham acupuncture the patients receiving active acupuncture increased cardiac work capacity significantly, expressed as dPRP (difference in pressure-rate-product between rest and maximum exercise) and maximal PRP during exercise (p<0.001). None of the other variables showed any significant differences between the two groups. Concerning exercise tolerance the median difference was 138 Wmin (95% Ci-12.5 to 325 Wmin), concerning the anginal attack rate the median difference was 29.5% (95% CI 55% to -11%) and with regard to nitroglycerin consumption the median difference was

5% (95% CI +67% to -44%).

Ballegaard S;Pedersen F;Pietersen A;Nissen VH;Olsen NV;

Effects of acupuncture in moderate, stable angina pectoris: a controlled study

Ref ID 9408 **RID:** 1109 1990 Jan

QUALITY

A. Selection bias (systematic differences between the comparison groups)

A4 Based on your answers t, in your opinion was selection bias present? If so, what is the likely direction of its effect?:

Unclear/unknown risk **Direction =**

B. Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)

B4 Based on your answers to the above, in your opinion was performance bias present? If so, what is the likely direction of its effect?:

Low risk of bias **Direction =**

C. Attrition bias (systematic differences between the comparison groups with respect to loss of participants)

C4 Based on your answers to the above, in your opinion was attrition bias present? If so, what is the likely direction of its effect?:

Low risk of bias **Direction =**

D. Detection bias (bias in how outcomes are ascertained, diagnosed or verified)

D6 Based on your answers to the above, in your opinion was detection bias present? If so, what is the likely direction of its effect?:

High risk of bias **Direction =**

Overall Study Quality -Strengths and Weaknesses:

Strengths- Randomised. Blinding of patients reported. All patients completed the trial. Baseline characteristics reported.
Weakness- Method of randomisation not reported. Allocation concealment not reported. No blinding (not possible due to the kind of intervention)

DETAILS

# of patients: N=49 (n=24 in genuine acupuncture and n=25 sham acupuncture)

Prevalence (Diagnostic):

Patient Characteristics	Inclusion criteria were: Clinically stable exercise induced angina pectoris for more than 6 months, two or more anginal attacks per week, consumption of two or more nitroglycerin tablets per week and positive exercise test (1 mm ST-segment depression in one or more leads). The exclusion criteria were: previous heart surgery, other known causes of chest pain, intermittent claudication, previous MI within the last 6 months, valvular heart disease, sever heart failure, arterial hypertension (WHO groups II and III), treatment with digitalis or anti-arrhythmic drugs, and previous acupuncture treatment for heart disease. Clinical characteristics of the study groups: Characteristic: Genuine acupuncture; Sham acupuncture No. of patients completing treatment: 24; 25 Male: female: 19:5; 19:6 Median age (years): 67; 66 Median no. of years with angina (range): 4 (0.5 to 25); 3 (0.5 to 13) Prior MI: 10; 10 Medical treatment BB: 7; 4 CCB: 7; 12 Diuretics: 6; 8 Nitroglycerin with prolonged effect: 3; 4 The study period consisted of 3 weeks of pre treatment control; 3 weeks treatment, during which the patient received either genuine or placebo acupuncture; 3 weeks of post treatment control. During the entire 9 week period the patient filled in a diary.
Interventions/ Test/ Factor being investigated	Genuine acupuncture. The genuine acupuncture was given according to traditional Chinese medicine, each patient receiving 10 treatments in the supine position within 3 weeks. The needles used were Chinese of stainless steel, 30 gauge and 1.5 inches long. After obtaining needle sensation (or the arrival of 'Qi') the needles were left in place for 20 min. The arrival 'Qi' is described as the reaction the patient feels when the needle is inserted to a certain depth in the acupoint. No electrical or mechanical stimulation of the needle was given. The treatment was carried out in the hospital on an out-patient basis.
Comparisons	Sham acupuncture. In the control group, the needles were inserted superficially through the skin, with no attempt to obtain needle sensation, in points within the same spinal segments as the acupoints, but outside the Chinese meridian system and not at trigger points. The needles were then left untouched. In all other respects the treatments were identical. All patients were told they were receiving genuine acupuncture, and that the study was a comparison between two different kinds of acupuncture.
Length of Study/ Follow-up	Just after the 9 week treatment period. Global evaluation at both immediately after the treatment and after 6 months.
Outcome measures studied	Exercise test; no. of anginal attacks; activity at the time of the pain; nitroglycerin consumption (diaries); daily well being on an ordinal scale, using the terms very good (given value 1), good (2), fair (3), not good (4), bad (5) ; global evaluation of the effect of the treatment on an ordinal scale: much improved, somewhat improved, slightly improved, unchanged, slightly worse, somewhat worse, much worse.

Results

Effect Size	Exercise test variables Those having genuine acupuncture increased exercise tolerance significantly (mean increase 9%, range- 25 to +184%) and had a significant delay in time to onset of pain (median delay 10%, range -32 to +107%) when compared to pre-treatment values. Those having sham treatment had no significant change in exercise variables. There were no significant between group differences. Individual relative changes (%) in exercise test variables from pre to post-treatment exercise test. All values expressed as median (range). Positive values indicate a post-treatment exercise test value greater than the pre-treatment exercise test value. Outcome: Genuine acupuncture (n=24) vs. Sham acupuncture (n=25)

Exercise tolerance (%): +9 (-25 to +184) vs. +4 (-16 to +135); NS
Maximal PRP (%): -1 (-12 to +47) vs. +5 (-22 to +25); NS
Delta PRP (%): + 3 (-38 to +145) vs. +4 (-28 to + 78); NS
Time to ST segment depression (%): 0 (-42 to +100) vs. 0 (-40 to +40); NS
Time to end of ST depression (%): +9 (-75 to +600) vs. 0 (-58 to +300); NS
Maximum ST depression (mm)*: 0 (-1.0 to +0.5) vs. 0 (-1.0 to +1.5); NS
Time with minimum 1 mm ST depression (%): +15 (-79 to +490) vs. +5 (-72 to +200); NS
Time to onset of pain (%): +10 (-32 to +107) vs. +10 (-39 to +55); NS
Post exercise pain duration (%): 0 (-47 to +700) vs. 0 (-77 to +78); NS

*Maximum ST depression expressed as absolute values.

Subjective variables
Within both groups there was a significant decrease in both anginal attack rate and nitroglycerin consumption. After treatment all patients receiving genuine acupuncture decreased nitroglycerin consumption (median change -54%, range -14 to -100%). Anginal attack rate was reduced in 13 of 14 patients (93%) (median range -41%, range +18 to -95%). Nitroglycerin consumption and anginal attack rate were reduced in 15 of 16 patients (94%) receiving sham acupuncture. The median being -53% (range +20 to -100%) and -55% (range +23% to -100%) respectively. Daily well being was improved in 14 out of 23 (61%) in both groups (median improvement +1 arbitrary value in both groups). Concerning global evaluation, 75% of the patients treated by genuine acupuncture reported improvement in their general condition after the end of the treatment and 6m months later 67% still felt the improvement. Among those treated by sham acupuncture 84% reported improvement and 6 months later 72% still felt it.

Note: The first exercise test was performed before the pre treatment control period to confirm the diagnosis. The second and third exercise tests were performed just before and just after the treatment period.

Source of funding:

Not reported.

Does the study answer the question?/Further Comments

Yes. In patients receiving genuine acupuncture there was a significant increase in exercise tolerance (median 9%) and in delay of onset of pain (median 10%). No significant changes were observed in patients receiving sham acupuncture. Within both groups there was a median reduction of 50% in anginal attack rate and nitroglycerin consumption, and there was no significant difference between the results achieved in the two groups.

McGillion MH;Watt WJ;Stevens B;Lefort SM;Coyte P;Graham A;

Randomized controlled trial of a psychoeducation program for the self-management of chronic cardiac pain

Ref ID 9172 **RID:** 803 2008 Aug

QUALITY

A. Selection bias (systematic differences between the comparison groups)

A4 Based on your answers t, in your opinion was selection bias present? If so, what is the likely direction of its effect?:

Low risk of bias

Direction =

B. Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)

B4 Based on your answers to the above, in your opinion was performance bias present? If so, what is the likely direction of its effect?:

Low risk of bias

Direction =

C. Attrition bias (systematic differences between the comparison groups with respect to loss of participants)

C4 Based on your answers to the above, in your opinion was attrition bias present? If so, what is the likely direction of its effect?:

Low risk of bias

Direction = There are more patients in the intervention group who were lost to follow-up but there are no systematic

D. Detection bias (bias in how outcomes are ascertained, diagnosed or verified)

D6 Based on your answers to the above, in your opinion was detection bias present? If so, what is the likely direction of its effect?:

Low risk of bias.

Direction = The study follow-up period was limited to three months after baseline for both groups.

Overall Study Quality -Strengths and Weaknesses:

This was a well conducted RCT of a psychoeducation programme Chronic Angina Self-Management Program (CASMP) in which those treated were compared to patients in a waiting list control group. The follow-up period was limited to three months after baseline. Therefore, the long-term sustainability of the observed intervention effects is not known. In addition, all psychoeducation sessions were delivered by a single facilitator. Future studies of this intervention should use multiple facilitators to enhance external validity and include longerterm follow-up.

DETAILS

# of patients:

n=130 were randomised, n=66 to the CASMP and n=64 to the waiting list control group.

Prevalence (Diagnostic):

Patient Characteristics

Sociodemographic Characteristics by Group

	Treatment (n = 66)	Control (n= 64)
Demographics	n (%)	n (%)
Mean age (years [SD])	67 (11)	70 (11)
Married/cohabitating	44 (67)	44 (69)
Male	53 (80)	50 (78)
Mean (SD) years living with angina	6 (6)	8 (8)
Comorbid conditions		
Heart failure	2 (3)	5 (8)

Asthma	4 (6)	2 (3)
Diabetes	18 (27)	9 (14)
Emphysema	1 (2)	1 (2)
Renal failure	2 (3)	1 (2)
Peptic ulcer	1 (2)	3 (5)
Thyroid problems	3 (5)	7 (11)
Other minor medical problem	34 (52)	27 (42)

SD=standard deviation

Interventions/ Test/ Factor being investigated

The Chronic Angina Self-Management Program (CASMP) is a standardized psychoeducation programme given in two-hour sessions weekly, over a six-week period. The goal of the CASMP is to improve HRQL by increasing patients' day to day angina self-management skills. The CASMP is an adaptation of Lorig et al.'s Chronic Disease Self-Management Program (CDSMP,1999 Stanford University). The programme was delivered by a registered nurse using a group format (e.g., 8-15 patients) in a comfortable classroom setting. Programme sessions were offered both day and evening and participants were encouraged to bring a family member or friend if they wished. A facilitator manual specified the intervention protocol in detail to ensure consistent delivery of the CASMP across sessions.The programme was designed to maximise discussion and group problem solving, it encouraged individual experimentation with various cognitive-behavioural self-management techniques and facilitates mutual support, optimism, and the self-attribution of success. Key pain related content includes relaxation and stress management, energy conservation, symptom monitoring and management techniques, medication review, seeking emergency assistance, diet, and managing emotional responses to cardiac pain.

Comparisons

Comparison is between patients in the CASMP and the waiting list control group. The latter patients were offered entry into the next available CASMP once post-test measures were completed.

Length of Study/ Follow-up

3 months from start of treatment or randomisation to waiting list control group.

Outcome measures studied

The primary outcome was Health Related Quality of Life (HRQL) which included the SF-36 and the SAQ (Seattle Angina Questionnaire). The secondary outcome was enabling skill, reflected by CSA patients' self-efficacy and resourcefulness to self-manage their pain. For the purposes of this review question results for HRQL, including SF-36 and SAQ, are reported here. HRQL was measured using the Medical Outcomes Study 36- Item Short Form (SF-36). The SF-36 is designed to capture multiple operational indicators of functional status, including behavioral function and dysfunction, distress and well-being, and self-evaluations of general health status. Eight subscales are used to represent widely measured concepts of overall quality of life: physical functioning (PF), role limitations due to physical problems (RP), social functioning (SF), bodily pain (BP), mental health (MH), role limitations due to emotional problems (RE), vitality (VT), and general health perception (GH). Raw scores were transformed to a 0 to100 scale where higher scores reflect better functioning.The SAQ is a disease-specific measure of HRQL for patients with CAD, consisting of 19 items that quantify five clinically relevant domains of CAD: physical limitation, angina pain stability and frequency, treatment satisfaction, and disease perception. The SAQ is scored by assigning each response an ordinal value and summing across items within each of the five subscales. Subscale scores are transformed (0-100) by subtracting the lowest score, dividing by the range of the scale, and multiplying by 100. Higher scores for each subscale indicate better functioning; no summary score for the five subscales is derived.

Results

MANOVA and ANOVA Tests for Significant Differences in SF-36 Change Scores Between Groups

	Change Treatment		Change Control	Difference in Change between Groups	
MANOVA		ANOVA			
	M (SD)		M (SD)	M (SD)	
F(df)	P	F(df)	P		
Physical health-related items					
PF	5.3 (9.4)		-0.68 (9.3)	5.95 (9.3)	4.39 (4,110)

0.003b	11.75 (1,114)	<0.001c						
RP	4.8 (12.7)	3.2 (9.6)	1.66					
(11.2)		1.47a	ns					
BP	4.4 (8.7)	2.1 (9.2)	2.31					
(8.95)		1.68a	ns					
GH	2.27 (7.7)	-1.6 (6.4)	4.33					
(7.0)		10.94 (1,114)	0.001c					
Mental health-related items								
RE	4.9 (12.2)	3.6 (12.2)	1.31 (12.2)	0.47				
(4,108)	ns	1.49a	ns					
SF	2.1 (10.9)	0.1 (9.5)	2.04					
(10.2)		0.28 (1,114)	ns					
VT	2.3 (8.6)	0.3 (7.3)	1.97					
(8.0)		1.77 (1,114)	ns					
MH	1.5 (8.8)	0.9 (7.9)	0.58					
(8.3)		0.14 (1,114)	ns					

NBS= Norm-based scores; PF= physical functioning; RP= role physical functioning; BP= bodily pain; GH= general health; RE = role emotional functioning; SF= social functioning; VT= vitality; MH= mental health.
Note: SD of mean change scores expected to be large, as range of scores not bound by zero.
a Mann-Whitney U test.
bP < 0.05.
cP<=0.01.
ns = Nonsignificant (P > 0.05).

MANOVA and ANOVA Tests for Significant Differences in SAQ Change Scores Between Groups

SAQ	Change Treatment		Change Control	Difference in Change between Groups	MANOVA	ANOVA
	M (SD)		M (SD)	M (SD)	F(df)	P
AF	11.4 (23.7)		2.2 (18.4)	9.23 (21.2)	3.23 (5,109)	0.009a
5.57 (1,115)	0.02a					
AS	18.0 (35.0)		2.9 (24.4)	15.07		
(30.0)			7.37 (1,115)	0.001b		
DP	9.9 (23.5)		3.3 (19.1)	6.61		
(21.4)			2.80 (1,115)	ns		
PL	7.1 (16.5)		1.6 (15.1)	5.55		
(15.8)			3.54 (1,113)	ns		
TS	9.7 (24.6)		4.8 (18.7)	4.82		
(21.8)			1.43 (1,115)	ns		

SAQ =Seattle Angina Questionnaire; AF = angina frequency; AS = angina stability; DP= disease perception; PL= physical limitation; TS= treatment satisfaction;
SD= standard deviation.
Note: SD of change scores expected to be large, as range of scores not bound by zero.
aP < 0.05.
bP<=0.01.
ns = nonsignificant (P > 0.05).

Effect Size

MANOVA and ANOVA Tests for Significant Differences in SF-36 Change Scores Between Groups

	Change Treatment		Change Control	Difference in Change between Groups	MANOVA	ANOVA
	M (SD)		M (SD)	M (SD)	F(df)	P
Physical health-related items						

PF	5.3 (9.4)	-0.68 (9.3)	5.95 (9.3)	4.39 (4,110)	0.003b	11.75 (1,114)	<0.001c
RP	4.8 (12.7)	3.2 (9.6)	1.66 (11.2)	1.47a	ns		
BP	4.4 (8.7)	2.1 (9.2)	2.31 (8.95)	1.68a	ns		
GH	2.27 (7.7)	-1.6 (6.4)	4.33 (7.0)	10.94 (1,114)	0.001c		
Mental health-related items							
RE	4.9 (12.2)	3.6 (12.2)	1.31 (12.2)	0.47 (4,108)	ns	1.49a	ns
SF	2.1 (10.9)	0.1 (9.5)	2.04 (10.2)	0.28 (1,114)	ns		
VT	2.3 (8.6)	0.3 (7.3)	1.97 (8.0)	1.77 (1,114)	ns		
MH	1.5 (8.8)	0.9 (7.9)	0.58 (8.3)	0.14 (1,114)	ns		

NBS= Norm-based scores; PF= physical functioning; RP= role physical functioning; BP= bodily pain; GH= general health; RE = role emotional functioning; SF= social functioning; VT= vitality; MH= mental health.
Note: SD of mean change scores expected to be large, as range of scores not bound by zero.
a Mann-Whitney U test.
bP < 0.05.
cP<=0.01.
ns = Nonsignificant (P > 0.05).

MANOVA and ANOVA Tests for Significant Differences in SAQ Change Scores Between Groups

SAQ	Change Treatment	Change Control	Difference in Change between Groups	MANOVA		ANOVA	
	M (SD)	M (SD)	M (SD)	F(df)	P	F(df)	P
AF	11.4 (23.7)	2.2 (18.4)	9.23 (21.2)	3.23 (5,109)	0.009a	5.57 (1,115)	0.02a
AS	18.0 (35.0)	2.9 (24.4)	15.07 (30.0)	7.37 (1,115)	0.001b		
DP	9.9 (23.5)	3.3 (19.1)	6.61 (21.4)	2.80 (1,115)	ns		
PL	7.1 (16.5)	1.6 (15.1)	5.55 (15.8)	3.54 (1,113)	ns		
TS	9.7 (24.6)	4.8 (18.7)	4.82 (21.8)	1.43 (1,115)	ns		

SAQ =Seattle Angina Questionnaire; AF = angina frequency; AS = angina stability; DP= disease perception; PL= physical limitation; TS= treatment satisfaction;
SD= standard deviation.
Note: SD of change scores expected to be large, as range of scores not bound by zero.
aP < 0.05.
bP<=0.01.
ns = nonsignificant (P > 0.05).

Source of funding:

This trial was made possible in part by a Canadian Institutes of Health Research Fellowship (No. 452939) and a University of Toronto Centre for the Study of Pain

Does the study answer the question?/Further Comments

Yes. The study found statistically reliable short-term improvements in HRQL for those who participated in the CASMP as compared to the control group; specific components of HRQL significantly improved included overall physical functioning and general health (SF-36) and frequency and stability of angina pain symptoms (SAQ).

Payne TJ;Johnson CA;Penzien DB;Porzelius J;Eldridge G;Parisi S;Beckham J;Pbert L;Prather R;Rodriguez G;

Chest pain self-management training for patients with coronary artery disease

Ref ID 242 **RID:** 863 1994 Jul

QUALITY

A. Selection bias (systematic differences between the comparison groups)

A4 Based on your answers t, in your opinion was selection bias present? If so, what is the likely direction of its effect?:

High risk of bias **Direction =** There is bias in that only 26 of the pain mgt group (43%) completed the programme and were the only ones who

B. Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)

B4 Based on your answers to the above, in your opinion was performance bias present? If so, what is the likely direction of its effect?:

Unclear/unknown risk **Direction =**

C. Attrition bias (systematic differences between the comparison groups with respect to loss of participants)

C4 Based on your answers to the above, in your opinion was attrition bias present? If so, what is the likely direction of its effect?:

High risk of bias **Direction =** It is not clear if those completing treatment were comparable to those not completing treatment. The study

D. Detection bias (bias in how outcomes are ascertained, diagnosed or verified)

D6 Based on your answers to the above, in your opinion was detection bias present? If so, what is the likely direction of its effect?:

Unclear **Direction =** Very little information is given on how outcomes were measured. However, only data for 43% of the intervention group were included.

Overall Study Quality -Strengths and Weaknesses:

This is a relatively small study. N=60 patients were randomised to the pain management group. N=26 completed treatment. The study then chose n=26 matched patients from the "pool" of controls. The analysis was performed on n=52 patients (n=26 controls and n=26 from the intervention group). The method of selecting patients for inclusion in the final analysis leads to a very high risk of bias. This is because patients who did not complete the study were excluded from the analysis (57%) and although n=26 of the control group were selected as matched controls the study did not report how many were in the original control group.

DETAILS

# of patients: n=52. N=26 completed pain management treatment. N=26 were selected as matched controls.

Prevalence (Diagnostic):

Patient Characteristics Demographic characteristics (for pain management and control group patients combined)

	Mean	SD	N
Age	57.60	5.88	52
Education	9.96	2.26	49
Race (% white)	93		52
% unemployed	76.6		52
% disabled	71.2		52

Interventions/ Test/ Factor being investigated A pain management programme administered over three consecutive weekly sessions (length of sessions not reported). The goals were to 1) educate patients regarding the role of psychological factors in pain and pain control and 2) teach participants an integrated set of self management skills to modify cognitions, behaviours and affective responses considered likely to adversely impact on the experience of chest pain. Specific skills taught included pacing of physical activities (e.g. taking scheduled breaks), modification of dysfunctional, stress engendering thoughts using cognitive reframing and problem solving techniques, and relaxation training via diaphragmatic breathing.

Comparisons The comparison is between a pain management programme + standard medical care and standard medical care alone.

Length of Study/ Follow-up 6 months.

Outcome measures studied No primary or secondary outcomes specified. Outcomes included: pain frequency and intensity; frequency of sl NTG usage; mood and psychological distress.

Results There were no significant differences between groups with regard to pain frequency, pain intensity, psychological and other factors at 6 months. Actual data for results not reported.

Effect Size There were no significant differences between groups with regard to pain frequency, pain intensity, psychological and other factors at 6 months. Actual data for results not reported.

Source of funding: Not reported.

Does the study answer the question?/Further Comments Unsure. This was a very small study with a high risk of bias. It found that there were short-term reductions in self-report of number of chest pain episodes in treated subjects but these were not evident at 6 month follow-up.

Richter A;Herlitz J;Hjalmarson A;

Effect of acupuncture in patients with angina pectoris

Ref ID 142 **RID:** 1117 1991 Feb

QUALITY

A. Selection bias (systematic differences between the comparison groups)

A4 Based on your answers t, in your opinion was selection bias present? If so, what is the likely direction of its effect?:

Unclear/unknown risk

Direction =

B. Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)

B4 Based on your answers to the above, in your opinion was performance bias present? If so, what is the likely direction of its effect?:

High risk of bias

Direction =

C. Attrition bias (systematic differences between the comparison groups with respect to loss of participants)

C4 Based on your answers to the above, in your opinion was attrition bias present? If so, what is the likely direction of its effect?:

Low risk of bias

Direction =

D. Detection bias (bias in how outcomes are ascertained, diagnosed or verified)

D6 Based on your answers to the above, in your opinion was detection bias present? If so, what is the likely direction of its effect?:

High risk of bias

Direction =

Overall Study Quality -Strengths and Weaknesses:

Strengths- Cross over study. Randomised. All patients completed the trial. Baseline characteristics reported.
Weakness- Small sample size. Method of randomisation not reported. Allocation concealment not reported. No blinding (not possible due to the kind of intervention)

DETAILS

# of patients:

N=21 (cross over)

Prevalence (Diagnostic):

Patient Characteristics

Twenty six patients with stable effort angina and at least five anginal attacks per week during the last 6 months, inspite of intensive antianginal treatment were selected. Only patients with chest pain and/or ST segment depression >1 mm in one or more leads on the ECG during exercise test in the run-in period were included. Two patients with clinical signs of heart failure were excluded and three further patients did not complete the study, complaining that acupuncture was painful. Thus the final data was based on 21 patients who fulfilled the study criteria.
The group consisted of 19 men and 2 women aged 35 to 73 years (mean 57 years). 14 patients had a history of previous MI, but not later than 6 months before inclusion in the study. Bypass surgery had been performed in 8 patients, in two of them repeatedly, while 5 patients were still waiting for operation. None of the patients had congestive heart failure. The antinaginal medical treatment patients had at entry of the study remained unchanged during the whole trial; 15 patients were treated with BB, either as monotherapy or in combination with CCB and/or

	nitrates. The remaining patients were treated by CCB and /or nitrates without BB.
Interventions/ Test/ Factor being investigated	Acupuncture. Acupuncture was performed by traditional Chinese technique by an acupuncturist. Original needles, 26-30 gauge and 0.5-2.5 inches long, manufactured in China of stainless steel, were employed. Once insertion was made at the acupuncture point, the needle was stimulated manually until the patient felt the so-called 'The Chi' sensation of heaviness, numbness and swelling. Needles were then left in acupuncture points for 30 min with no further stimulation. The treatment was given 3 times per week during the 4 week period.
Comparisons	Tablet placebo.
Length of Study/ Follow-up	Immediately after the 4 treatment period (2 weeks wash out period between the treatment periods)
Outcome measures studied	Exercise test, self rating quality of life questionnaire, no. of anginal attacks.
Results	
Effect Size	During acupuncture treatment, 14 patients showed a reduced number of anginal attacks compared with placebo. The no. of attacks was unchanged in the remaining 7 patients; no worsening was observed in any of the patients. In the whole group, the average number of anginal attacks/week was 12.1 during the run-in period, 6.1 during the acupuncture period and 10.6 during the placebo period. The differences between acupuncture and both run-in and placebo periods were statistically significant ($p<0.01$). The results of the exercise tests did not show any significant difference in maximal physical performance at the end of the acupuncture period compared with placebo, the mean values being 104.2 W and 101.4 W respectively. However, maximal workload until onset of chest pain was significantly increased after acupuncture compared with placebo (94.3 W vs. 81.9 W, $P<0.05$). Mean chest pain score at maximal workload improved significantly after acupuncture compared with placebo (mean (0.81 W and 1.38, $p<0.01$). ST segment depression at maximal workload was significantly reduced after acupuncture compared with placebo (mean 0.71 mm vs. 1.03 mm, $p<0.01$). Similar results were obtained for S segment depression at maximal comparable workload (mean 0.63 mm vs. 0.87 mm, $p<0.01$). [Standard deviations not reported]. Concerning the self-rating life quality questionnaire, the score was significantly improved for chest pain, physical performance, peripheral coldness, pessimism, vertigo and relaxation ($p<0.05$). The statistical significance could not be proved for anxiety, tiredness, sleep disturbances and gastro-intestinal symptoms. No adverse effect of acupuncture was observed. [mean values and standard deviations not reported]
Source of funding:	not reported
Does the study answer the question?/Further Comments	Yes. After treatment with acupuncture patients had fewer anginal attacks per week and chest pain during exercise improved at higher workloads, the intensity of pain was decreased and ST segment depression was reduced.

Study Type	Cohort

Loh PH;Cleland JG;Louis AA;Kennard ED;Cook JF;Caplin JL;Barsness GW;Lawson WE;Soran OZ;Michaels AD;

Enhanced external counterpulsation in the treatment of chronic refractory angina: a long-term follow-up outcome from the International Enhanced External Counterpulsation Patient Registry

Ref ID 9395 **RID:** 1126 2008 Apr

QUALITY

A. Selection bias (systematic differences between the comparison groups)

A4 Based on your answers t, in your opinion was selection bias present? If so, what is the likely direction of its effect?:

Low risk of bias

Direction = This is a Before-After study.There was no selection bias in selection of participants from the registry The study

B. Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)

B4 Based on your answers to the above, in your opinion was performance bias present? If so, what is the likely direction of its effect?:

Unclear/unknown risk

Direction =

C. Attrition bias (systematic differences between the comparison groups with respect to loss of participants)

C4 Based on your answers to the above, in your opinion was attrition bias present? If so, what is the likely direction of its effect?:

Low risk of bias

Direction = ITT not used.

D. Detection bias (bias in how outcomes are ascertained, diagnosed or verified)

D6 Based on your answers to the above, in your opinion was detection bias present? If so, what is the likely direction of its effect?:

No

Direction = This is a Before-After study.The study had an appropriate length of follow-up.

Overall Study Quality -Strengths and Weaknesses:

Strengths-This is a Before-After study. The study had an appropriate length of follow-up. 1061/1427 (74.4%) patients completed 3 year follow-up, where as 220 (15.4%) died. However, 146 (10.2%) patients did not complete their 3 year follow-up. The study was conducted prospectively.
Limitations-ITT not used.
This is the 3 year follow-up of the patients in the International EECP Patient Registry (IEPR)

DETAILS

# of patients: N=1427

Prevalence (Diagnostic):

Patient Characteristics

Selection: Five thousand patients from 99 American and 9 international centres were enrolled between Jan 1998 and July 2001. Consecutive patients from each centre who had at least 1 hour of EECP treatment were enrolled. To avoid selection bias and potential bias introduced by poorly compliant centres, only patients from centres with at least 80% compliance in follow-up data submission were included.
Inclusion: One thousand four hundred and twenty seven (1427) patients from 36 centres were included. 1061(74.4%) patients completed 3 year follow-up, where as 220 (15.4%) died. However, 146 (10.2%) patients did not complete their 3 year follow-up. They were followed for a median 15.8 months and were included in analyses for post treatment outcome and follow-up clinical events.

Baseline characteristics (n=1427):
Age (years): 66.3±10.8
Age >65 years:57.3
Men: 72.2%
LEF (%): 46.6±14.8
LVEF <35%: 19.8%
Duration of CAD (years): 10.8±8.2
Prior MI: 70.0%
Prior PCI: 67.1%
Prior CABG: 69%
Multivessel CAD: 78%
Unsuitable for revascularisation: 88%
Heart failure: 34.8%
Non cardiac vascular disease: 30.2%
Prior EECP: 3.8%
Diabetes mellitus: 44%
Hypertension: 70.5%
Hypercholesterolemia: 81.3%
Anginal status:
CCS class I: 2.2%
CCS class II: 8.6%
CCS class III: 62.8%
CCS class IV: 26.4%
Angina frequency (episodes/week): 6 (3-14)
Nitroglycerin use (times/week): 3 (0-8)

Interventions/ Test/ Factor being investigated

EECP . a standard course of 35 one hour treatment sessions was recommended. The patients received a mean of 33.3±9.6 hours of treatment over a mean period of 48 days.

Comparisons

Length of Study/ Follow-up

3 years (median 37 months)

Outcome measures studied

The primary outcome measure was Anginal status (CCS class). The other outcomes were weekly angina episode, nitroglycerin use , QOL (using a simple 5 point scale where 1 represents the worst and 5 represents the best QOL), clinical events (PCI, CABG, MI, death, MACE (composite of death/MI/CABG/PCI) and hospitalisation.

Results

Effect Size

Angina:
Immediately post EECP, the proportion of patients who suffered from CCS Class III/IV angina reduced from 89.2% to 24.9%, p<0.001. the CCS class improved by atleast 1 class in 77.9% of the patients and by 2 classes in 38%. 16.3% of patients had no angina.

These were sustained in 74% patients whose anginal status was documented at 3 year follow-up.

At 3 years, 36.4% of the patients had class II or milder angina.
Number of patients (n=1033) [all values median (interquartile range)]
Pre EECP vs. after 3 years
Weekly angina (episodes/week): 6 (3-14) vs. 1 (0-3)*
Weekly nitroglycerin use (times/week): 3 (0-8) vs. 0 (0-2)
*p<0.001

Cumulative 3 year repeat EECP and major cardiovascular event rates:
(Percentage (95% CI))
Repeat EECP: 22.5 (20.1 -24.9)
PCI: 16.4 (14.3 -18.5)
CABG: 7.5 (6-9)
MI: 11.8 (10-13.7)
Death- 17 (14.9-19.1)
MACE**: 40.8 (38.8-43.5)
**MACE was rare and included MI (0.8%), PCI (0.8%), CABG (0.6%), and death (0.5%).
Of the patients who responded to the QOL questionnaires there was sustained improvement in their QOL after 3 years, p<0.001.(results reported graphically).

A MACE was rare and included MI (0.8%), CABG (0.6%), and death (0.5%)

Univariate and multivariate analysis:
Seventy-six percent of the patients had immediate improvement in CCS class without any cardiovascular events. Univariate logistic regression analysis showed that men, severe pre-treatment angina (CCS III/IV), and absence of a history of HF, diabetes, or hypertension were associated with such an outcome. A CCS III/IV class (OR 1.80 [1.25–2.59]) and freedom from HF (OR 1.82 [1.41–2.32]) were independent predictors of favorable immediate response on multivariate analysis.

Source of funding:

Vasomedical Inc.,Westbury, NewYork, USA.

Does the study answer the question?/Further Comments

Yes. Immediately post EECP, the proportion of patients who suffered from CCS Class III/IV angina reduced from 89.2% to 24.9%, p<0.001. the CCS class improved by atleast 1 class in 77.9% of the patients and by 2 classes in 38%. 16.3% of patients had no angina. These were sustained in 74% patients whose anginal status was documented at 3 year follow-up. MACE was rare and included MI (0.8%), PCI (0.8%), CABG (0.6%), and death (0.5%).

Study Type	Prognostic

Mannheimer C;Carlsson CA;Emanuelsson H;Vedin A;Waagstein F;Wilhelmsson C;

The effects of transcutaneous electrical nerve stimulation in patients with severe angina pectoris

Ref ID 9411 **RID:** 1116 1985 Feb

QUALITY

A. Selection bias (systematic differences between the comparison groups)

A4 Based on your answers t, in your opinion was selection bias present? If so, what is the likely direction of its effect?:

Unclear/unknown risk **Direction =**

B. Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)

B4 Based on your answers to the above, in your opinion was performance bias present? If so, what is the likely direction of its effect?:

Low risk of bias **Direction =**

C. Attrition bias (systematic differences between the comparison groups with respect to loss of participants)

C4 Based on your answers to the above, in your opinion was attrition bias present? If so, what is the likely direction of its effect?:

Unclear/unknown risk **Direction =**

D. Detection bias (bias in how outcomes are ascertained, diagnosed or verified)

D6 Based on your answers to the above, in your opinion was detection bias present? If so, what is the likely direction of its effect?:

High risk of bias **Direction =**

Overall Study Quality -Strengths and Weaknesses:

Strengths- Randomised. ST segment changes were measured blindly by two independent observers.
Weakness- Method of randomisation not reported. Allocation concealment not reported. Small sample size. Loss to follow-up not reported. ITT not reported. No blinding (not possible due to the kind of intervention)

DETAILS

# of patients: N=23 (n=12 TENS and n=11)

Prevalence (Diagnostic):

Patient Characteristics	23 consecutive patients (4 women and 19 men) between the ages 41 and 71 years (mean 58 years) were recruited from the outpatient clinic. All patients had severe angina pectoris (duration 1 to 2 years, functional class III or IV, NYHA). No patient had obstructive or restrictive pulmonary disease, intermittent claudication, valvular heart disease, or had had a MI within the last 6 months. All but 4 patients had had a previous MI. All patients had been considered for aortocoronary bypass surgery: one patient had undergone such a operation, five were waiting for surgery, and the remaining were being considered for surgical treatment. The antianginal treatment being given the patients at entry in to the study was regarded as optimal and had been carefully chosen. No changes in treatment were made during the study. Nine patients received digitalis and 12 diuretics.
Interventions/ Test/ Factor being investigated	TENS (Transcutaneous electrical nerve stimulation) treatment A commercially available transcutaneous nerve stimulator was used. The patients in the TENS group were carefully instructed about the use of TENS and they treated themselves at home according to a certain schedule. The patients were instructed to take three TENS treatment sessions of at least 1 hr each per day (morning, noon and evening). The treatment period lasted 10 weeks. The patients in TENS group were instructed not use TENS 2 hr before and during the exercise test. The treatment group maintained their drug regimens but were instructed to use TENS first in the event of an anginal attack and to use short acting nitroglycerin only if TENS failed to give relief.
Comparisons	control group did not receive TENS .Control patients continued with their antinaginal
Length of Study/ Follow-up	After 2 weeks of treatment
Outcome measures studied	Maximal total work during exercise was determined as a product of workload in watts and time in mins (W.min); ST segment depression during and after exercise; pain and dyspnea reported by the patient during and after exercise. The chest pain and dyspnoea reported were graded according to a visual scale placed in front of the patient. The scale ranged from 0 to 5, with 0 signifying no discomfort, 3 discomfort equivalent with that which ordinarily stopped the patients activities, 4 sever, and 5 maximal discomfort.; frequency of anginal attacks and consumption of short acting nitroglycerin per week.
Results	
Effect Size	2 weeks after treatment Treatment group (n=11) vs. control group (n=10) Mean exercise tolerance (W.min) : mean (SD) 523 (231) vs. 532 (139) (NS) Mean ST segment depression (mm) (during exercise) : mean (SD) 2.8 (1.3) vs. 3 (1.4) ($p<0.001$) Mean ST segment depression (mm) (after exercise) : mean (SD) 3 (1.2) vs. 2.8 (1.5) ($p<0.01$) Mean frequency of anginal attacks: mean (SD) 19 (23) vs. 23 (19) ($p<0.05$) Nitroglycerin consumption per week: mean (SD) 31 (43) vs. 14 (11) ($p<0.05$) Note: 3 parts of the study: 1) Run –in period for 3 weeks when patients became familiarised with the testing procedure 2) Treatment period for 10 weeks. 3) Post treatment period which was identical for both TENS and control group. During this period the treatment group did not receive TENS. – over a 2 week period
Source of funding:	Not reported

Does the study answer the question?/Further Comments	Yes. After 2 weeks of a 10 weeks of treatment , the TENS treatment group had decreased ST segment depression (mm), reduced frequency of anginal attacks and reduced consumption of nitroglycerin tablets compared with the control group. But there was no significant difference between the group for mean exercise tolerance (W.min).

Evidence Table

Question: What is the clinical /cost effectiveness of using drug therapy (short acting nitrates, BB,CCB, long acting nitrates, ACE/ARBs, nicornadil, Ivabradine, Ranolazine, statins) in patients with normal coronary arteries (syndrome X) ?

Study Type	Randomised Controlled Trial

Bugiardini R;Borghi A;Biagetti L;Puddu P;

Comparison of verapamil versus propranolol therapy in syndrome X

Ref ID 1694 **RID:** 849 1989 Feb 1

QUALITY

A. Selection bias (systematic differences between the comparison groups)

A4 Based on your answers t, in your opinion was selection bias present? If so, what is the likely direction of its effect?:

Unclear/unknown risk **Direction =**

B. Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)

B4 Based on your answers to the above, in your opinion was performance bias present? If so, what is the likely direction of its effect?:

Low risk of bias **Direction =**

C. Attrition bias (systematic differences between the comparison groups with respect to loss of participants)

C4 Based on your answers to the above, in your opinion was attrition bias present? If so, what is the likely direction of its effect?:

Low risk of bias **Direction =**

D. Detection bias (bias in how outcomes are ascertained, diagnosed or verified)

D6 Based on your answers to the above, in your opinion was detection bias present? If so, what is the likely direction of its effect?:

No **Direction =**

Overall Study Quality -Strengths and Weaknesses:

Strengths: double blind randomised crossover ; no attrition; low risk of performance bias
Weakness: small sample size

DETAILS

# of patients: N=16 crossover design

Prevalence (Diagnostic):

Patient Characteristics	Inclusion: diagnostic transient ischemic ST depression (>=0.15mV lasting >1min) documented by 48 hours Holter monitoring; typical chest pain and significant ST depression during exercise stress testing ; no angiographic evidence of coronary epicardial artery spasm during ergonovine testing (total dose 0.650mg, intravenously) Baseline characteristics: 15 women and 1 man, mean age 47.4±6 years (range 34 to 58)
Interventions/ Test/ Factor being investigated	Verapamil 320mg daily Propanolol 120-160mg daily (The optimal dose of propanolol for each patient was determined 2-3 weeks before the double blind study. Beta blockade was considered adequate of resting heart beat rate was <=60 beats /min, which occurred at dose of 120mg a day in 6 patients and 160mg in remaining 10) Patients began study with 2-day run-in period.Then randomised to first treatment phase for 1 week.Then 7-day placebo washout period. Then crossover to other drug regimen for 1 week
Comparisons	propanolol vs verapamil vs placebo
Length of Study/ Follow-up	no follow-up, outcomes measure during run-in and the last 2 days of therapy
Outcome measures studied	number of ischemic episodes per 24 hours ; duration of ischemic episodes (min); heart rate all measured through 48 hour ambulatory monitoring
Results	Mean ischemic episodes and duration of ischemia during ambulatory ECG monitoring Mean ischemic episodes Mean duration of ischemia (minutes) Run-in Plac Prop Ver Run-in Plac Prop Ver Mean ±SD 4.2±2 ; 3.9±1.8 ; 0.7±0.6* ; 3.4±1.7 30±18; 29±18 ; 4±5* ; 27±15 *p<0.0005vs placebo Plac=placebo ; Prop=Propanolol ; SD=standard deviation ; Ver=verapamil Heart rate: the mean daytime and nocturnal heart rates were lower with propanolol than with placebo and verapamil (results presented in graph). Heart rate at the onset of ST depression was higher (>=10 beats/min) than that measured in the 5minutse preceding ischemia in 95% of the episodes (results from graphs).
Effect Size	
Source of funding:	research grant from University of Bologna
Does the study answer the question?/Further Comments	Yes. In the group as a whole, the number of ischemic attacks during the 48hr run-in period phase was not significantly different from that observed during placebo. Propanolol led to a significant decrease in number of episodes per 24hrs compared to placebo (p<0.0005). Conversely the number of episodes per 24hr during verapamil therapy was not significantly different from that observed during placebo Based on the results, the authors conclude that transient myocardial ischemia in syndrome X is mostly precipitated by an increase in oxygen consumption, presumably due to a heightened sympathetic activity. Accordingly beta blockers may represent the first line of treatment.

Cannon RO;Watson RM;Rosing DR;Epstein SE;

Efficacy of calcium channel blocker therapy for angina pectoris resulting from small-vessel coronary artery disease and abnormal vasodilator reserve

QUALITY

A. Selection bias (systematic differences between the comparison groups)

A4 Based on your answers t, in your opinion was selection bias present? If so, what is the likely direction of its effect?:

Unclear/unknown risk

Direction =

B. Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)

B4 Based on your answers to the above, in your opinion was performance bias present? If so, what is the likely direction of its effect?:

Low risk of bias

Direction =

C. Attrition bias (systematic differences between the comparison groups with respect to loss of participants)

C4 Based on your answers to the above, in your opinion was attrition bias present? If so, what is the likely direction of its effect?:

Low risk of bias

Direction =

D. Detection bias (bias in how outcomes are ascertained, diagnosed or verified)

D6 Based on your answers to the above, in your opinion was detection bias present? If so, what is the likely direction of its effect?:

unclear

Direction =

Overall Study Quality -Strengths and Weaknesses:

strength: double blind randomised crossover, lead-in phase to minimise side effects of treatment

weaknesses: randomisation and allocation concealment unclear, small sample size

DETAILS

# of patients: N=26

Prevalence (Diagnostic):

Patient Characteristics

Inclusion: patients admitted for evaluation of chest pain syndromes despite angiographically normal coronary arteries; normal epicardial arteries

Exclusion: hypertension, valvular heart disease

Baseline characteristics: 11 men and 15 women, aged 38 to 64 (mean 53)

Interventions/ Test/ Factor being investigated	calcium channel blocker: Patients randomised to receive either drug or an identically prepared placebo, each for 28 days on an outpatient basis. The drug and dosage used were determined from the unblinded lead-in phase: 17 patients received verapamil, 40-160mg 4 times a day (mode 80) and 9 patients received nifedipine 10-30mg 4 times a day (mode 10). A diary was kept to record episodes of chest pain and nitroglycerin consumption. No other medications were allowed during either drug or placebo periods. At the end of each 28-day period, patients underwent bicycle exercise testing. After 2 days without receiving any medication the second study medication phase began.
Comparisons	calcium channel blocker vs placebo
Length of Study/ Follow-up	28 days
Outcome measures studied	angina episodes ; nitroglycerin consumption; exercise duration
Results	Diary analysis: 22/26 patients During drug phase patients had fewer episodes of chest pain (21±21 vs 35 ±27 episodes $p<0.001$) and consumed fewer nitroglycerin tablets (23±27 vs 41±50 $p<0.001$) compared with the placebo phase. Exercise testing: Exercise duration :22/26 completed both phases of the study : exercise duration during the drug phase was slightly but significantly increased (278 ± 129 vs 231±136 seconds, $p<0.025$) compared to the placebo phase. Chest pain: 25/26 underwent exercise testing during the drug phase and 22/26 during placebo treatment. When the subjective endpoints were analysed , there was a greater frequency of chest pain as an endpoint during the placebo phase exercise test than during the drug phase exercise test, with 16/22 (73%) having chest pain during placebo phase exercise testing vs 9/25 (36%) during drug phase exercise testing ($p<0.01$)
Effect Size	
Source of funding:	not reported
Does the study answer the question?/Further Comments	Calcium channel blockers appear effective in reducing frequency and severity of angina and improving exercise tolerance in patients with chest pain resulting from abnormal vasodilator reserve. However, a few patients were unimproved and others continued to have residual chest pain even during calcium channel blocker therapy. Hence although these drugs are extremely helpful in the management of most patients with this syndrome, there appears to be additional reasons for limited coronary flow reserve, which are calcium channel blocker resistant.

Chen JW;Lee WL;Hsu NW;Lin SJ;Ting CT;Wang SP;Chang MS;

Effects of short-term treatment of nicorandil on exercise-induced myocardial ischemia and abnormal cardiac autonomic activity in microvascular angina

Ref ID 820 **RID:** 852 1997 Jul 1

QUALITY

A. Selection bias (systematic differences between the comparison groups)

A4 Based on your answers t, in your opinion was selection bias present? If so, what is the likely direction of its effect?:

Unclear/unknown risk

Direction =

B. Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)

B4 Based on your answers to the above, in your opinion was performance bias present? If so, what is the likely direction of its effect?:

Low risk of bias

Direction =

C. Attrition bias (systematic differences between the comparison groups with respect to loss of participants)

C4 Based on your answers to the above, in your opinion was attrition bias present? If so, what is the likely direction of its effect?:

Low risk of bias

Direction =

D. Detection bias (bias in how outcomes are ascertained, diagnosed or verified)

D6 Based on your answers to the above, in your opinion was detection bias present? If so, what is the likely direction of its effect?:

Unclear

Direction =

Overall Study Quality -Strengths and Weaknesses:

strengths: randomised, crossover design so no loss at follow up

weaknesses: randomisation, allocation concealment and blinding unclear, small sample size

DETAILS

# of patients: N=13

Prevalence (Diagnostic):

Patient Characteristics

10 men 3 women aged 51 to 66 (mean 57 ±6). 6 received placebo first then nicorandil, and 7 received nicorandil first followed by placebo.
6 nonsmokers, 5 exsmokers and 2 current cigarette smokers.

Inclusion consecutive patients who had previously normal coronary angiograms but still suffered stable angina for >3 months

Exclusion: diabetes mellitus, hypertension, left ventricular hypertrophy, valvular heart disease including mitral valve prolapse, sinus nodal dysfunction or conduction disturbance, variant angina, unstable angina, myocardial infarction, congestive heart failure, impaired renal function, thyroid disease. Patients with a difference of exercise duration >60sec or >15% between the 2 examinations 2 weeks apart

Interventions/ Test/ Factor being investigated	Nicorandil 5mg 3 times a day ; placebo tablet 3 times a day
Comparisons	nicorandil vs placebo
Length of Study/ Follow-up	treatment lasts 2 weeks outcomes measured at the end of each treatment phase
Outcome measures studied	heart rate ; blood pressure ; total exercise duration ; HR x BP ; time to 1mm STD; maximum STD
Results	Exercise performance and systemic hemodynamics before and during treadmill exercise test in microvascular angina patients with placebo or nicorandil: Placebo ; Nicorandil ; p values At baseline: HR (beats/min) 74±13 ; 74±16 ; 0.801 Systolic BP (mmHg) 132±14 ; 128±21 ; 0.642 Diastolic BP (mmHg) 69±5 ; 69±7 ; 0.211 During treadmill exercise test 1mm STD HR 136±22 ; 138±19 ; 0.223 Systolic BP 171±22 ; 176±30 ; 0.484 HR x BP (beat x mmHg/min) 23351±5256 ; 25371±7034;0.293 Time to 1mmSTD (s) 273±72 ; 342±104 ; 0.026 Peak exercise HR 147±22 ; 149±22 ; 0.209 Systolic BP 184±12 ; 184±32 ; 0.944 HR x BP 27171±4395 ; 27414±6150 ; 0.847 Total exercise duration (s) 405±64 ; 443±78 ; 0.036 Maximum STD (mm) 1.9±0.9 ; 1.5±0.6 ; 0.083 BP=blood pressure HR=heart rate STD=ST-segment depression
Effect Size	
Source of funding:	not reported
Does the study answer the question?/Further Comments	Results showed that both time to 1mmST depression and total exercise duration were significantly prolonged with nicorandil treatment compared with placebo. Maximum exercise ST depression also tended to be less with nicorandil treatment than with placebo. Compared with 10 healthy control subjects study patients had significantly reduced heart rate variability in both low- and high-frequency bands while receiving placebo. The authors concluded that 2-week oral nicorandil therapy moderately improved exercise-induced myocardial ischemia without modifying the already altered cardiac autonomic activity, suggesting that nicorandil might have a direct vasodilatory effect on coronary microvasculatures in patient with microvascular angina

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Lanza GA;Colonna G;Pasceri V;Maseri A;

Atenolol versus amlodipine versus isosorbide-5-mononitrate on anginal symptoms in syndrome X

Ref ID 7268 RID: 845 1999

QUALITY

A. Selection bias (systematic differences between the comparison groups)

A4 Based on your answers t, in your opinion was selection bias present? If so, what is the likely direction of its effect?:

Unclear/unknown risk

Direction =

B. Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)

B4 Based on your answers to the above, in your opinion was performance bias present? If so, what is the likely direction of its effect?:

Unclear/unknown risk

Direction =

C. Attrition bias (systematic differences between the comparison groups with respect to loss of participants)

C4 Based on your answers to the above, in your opinion was attrition bias present? If so, what is the likely direction of its effect?:

Low risk of bias

Direction =

D. Detection bias (bias in how outcomes are ascertained, diagnosed or verified)

D6 Based on your answers to the above, in your opinion was detection bias present? If so, what is the likely direction of its effect?:

Unclear

Direction =

Overall Study Quality -Strengths and Weaknesses:

stength: crossover randomised
weaknesses: small sample size, unclear randomisation and allocation concealment

DETAILS

# of patients:

N=10 randomised double blind crossover

Prevalence (Diagnostic):

Patient Characteristics

6 women, age 57 ±6 years
Recent diagnosis of syndrome X (demonstration of totally normal arteries at angiography in subjects with history of effort angina and ischemic-like ST segment changes (>=1mm horizontal or downsloping ST depression 80ms after the J point) on exercise testing). Not taking specific drugs nor any agents of the 3 classes of drugs

Exclusion: other cardiac and systemic diseases, including hypertension and diabetes

Interventions/ Test/ Factor being investigated	Beta blocker (atenolol) ; nitrate (isosorbide-5-mononitrate [ISMN]);Calcium antagonist (amlodipine) 4 wks washout then 4 wks atenolol/amlodipine/ISMN After each, assessment of chest pain episodes reported in diary + self assessment of quality of life
Comparisons	atenolol vs wash out ; amlodipine vs washout ; ISMN vs washout
Length of Study/ Follow-up	4 weeks treatment
Outcome measures studied	number of anginal episodes ; duration of chest pain ; severity of chest pain ;
Results	Results: Baseline ; ISMN ; Amlodipine ; Atenolol No of anginal episodes/4wks/patient 24±18; 24±22 ; 22±22 ; 15±13* Duration of chest pain episodes (min) 12±6 ; 11±7 ; 16±17 ; 14±13 Severity of chest pain (scale 1-5) 2.5±0.9 ;2.3±1.2 ; 2.7±1.0 ; 2.5±1.2 Sublingual nitrate consumption 5.8±8 ;10.1±18 ; 6.6±14 ; 5.0±10 Quality of life (scale 0-100mm) 22±17 ;30±27 ; 51±25* ; 59±29* *p<0.05 versus baseline Mean number of chest pain episodes during each of the 4 wk treatment periods: Nitrate and Amlodipine no significant difference compared to washout, Atenolol significantly different (p<0.05) (read from graph)
Effect Size	
Source of funding:	not reported
Does the study answer the question?/Further Comments	Atenolol, but not amlodipine or ISMN was effective in controlling chest pain episodes in patients with CSX, suggesting that it should be the preferred drug when starting pharmacologic therapy in these patients.

Pizzi C;Manfrini O;Fontana F;Bugiardini R;

Angiotensin-converting enzyme inhibitors and 3-hydroxy-3-methylglutaryl coenzyme A reductase in cardiac Syndrome X: role of superoxide dismutase activity

Ref ID 9042 **RID:** 874 2004 Jan 6

QUALITY

A. Selection bias (systematic differences between the comparison groups)

A4 Based on your answers t, in your opinion was selection bias present? If so, what is the likely direction of its effect?:

Low risk of bias

Direction =

B. Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)

B4 Based on your answers to the above, in your opinion was performance bias present? If so, what is the likely direction of its effect?:

Low risk of bias

Direction =

C. Attrition bias (systematic differences between the comparison groups with respect to loss of participants)

C4 Based on your answers to the above, in your opinion was attrition bias present? If so, what is the likely direction of its effect?:

Low risk of bias

Direction =

D. Detection bias (bias in how outcomes are ascertained, diagnosed or verified)

D6 Based on your answers to the above, in your opinion was detection bias present? If so, what is the likely direction of its effect?:

low risk

Direction =

Overall Study Quality -Strengths and Weaknesses:

DETAILS

# of patients:

N=22 atorvastatin and ramipril
N=23 placebo

Prevalence (Diagnostic):

Patient Characteristics

Baseline

Parameter	atorvastatin + ramipril	placebo
Age	59.6±	57.6±9.6
Female gender n(%)	19(86)	21(91)
BMI	25.6±2.1	26.1±2.3
Diabetes n(%)	2(9)	2(9)
Smoking n(%)		
Never smoked	13(59)	17(74)
Currents mokers	9(41)	6(26)
Family history	7(32)	9(39)

Seattle Angina Questionnaire Domain Score

	Atorvastatin+ramipril	Placebo
Angina stability	52.4±10.1	54.4 ±13.6
Angina frequency	50.2 ±7.6	50.8 ±12.7
Quality of Life	50.7 ±6.6	52.7 ±10.9

	Summary score 51.3 ±6.4 52.6±11.9 Inclusion: typical chest pain at rest and/or on effort ; normal 12-lead ECG at rest ; ischemia-like ECG changes during exercise stress test (horizontal or downsloping ST-segment depression >0.1mV) ; myocardial reversible perfusion abnormalities during exercise stress as assessed by single-photon emission-computed tomography ; normal left and right ventricular function at rest as assessed by echocardiography ; absence of valvular heart disease and myocardial hypertrophy ; normal coronary angiograms at visual analysis and absence of coronary artery spasm during intravenous ergonovine test. Exclusion: hyperlipidemia (cholesterol >220mg/dL) or treatment with statins or ACE-1 for any reason ; malignancy ; kidney or liver failure; ongoing drug or alcohol abuse ; systemic inflammatory diseases ; contraindication to ACE-1 and statins
Interventions/ Test/ Factor being investigated	All patients received diltiazem 180mg daily. Patients instructed to take 3 capsules a day (drugs or placebo), the first capsule (5mg of ramipril) in the morning after breakfast and the remaining 2 (one of 5mg ramipril, the other of 40mg atorvastatin) in the evening after dinner.
Comparisons	ramipril + atorvastatin vs placebo
Length of Study/ Follow-up	6 months
Outcome measures studied	Seattle Angina Questionnaire (angina stability, frequency, quality of life) ; Exercise stress test (exercise duration, ST depression, flow-mediated dilation of brachial artery)
Results	Results Seattle Angina Questionnaire Domain Score Parameter Atorvastatin+ramipril Placebo P-value Angina stability 84.2±10.5 62.6 ±13.2 <0.001 Angina frequency 82.1 ±13.8 62.4 ±10.5 <0.001 Quality of Life 86.5 ±11.7 61.9 ±9.4 <0.001 Summary score 84.2 ±9.8 63.3±8.6 <0.001 Probability values are reported for comparison by 2-way ANOVA, comparing differences attributable to treatment Exercise stress test Parameter Atorvastatin+ramipril Placebo P-value Peak exercise duration(s) 555.6 ±84.6 488.4±79.2 0.045 ST depression (mv) 0.12±0.3 0.21±0.8 0.003 Flow-mediated dilation of brachial artery (%) 4.2 ±1.7 2.3 ±1.2 0.001 Probability values are reported for comparison by 2 way ANOVA, comparing differences attributable to treatment
Effect Size	
Source of funding:	not reported
Does the study answer the question?/Further Comments	Six months of therapy with atorvastatin and ramipril improved endothelial function and quality of life of patients with cardiac syndrome X. Treatment prevented chest pain and ST depression at follow up exercise testing in 41% of patients. Patients who received atorvastatin and ramipril had significantly improved flow-dependent endothelium-mediated dilation

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Radice M;Giudici V;Pusineri E;Breghi L;Nicoli T;Peci P;Giani P;De AL;

Different effects of acute administration of aminophylline and nitroglycerin on exercise capacity in patients with syndrome X

Ref ID 912 **RID:** 851 1996 Jul 1

QUALITY

A. Selection bias (systematic differences between the comparison groups)

A4 Based on your answers t, in your opinion was selection bias present? If so, what is the likely direction of its effect?:

Unclear/unknown risk **Direction =**

B. Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)

B4 Based on your answers to the above, in your opinion was performance bias present? If so, what is the likely direction of its effect?:

Unclear/unknown risk **Direction =**

C. Attrition bias (systematic differences between the comparison groups with respect to loss of participants)

C4 Based on your answers to the above, in your opinion was attrition bias present? If so, what is the likely direction of its effect?:

Low risk of bias **Direction =**

D. Detection bias (bias in how outcomes are ascertained, diagnosed or verified)

D6 Based on your answers to the above, in your opinion was detection bias present? If so, what is the likely direction of its effect?:

Low risk **Direction =**

Overall Study Quality -Strengths and Weaknesses:

Strength :crossover design

Weaknesses: unsure of randomisation, allocation concealment methods

DETAILS

# of patients: N=20

Prevalence (Diagnostic):

Patient Characteristics 1 man, 19 women, aged 45-65 years (mean 54.8 ±6.4)

Inclusion: history of stable angina with chest pain elicitede solely or primarily by physical exertion; positive exercise test result; normal coronary angiographic findings ; no evidence of spontaneous or induced coronary spasms.

	Exclusion: left ventricular hypertrophy, systemic hypertension, previous myocardial infarction, cardiomyopathy, valvular heart dsease or mitral prolapse, diabetes, glucose intolerance
Interventions/ Test/ Factor being investigated	aminophylline 400mg/day ; nitroglycerin 0.3mg/day. On 2 consecutive days patients underwent 3 maximal bicycle ergometer tests in the sitting position with an initial workload of 30W and increments of 20W every 2 minutes. The first test was performed without any medication and was considered the baseline test. 30 minutes after the baseline test patients repeatred the test after either sublingual nitroglycerin or oral aminophylline. The exercise test began 5 minutes after nitroglycerin administration, or 90 min after aminophylline, respectively. A 12-lead ECG and BP measurements were recorded at rest and at 1 min intervals during exercise and for >=5min during recovery.
Comparisons	aminophylline vs nitroglycerin
Length of Study/ Follow-up	no follow up, measurements during the exercise and during recovery
Outcome measures studied	Time to 1mm ST depression
Results	Basal ; Aminophylline p value ; Nitroglycerin p value Time to 1mm ST Depression: 3.5 ±1.6 ; 5.5±1.6 <0.01 ; 3.6±1.7 <0.01
Effect Size	
Source of funding:	not reported
Does the study answer the question?/Further Comments	The study shows that oral preparation of aminophylline does not cause unacceptable adverse effects and induces a remarkable improvement in exercise tolerance in patients with syndrome X

Romeo F;Gaspardone A;Ciavolella M;Gioffre P;Reale A;

Verapamil versus acebutolol for syndrome X

Ref ID 1761 **RID:** 848 1988 Aug 1

QUALITY

A. Selection bias (systematic differences between the comparison groups)

A4 Based on your answers t, in your opinion was selection bias present? If so, what is the likely direction of its effect?:

Unclear/unknown risk

Direction =

B. Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)

B4 Based on your answers to the above, in your opinion was performance bias present? If so, what is the likely direction of its effect?:

Unclear/unknown risk

Direction =

C. Attrition bias (systematic differences between the comparison groups with respect to loss of participants)

C4 Based on your answers to the above, in your opinion was attrition bias present? If so, what is the likely direction of its effect?:

Low risk of bias

Direction =

D. Detection bias (bias in how outcomes are ascertained, diagnosed or verified)

D6 Based on your answers to the above, in your opinion was detection bias present? If so, what is the likely direction of its effect?:

unclear

Direction =

Overall Study Quality -Strengths and Weaknesses:	Strength: randomised double blind crossover trial, no loss at follow up weaknesses: randomisation, blinding, allocation concealment not reported. Small sample size

DETAILS

# of patients:	N=30 patients included in the crossover study. They were divided into 2 subgroups according to median of pressure-rate product (mmHg x beats/min):
Prevalence (Diagnostic):	
Patient Characteristics	Inclusion criteria: Exertional angina At least 2 positive comparable exercise tests performed on separate days in the month before the study Angiographically normal epicardial coronary arteries Absence of coronary artery spasm after infusion of ergonovine maleate No evidence of cardiomyopathy, valvular heart disease, systematic hypertension (>150/95 mm Hg), diabetes mellitus and collagen disease Baseline information: 27 women (9 with menstrual cycles) and 3 men (mean age 50 ±9 years)
Interventions/ Test/ Factor being investigated	acebutolol vs. verapamil

Comparisons	Acebutolol (a β1 specific blocking agent) vs. verapamil (calcium channel blocker) Acebutolol 400mg a day for 4 weeks Verapamil 80mg 4 times a day for 4 weeks 1 week washout period before treatment and in between treatment
Length of Study/ Follow-up	immediately post treatment
Outcome measures studied	After each period of treatment patients underwent exercise test which was continued up to the maximal predicted heart rate or ST depression >=0.1mV Recorded: Heart rate Systolic BP Double product Total exercise duration at the time of ST depression =0.1mV or at max predicted heart rate
Results	Resting double product and double product and total exercise duration at the time of ST depression = 0.1mV: Rest DP ;Stress DP; ED Group1 B 10560±1980; 23490±3480 ; 326±110 V 9750±2835* ; 24230±3665**; 362±93** A 9080±1240; 23430±3370;318±101 Group 2 B 11020±2200; 29235±4570; 246±80 V 10650±1890*;31040±4140**; 288±80** A 8960±1300**;30830±4430**;288±66** Values are mean ± SD *p<0.01 ; **p<0.001 A=acebutolol; B=basal (without therapy); V=verapamil; DP=double product; ED=total exercise duration
Effect Size	
Source of funding:	not reported
Does the study answer the question?/Further Comments	Group 1 showed a significant increase in exercise tolerance expressed as double product and total exercise test duration at the time of ST depression=0.1mV after verapamil, but no significant improvements after acebutolol. Group 2 revealed a significant improvement in exercise tolerance and duration both after verapamil and acebutolol. The different results obtained using a calcium channel blocker and a beta1 specific blocker in the 2 subgroups of syndrome X patients suggest that different mechanisms could be involved in the pathogenesis of myocardial ischemia; in fact, verapamil was effective in both groups in improving exercise tolerance and duration, probably by increasing coronary vasodilatory capacity. However, the same result was obtained with acebutolol in patients with higher sympathetic response to stress suggesting that, at least in this group of patients, an anomalous sympathetic drive may be an important contributor to the pathogenesis of myocardial ischemia.