Systematic review of the efficacy and safety of transmyocardial and percutaneous laser revascularisation for refractory angina pectoris

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Contributions of authors

Fiona Campbell and Josie Messina screened the search results, assessed studies for inclusion, undertook data extraction and quality assessment, conducted data analysis and drafted the review. Fiona Campbell drafted the scope and acted as review lead. Anna Cantrell developed and drafted sections concerning search strategies and search results. Patrick FitzGerald provided advice on statistical analysis and conducted the meta-analyses. Carolyn Czoski-Murray supervised the conduct of the review and commented on drafts of the review.

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EXECUTIVE SUMMARY

Chronic angina pectoris is caused by inadequate delivery of oxygen to the heart muscle and is usually a result of coronary artery disease. Its effects can be very disabling, causing pain in the chest, shoulder, arm or throat area, particularly during exertion. Most patients with angina due to coronary artery disease respond adequately to treatment with antianginal medication, coronary angioplasty, or coronary-artery bypass surgery. Some patients, however, present with angina that is not controlled (or refractory) to such treatment. Transmyocardial laser revascularisation (TMLR) was developed as a potential treatment for such groups of patients.

TMLR involves the creation of shallow channels within the wall of the heart muscle using a laser beam. The aim is that these channels allow blood flow from the ventricular cavity into the myocardium and therefore into the coronary circulation thereby relieving myocardial ischemia and the symptoms of angina.[1] The procedure can be carried out as an open procedure via a thoracotomy (transmyocardial laser revascularisation – TMLR) or as a percutaneous procedure (percutaneous laser revascularisation – PMR).

Objective

The evidence base for the procedure is conflicting and the theoretical basis underpinning its effects is poorly understood. The objective of this review was to examine the effectiveness and safety of transmyocardial laser revascularisation and percutaneous laser revascularisation for patients with refractory angina pectoris.

Methods

Information specialists searched electronic databases using terms agreed by the review team in consultation with clinical advisors. We also scanned bibliographies of retrieved papers to identify any relevant papers that were not screen during electronic searches. Searches were restricted to publications from 1980 onwards and to those published in the English language. The search strategies were designed to retrieve all relevant publications for the PMR and TMLR surgeries. Studies were included if they met the following criteria for design, types of participants, interventions and outcomes

Types of studies:

- RCTs (full text)
- Non-randomised comparative studies (full text);
- Case series with a minimum sample size of 100 patients for TMLR and no sample size restrictions for PMR as there were so few studies.

Types of participants:

Participants were described as having refractory angina. Refractory angina was

- Patients over 18 years with refractory angina defined a chronic condition characterised by the presence of angina, caused by coronary insufficiency in the presence of coronary artery disease, which is not adequately controlled by a combination of medical therapy, angioplasty, and coronary artery surgery.

Types of interventions:

- Laser revascularisation of myocardium using either a Holmium: YAG laser, carbon dioxide laser or excimer laser. The comparator could be continued medical management or another surgical or percutaneous procedure.

Types of outcome:

- Mortality rate, exercise tolerance test, angina score, quality of life and left ventricular ejection fraction
- Adverse events including perioperative mortality rates

Two reviewers screened titles/abstracts, and two reviewers completed the task of data extracting all RCTs and observational studies. Both reviewers assessed the quality of the included RCTs, but one reviewer assessed observational study quality using a checklist according to study design.

Meta-analyses was completed by a statistician and results were analysed by the lead reviewer. Meta-analysis and meta-regression analyses were carried out using Stata (v10, StataCorp, 2007)[2] commands *metan* and *metareg*

Results

From the 102 papers retrieved from the initial search, 29 studies were included in the review, of which 16 were RCTs (10 trials of TMLR and 6 of PMR) and 13 were non-randomised studies (8 studies of TMLR and 5 of PMR). The papers were published between 1999 and 2006. RCT data was used to explore effectiveness and non-randomised evidence was used in addition to the RCT evidence to consider safety. A total of 4507 patients were included in all the studies in the review.

TMLR – efficacy

The 10 RCTs included ranged in size from 20 to 275 participants (total 1359). The most commonly used laser was either the Holmium: YAG laser or the carbon dioxide laser. Control groups were medical management (7 trial), CABG (2 trials) and thoracic sympathectomy (1 trial). The methodological quality of the trials was mixed. Two were considered at high risk of bias as they allowed cross over of patients from control to treatment group. Only one trial blinded patients to treatment group.

1. Objectively assessed efficacy outcomes

Mortality rates at 12 months follow-up did not differ between groups (OR 0.83 CI 0.49 to 1.41). Objective outcome measures; i.e. myocardial perfusion tests and left ventricular ejection fraction showed no difference between intervention and control group or between baseline and final values.

2. Patient report outcomes

More subjective outcome measures including exercise tolerance, angina score and quality of life scores showed a different pattern of effect. Exercise tolerance showed a benefit with treatment, with total exercise time increased at 12 months by 81.9 seconds (95%CI 26.7 to 137.3). This effect was lost however when a sensitivity analysis explored the effect of blinding on exercise tolerance. When patients were blind to their treatment group there was no difference in exercise tolerance between groups. Angina score was reduced significantly in the treatment groups by -1 CCSA class (95% CI -1.7 to -0.3).

TMLR - safety

Perioperative mortality rates were evaluated using data from the included RCTs. When TMLR is compared with medically managed controls and thoracic sympathectomy (1 trial) there is a statistically significant increase in the odds of perioperative death (OR 0.35 95% CI 0.13 to 0.93). In a narrative analysis of the non-randomised studies there appears to be a range harmful events more likely to affect the intervention group, including myocardial infarction and heart failure.

PMR - efficacy

The six included RCTs ranged in size from 68 to 275 with a total of 1040 participants. The intervention was carried out using a Holmium: YAG laser. The majority of the participants were male and most of the studies were conducted in the USA. Three trials compared the laser intervention with ongoing maximal medical management, two with sham therapy and one with spinal cord stimulation. Three trials blinded patients and data collectors to the treatment group.

1. Objectively assessed efficacy outcomes

Mortality rates showed no statistically significant difference between intervention and control groups. (odds ratio 0.74 95% CI 0.32 to 1.7). One trial assessed myocardial perfusion using SPECT myocardial imaging following an adenosine infusion. It found no significant differences between intervention and control group. Two trials measured left ventricular

ejection fraction and found no difference between groups or between baseline and final values.

2. Patient report outcomes

Exercise tolerance was reported in all the trials. At 12 months there was a statistically significant increase of 17.7 seconds (95% CI 4.4 to 31.0) but this result is unlikely to be clinically significant. A sensitivity analysis adjusting for blinding of patients found that the results were non-significant at 12 months. Angina score was measured by all of the trials. At 12 months there was a significant improvement in the number of patients who had improved their angina score by 2 or more classes. This result was not significant at 6 months when the meta-analysis included the results from two trials where patients were blinded to treatment.

Quality of life was measured and reported in five trials. Only one trial found a statistically significant difference between intervention and control groups.

PMR- safety

Perioperative mortality rate data was derived from the included RCTs and did not show any difference between treatment and intervention group (odds ratio 1.35 95% CI 0.37 to 4.92). In a narrative analysis of the non-randomised studies there appears to be risks of experiencing a range of cardiovascular and vascular adverse events with treatment, including myocardial haematoma, bradycardia and bundle-branch block.

TMLR and PMR are interventions with a poorly understood mechanism of effect. While theories are postulated, they remain unconfirmed. The patients studied in these trials had severe angina symptoms and had exhausted all forms of conventional therapy. They are likely to be motivated to want a novel therapy that might provide symptom relief.

This review has shown that for those outcomes where there is an objective measure of heart function, i.e. myocardial perfusion and left ventricular ejection fraction no effect is seen with treatment. This is despite a range of methods used to measure the outcomes as seen in the included trials.

Patient reported outcomes which include exercise tolerance tests, angina score, and quality of life show a statistically significant effect in favour of treatment. This effect is however lost or much reduced where patients are blinded.

The concomitant postoperative mortality risk with TMLR and the associated risks of adverse effects raise concerns about the safety also of these interventions.

The wider applicability of these findings must also be considered. The majority of participants in these trials were male and the majority of trials undertaken in the USA. There is no evidence to assume the benefits seen in subjective outcome measures would be the same in different patient populations.

ABBREVIATIONS

CABG- coronary artery bypasses graft
CAD- coronary artery disease
CCS- Canadian cardiovascular score
LVEF- left ventricle ejection fraction
PCI- percutaneous coronary intervention
PMR- percutaneous laser revascularisation
TMLR- transmyocardial laser revascularisation

GLOSSARY ANGINA REVIEW TERMS

Angina Pectoris is chest discomfort (usually described as pressure or pain) occurring beneath the breastbone when the heart is not getting enough oxygen. Typically, it occurs with exercise or emotional stress, lasts only a few minutes, and goes away with rest. Angina pectoris, or simply "angina," results when blood flow to the heart muscle is inadequate because heart arteries have been narrowed by cholesterol deposits or when there is an imbalance between oxygen demand and oxygen supply caused by hypertension or vascular disease.[3]

Bruce Protocol Stress Test is a treadmill test to assess possible coronary artery disease, as well as physical fitness. Treadmill speed and incline increase until the subject has reached exhaustion. A subject's time is recorded as the test score. A modified Bruce Protocol Test, which assesses patients at a lower workload, is often employed in angina studies where patients are likely to be sedentary and elderly.

The fist two stages of the Modified Bruce Test are performed at a 1.7 mph and 0% grade and 1.7 mph and 5% grade, and the third stage corresponds to the first stage of the Standard Bruce Test protocol as listed above.[4]

Canadian Cardiovascular Society (CCS) angina classification, developed in 1972, builds on the classification scheme set out by the New York Heart Association; however, classification criteria are more detailed specifying physical activities, events, and emotional states that may induce angina. Functional classes range from I through IV, with class IV being the most disabling form of angina resulting in pain/discomfort during *any* physical task.

Coronary Artery Bypass Graft (CABG) surgery is a type of operation used to restore normal blood flow to the heart muscle when arteries that supply blood to the heart are

blocked or narrowed. CABG surgery involves taking a short length of blood vessel—often a vein from the thigh or the lower leg or the internal mammary artery beneath the breastbone—and using it to connect the diseased blood vessel beyond the blockage site. CABG is the most common major surgery performed in the United States; three-fourths of patients today are still active 15 years after surgery. See also open-heart surgery.[4]

(Left Ventricle) Ejection Fraction (Ef) refers to the process by which blood is pumped out of the ventricle with every beat. When blood is pumped out of the left ventricle it is termed Left Ventricle Ejection Fraction (LVEF). For a normal and healthy heart, ejection fraction should be between 55 and 70 percent; however, damaged hearts may have decreased Efs. LVEF can be measured in several ways: echocardiography, ultrasounds, MRI, fast scan cardiac computed axial tomography (CT) imaging, ventriculography, Gated SPECT, and the MUGA scan.

Myocardial infarction/heart attack is a medical emergency that occurs when a blood clot forms suddenly in a heart artery and causes a blockage, usually after the surface of cholesterol plaque in the artery breaks. A heart attack, also called a myocardial infarction, usually produces chest pain and shortness of breath. It may also cause sudden death. If nothing is done to reopen the blocked artery, the heart muscle will die and be replaced by scar tissue. More than one million heart attacks occur every year in the United States; it is the leading cause of death from heart disease. Most of these deaths occur outside the hospital.[3]

New York Heart Association (NYHA) scale classifies a patient's cardiovascular (dis)abilities and degree of symptoms during a point in time. Classifications allow for comparison between patients, as well provide a method for patient monitoring over time. Functional classes range from I through IV, with IV being the most disabling form of angina resulting in pain/discomfort during *any* physical task.

SF-36 is a shortened version of a prior USA health survey with eight sections (see below) designed to assess various aspects of a patient's health status. Data obtained from this survey can be useful in evaluating patients before and after surgery, understanding the cost-effectiveness of a treatment, and monitoring and comparing disease burden.

- vitality
- physical functioning
- bodily pain
- general health perceptions

- physical role functioning
- emotional role functioning
- social role functioning
- mental health

Stress Test involves studying the heart during exercise to identify the presence of ischemic heart disease or the risk of developing problems while doing strenuous activities. The patient typically walks on a treadmill or peddles a stationary bicycle while connected to an electrocardiograph (ECG) machine. The ECG measures heart rhythms and can suggest when the heart muscle is not receiving adequate blood supply with exertion. To improve its accuracy, a stress test is often accompanied by an imaging technique (nuclear myocardial imaging or echocardiography). In some instances, drugs may be used to simulate heart activity during exercise. The stress test has three primary uses: 1) It is particularly helpful for people with cardiac risk factors who are about to begin an exercise programme, 2) it helps cardiologists evaluate chest pain, 3) it can be used to evaluate the benefits of treatment over time.[3]

1 OBJECTIVE OF THE REVIEW

The aim of this study was to systematically review the evidence for the efficacy and safety of transmyocardial laser revascularisation (TMLR) and percutaneous laser revascularisation (PMR) for the treatment of refractory angina pectoris.

2 BACKGROUND

2.1 Description of the underlying health problem

2.1.1 Definition

Chronic angina pectoris is caused by inadequate delivery of oxygen to the heart muscle and is usually a result of coronary artery disease. It generally manifests as a feeling of heaviness in the chest, shoulder arm or throat area, particularly during exertion. Most patients with angina due to coronary artery disease respond adequately to treatment with antianginal medication, coronary angioplasty, or coronary-artery bypass surgery. Some patients, however, present with angina that is refractory to such treatment. Patients with distal stenoses, diffused coronary artery disease, small coronary arteries, or pervious failed procedures are unlikely to be revascularised and will likely experience angina symptoms that may require hospitalisation. [5]

This group of patients is described as having **chronic refractory angina pectoris** which is defined as, **"a chronic condition characterised by the presence of angina, caused by coronary insufficiency in the presence of coronary artery disease, which cannot be adequately controlled by a combination of medical therapy, angioplasty, and coronary artery surgery. The presence of reversible myocardial ischemia should be clinically established to be the cause of symptoms".[6]**

Angina severity and the functional limitations arising from it can be measured using different scales. The Canadian Cardiac Society Angina score uses a four-point scale from class I with angina present only with strenuous or rapid or prolonged exertion to class IV where there is an inability to carry on any physical activity with out discomfort and anginal symptoms may be present at rest.

The New York Heart Association (NYHA) angina scale also uses a four-point scale and categorises impairment from Class I where ordinary physical activity does not cause undue fatigue, palpitation, dyspnoea or anginal pain to class IV where patient have an inability to carry on any physical activity without discomfort.

The Seattle Angina score encompasses encompasses 19 questions within 5 categories (physical limitation, angina stability, angina frequency, satisfaction with treatment, disease perception). Scores range from 0 to 100, where higher scores indicate better levels of functioning.

The Duke Activity Status Index is a weighted 12 question survey covering activities of living, scores range from 0 to 58.2 points with higher scores indicating better functioning.

2.1.2 Epidemiology and Disease burden

In the UK, 2-3% of the population have angina with rates slightly higher amongst men over the age of 55 (14.9%) than amongst women (9.1%). An increasing proportion of these patients suffer from refractory angina which carries a very heavy disease burden, very negatively impacting upon quality of life and functional capacity. [7,8]

2.2 Current management and alternative procedures

Refractory angina is by definition unresponsive to the standard medical or interventional therapies. Nevertheless, anti-anginal medication is often used as background treatment. Other treatment options include transcutaneous electrical nerve and spinal cord stimulation, and external counterpulsation. Alternative surgical procedures include open laser transmyocardial revascularisation

2.3 The interventional procedure under review

The growing number of patients with diffuse obstructive coronary artery disease not amenable to coronary artery by-pass grafting or catheter based interventions has stimulated efforts to develop alternative approaches. Myocardial revascularisation involves the attempted creation of channels by drilling holes within the wall of the heart muscle The use of high-energy lasers for this purpose was first described by Mirhoseini et al in 1983[1]. The original concept of direct myocardial revascularisation was to carry blood from the ventricular cavity into the myocardium and therefore into the coronary circulation thus relieving myocardial ischaemia and the symptoms of angina. The theory was based on the model of the reptilian heart, in which the left ventricle is directly perfused from endothelium-lined channels that radiate out from the left ventricular cavity.

The procedure can be carried out as an open procedure via a thoracotomy (transmyocardial laser revascularisation – TMLR) or as a percutaneous procedure (percutaneous laser revascularisation – PMR).

2.3.1 TMLR

TMLR is carried out under general anaesthesia. A lateral thoracotomy is performed and the pericardium opened, usually without cardiopulmonary bypass. Laser ablation (using a variety of devices) is undertaken to drill holes in the myocardium, which has previously been identified as being viable for revascularisation by echocardiography or myocardial perfusion scan. The procedure may be guided by transoesophageal echocardiography. The procedure could be undertaken concurrently with a CABG procedure.

2.3.2 PMR

PMR involves attempting to create shallow channels in the myocardium which are thought to encourage revascularisation which in turn increases overall blood supply. The procedure is undertaken under local anaesthesia. The myocardium is first identified as being viable for revascularisation by echocardiography or myocardial perfusion scan. Revascularisation is then performed by laser ablation via a delivery catheter drilling a number of parallel channels in the myocardium. The procedure is usually guided by fluoroscopic imaging.

2.3.3 Underlying mechanisms describing intervention effect

Mirhoseini's '86[1] theory of improving myocardial blood glow via transmyocardial channels mimicking the reptilian heart have subsequently been discounted as the myocardial channels close after a short time.[9] Alternative theories as to why the procedure may be effective have been suggested and include:

Angiogenesis is one of several theories explaining the benefits of revascularisation surgeries such as PMR and TMLR. The stimulation of new blood vessel growth in the heart is said to aid in restoring and improving blood flow and function of the myocardium.[5] During the process of angiogenesis endothelial cells are forming new vessels which eventually grow into network of endothelial tubes that will mature and become functionally important.[6] In the later stages of angiogenesis, newly creates vessels become covered by a muscular coating resulting in a change in blood vessels diameter due to the visco-elastic characteristics of the newly formed vessels. [6] TMLR and PMR procedures aim to revascularise the heart and have the primary aim of increasing blood flow.

Denervation is another theory explaining the potential benefits of TMLR and PMR. This describes the destruction of nerve fibres in the cardiac pathways which can alter patient's perception of their angina. The superficial location of sympathetic fibres in the epicardium of the left ventricle and the belief that perception of anginal pain is conveyed by afferent sympathetic fibres together with the immediate relief of angina after TMR led to the proposition that the effect of TMR may be mediated by sympathetic denervation, but this concept has been disputed. [10]

Placebo effect is a well recognised factor but is poorly understood in clinical trails.[11]The fundamental cause of the placebo effect is a patient's belief that a treatment may be beneficial. [12] Much of the placebo effect is psychological and can be enhanced by interaction with the physician and the sensory impact of the treatment. [12] A placebo is a procedure or medication with no effect that is given to patients as either part of treatment or in clinical trial for its symbolic value. The resulting response from the given treatment is the placebo effect that operates on the basis of what the patient feels and less on objective disease or illness. [11] Interventions such as TMLR and PMR maybe linked to the placebo effect since outcome measures, such as angina score classifications and quality of life surveys, focus on a patient's subjective meaning of health and illness.

3 METHODS FOR REVIEWING SAFETY AND EFFICACY

3.1 Search strategy

A comprehensive literature search was performed in July 2008. Searches were designed to retrieve:

- Papers describing the clinical effectiveness of laser surgery for angina
- Papers on the safety of laser surgery for angina.

The following electronic bibliographic databases were searched:

1. BIOSIS previews (Biological Abstracts)
2. British Nursing Index (BNI)
3. Cumulative index to nursing and allied health literature (CINAHL)
4. Cochrane Database of Systematic Reviews (CDSR)
5. Cochrane Central Register of Controlled Trials (CENTRAL)
6. Embase
7. Medline
8. Medline In-Process & Other Non-Indexed Citations
9. NHS Database of Abstracts of Reviews of Effects (DARE)
10. NHS Health Technology Assessment (HTA) Database
11. Science Citation Index (SCI)
12. Social Sciences Citation Index (SSCI)

To retrieve clinical effectiveness papers systematic review and randomised controlled trials filters were used where appropriate.

To retrieve papers on the safety of laser surgery for angina a list of terms related to safety were compiled and used in the search process where appropriate.

Attempts were also made to identify 'grey' literature by searching appropriate databases (e.g. Kings Fund, DH-Data) current research registers (e.g. National Research Register, Current Controlled Trials Register, ReFer Research Finding Register). A general internet search was also conducted using a standard search engine (Google) and a meta-search engine (Copernic). The reference lists of included studies and relevant review articles were also checked. No date or language restrictions were applied to these searches. Appendix 1 documents full details of the search strategies used.

3.2 Study Selection

Potentially relevant trial reports were retrieved and assessed and those fulfilling criteria listed below were included. Decisions were checked by a second reviewer with difference resolved by discussion.

3.2.1 Types of studies

- Randomised controlled trial with one year follow-up
- TMLR - Non randomised studies with over 100 participants and for 1 year follow-up
- PMR – Non randomised studies
- Studies published in English

3.2.2 Types of participants

- Enrolled adult patients with refractory angina defined as a chronic condition characterised by the presence of angina, caused by coronary insufficiency in the presence of coronary artery disease, which could not be adequately controlled by medical therapy, angioplasty, and coronary artery surgery. This corresponds to class III or IV of the Canadian Cardiovascular Society score.

3.2.3 Types of intervention

- Where the intervention involved the attempted creation of channels in the myocardium using a laser device. Devices included the Holmium: YAG laser, carbon dioxide laser and excimer laser. We also included studies where the intervention was carried out in conjunction with another procedure such as CABG.
- For RCTs the comparator could be continued medical management or another additional surgical or percutaneous procedure.

3.2.4 Types of outcome

Included studies reported at least one of the following outcomes.

We considered the following outcomes in the assessment of efficacy:

- Mortality rate
- Myocardial perfusion
- Left ventricular ejection fraction
- Exercise tolerance tests
- Angina Score
- Quality of life

In an assessment of safety we considered:

- Perioperative mortality rates (deaths within 30 days of surgery)

- All described adverse events
- Morbidity, looking specifically at the incidence of myocardial infarction, unstable angina, heart failure, pneumonia, bleeding/haemorrhage, arrhythmia, rupture of mitral valve, infection (other than pneumonia).

3.3 Data extraction

One reviewer screened the titles of all papers identified by the search strategy. A second reviewer checked all the exclusions to ensure no relevant studies were missed. Full text copies of all potentially relevant papers were retrieved. A data extraction form was developed in consultation with clinical advisors and piloted. Data on quality, characteristics of participants, intervention and relevant outcomes were independently extracted by two reviewers.

3.4 Quality assessment

Two reviewers assessed the quality of the studies using one of two separate checklists based on study design. Randomised controlled trial quality was assessed by looking at 4 key methodological domains; method of randomisation, allocation concealment, blinding of participants, outcome assessors and care givers and intention to treat analysis. Where reported the methods adopted by the trialists were described.

An 18-question checklist was used to assess the quality of non-randomised comparative studies with the same checklist minus four questions used to assess the quality of case series (appendix 4). The checklist was adapted from several sources, including the NHS Centre for Reviews and Dissemination's guidance for those carrying out or commissioning reviews,[13] Verhagen and colleagues,[14] Downs and Black[15] and the Generic Appraisal Tool for Epidemiology (GATE).

3.5 Data analysis

Meta-analysis and meta-regression analyses were carried out using Stata (v10, StataCorp, 2007)[2] commands *metan* and *metareg*. A metaregression is a meta-analysis adjusted for known sources of heterogeneity, which may or may not involve treatment effects. The adjustment is usually carried out using a weighted version of regression, linear or non-linear depending on the outcome type, where the weights reflect the accuracy of the estimated outcome of interest.

Meta-analyses were carried out using fixed- and random-effects approaches. When the standard heterogeneity test for the fixed-effects results, based on (Cochrane's) Q statistic, yielded a p-value less than 5% a further random-effects analysis was carried out and those results were presented. Metaregression on study-level covariates was carried out using the approach of Thompson and Sharp (1999)[16], which is effectively an extension of random

effects meta-analysis. The weights used are the inverse of the estimated variance of the outcome measure, which are adjusted to reflect heterogeneity of outcomes between studies.

While Cochran's Q is regarded is the standard test statistic for heterogeneity in meta-analyses, it is known to underestimate the level of heterogeneity between studies if the number of trials is small ($n < 20$), such as in this case, and overestimates it when the number of studies is large. As a result I^2 (Higgins and Thompson)[17] which is related to Q by the formula $I^2 = 100(Q - k)/Q$, where $k = n - 1$, has become the preferred measure of heterogeneity in meta-analysis for established software (eg, Revman: Review Manager Version 5.0, 2008[18]). It is usually presented in graphical results, with a p-value for the probability that there is no heterogeneity (or $I^2 = 0$). We followed the same convention.

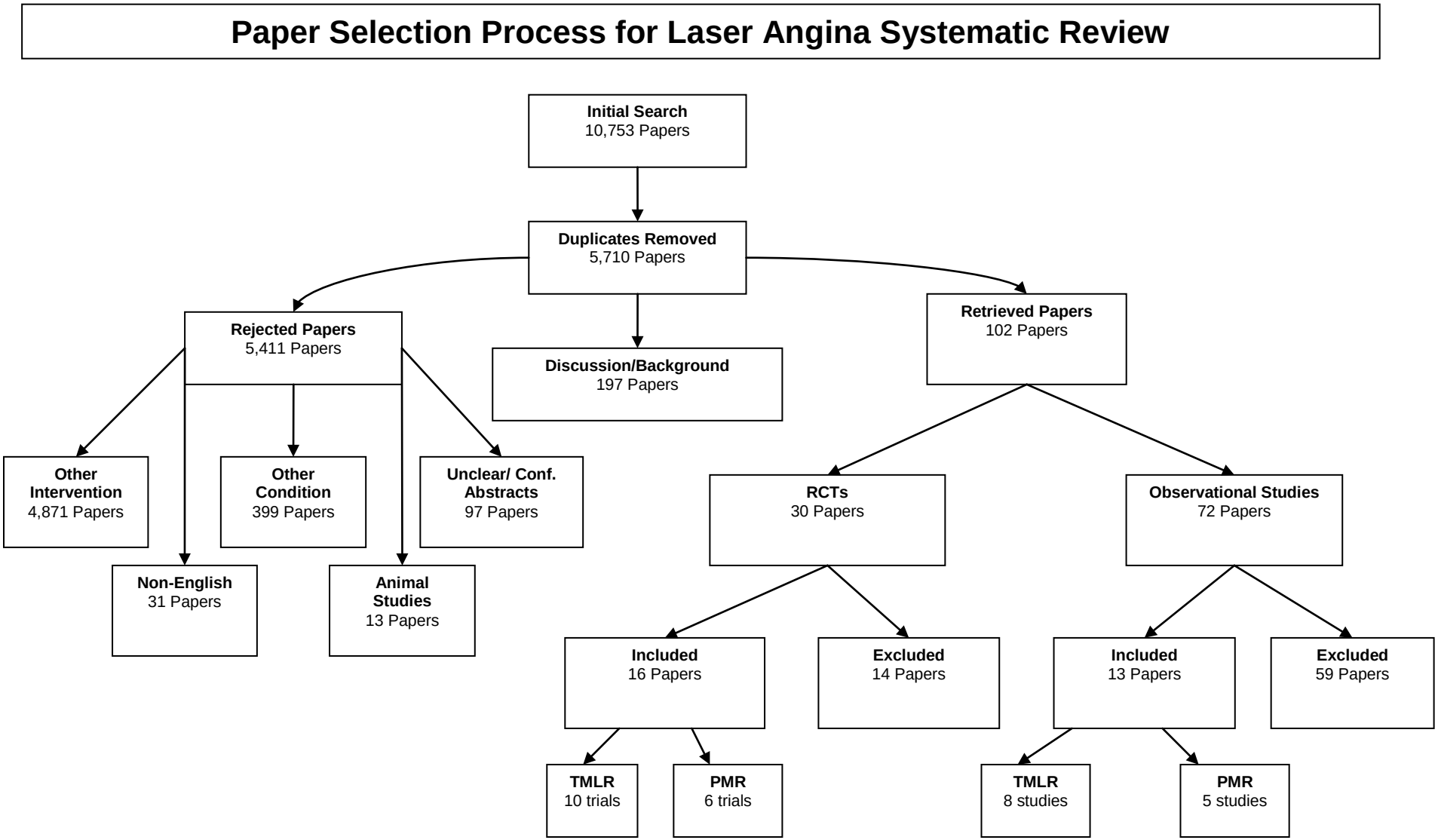
For continuous measures, outcome measures analysed were estimated mean changes over time (usually baseline to six months or baseline to 12 months) for each treatment group. These were compared between different treatment groups for the time points of interest (six or twelve months). Corresponding mean-change standard errors for each treatment group were used where possible. Where these were not available, they were estimated assuming independence within groups over time. This approach is conservative in the sense that ignoring dependence (due to positive correlation) between repeated measures within treatment groups over time generally leads to an overestimate of the required standard error. The outcome measure analysed for dichotomous outcomes was the odds-ratio, compared to baseline, for the other time points of the study. Correlation between repeated measures within treatment group was again ignored, which has a similar effect as for mean-changes, that is, yielding larger standard errors which, in turn reduce the probability of significance.

4. RESULTS

4.1 Identification of included studies for TMLR and PMR

The search strategy found 5,710 potentially relevant references, which was narrowed to 102 papers following title and abstract screening electronically (see figure 1). We retrieved full copies of 102 references, of which we excluded 73. Fifty nine nonrandomised studies studies were excluded because they had less than 100 participants or were followed up for less than 12 months. Eight papers were excluded as they were multiple publications of one included trial. Six studies were excluded as they did not meet the inclusion criteria. The excluded studies are listed in appendix 2. The remaining 16 RCTs (10 TMLR and 6 PMR) and 13 non randomised studies (8 TMLR and 5 PMR) were included in the review.

Figure 1 **Flow Diagram of included studies for TMLR and PMR**



4.2 TMLR - Description of RCTs

4.2.1 Participants

The number of participants in each trial ranged from 20 to 275 with a total of 1359. A description of their baseline characteristics are summarised in table 1. Five trials were conducted in the USA [19,20, 21,22,23,] three in the UK [24,10,25,,] one in Norway [26] and one in the Netherlands.[27] The mean age of the participants ranged from 60 to 65.1 years. The majority of the participants were male, ranging from 72 to 100% (median 86% male). The low proportion of females in these trials would limit the external validity of these trials to a wider population. The prevalence of diabetes in the trial participants varied considerably from 5% to 42.4%. This characteristic was reported in seven of the trials.[26,19,20,10,24,25,27] The prevalence of hypertension in the trial participants also varied from 55% to 95% as reported in seven studies.[26,19,21,22,10,23,24] The participants in the Loubani '03[24] study have the lowest rates of diabetes and hypertension. This trial had broader inclusion criteria and included patients who were able to undergo CABG. The number of participants who had undergone previous CABG ranged from 75 to 92.6% [19,21,10,28] and mean LVEF was above 47% in three trials reporting this characteristic. [26,19,28]

Median 62.4

Table 1 Summary of patient characteristics in RCTs - TMLR

Trial	Total Number	Setting	Age	Male (%)	Diabetes (%)	Hypertension (%)	Previous CABG (%)	Mean LVEF
Aaberge '00[26]	100	Norway	62.5	86	25	95	NR	49
Allen '99[19]	275	USA	60	75.3	42.4	70.5	86.1	47
Allen '00[20]	266	USA	63.5	72	44	NR	NR	NR
Burkhoff '99*[1][21]	182	USA	64	90.7		80.8	87.3	
Frazier '99[22]	192	USA	61	82.3		67.2	NR	
Galińanes '04[10]	20	UK	65.1	80	30	65	75	NR
Jones '99*[2][23]	86	USA	62.2	100		73.3	NR	
Loubani '03[24]	20	UK	64.3	90	5	55	NR	
Schofield '99[25]	188	UK	60.5	89.9	17.6	NR	92.6	48.5

Van der Sloot '04[27]	30	The Netherlands	60.4	90	16.6	NR	NR	

NR: not reported
*[1]more patients in the control group had hypertension and hyperlipidaemia.
*[2] significantly more patients in the surgical group had hypertension

4.2.2 Interventions and control groups

Seven of the trials compared transmyocardial laser revascularisation versus continued medical management.[26,20,21,22,23,25,27] In one trial[10] the control group received thoracic sympathectomy. In two[19,24] trials the laser treatment was combined with coronary artery bypass graft (CABG) versus CABG alone. These are summarised below in table 2. The Holmium: YAG laser was used in six studies[19,20,21,10,23,24] the CO_2 laser was used in three studies [26,22,25] and the XeCl (excimer) laser used in one study.[27] The mean number of channels created in the myocardial muscle varied between 18 and 48 (median 36).

Table 2 Summary of interventions - TMLR

Trial	Intervention details			Control Group
	Laser Type	Mean Channels n (sd)	Adjunct procedures	
Aaberge '00[26]	CO_2 laser	48 (7)		Medical management
Allen '99[19]	Holmium:YAG (Ho:YAG)	25 (10	CABG	CABG
Allen '00[20]	Holmium:YAG (Ho:YAG)	40 (8)		Medical management
Burkhoff'99 [21]	Holmium:YAG (Ho:YAG)	18 (median) (9 to 42)		Medical management
Frazier '99[22]	CO_2 laser	36 (13)		Medical management
Galińanes '04 [10]	Holmium:YAG (Ho:YAG)	42 (11)		Thoracic sympathectomy
Jones '99[23]	Holmium:YAG (Ho:YAG)	NR		Medical management
Loubani '03[24]	Holmium:YAG (Ho:YAG)	18.6 (4.2)	CABG	CABG
Schofield '99[25]	CO_2 laser	30 median (6 to 75)		Medical management
Van der Sloot[27]	XeCl Laser	46 (10)		Medical management

4.2.3 Methodological quality of randomised controlled trials- TMLR

All ten trials were described as randomised but the method of randomisation was only described in three trials.[19,21,25] Concealment of allocation was only described as having been conducted in five studies.[26,21,10,23,25] Trials with inadequate allocation concealment have been shown to exaggerate treatment effects by 41%[29] and therefore should be interpreted cautiously. Two trials[19,30] adopted a method enabling patients from the control arm to cross over to the intervention arm. Values before cross over were not reported thereby undermining the purpose of randomisation and leaving the results vulnerable to bias. These studies had over 50% missing data in final outcome measure and the risk of bias was such these studies were excluded from the meta-analyses for effectiveness outcomes. One study was able to blind patients[20] to their intervention, as both control and intervention were receiving a surgical procedure. In two studies there was blinded assessment of outomes[26,23] or selected outcomes.[19,21,22,10,25] Four studies[19,21,22,23] were funded by the manufacturers of the lasers used by the trialists. Three studies[20,10,24] did not to report their funding source. Inappropriate influence of funders can be a potential source of bias in clinical studies and there must be caution in their interpretation.[31] The meta-analysis took account of this potential bias and made adjustments to allow for this (see section 3.5).

A summary assessment of the risk of bias for the outcomes of each trial has been derived from the domains described above. Three studies[19,21,22] were judged to be at high risk of bias, i.e. that their methods seriously weaken confidence in the results and the bias is sufficient to affect the interpretation of results. Five were considered, in this context, at low risk of bias[26,20,10,23,25] i.e. that most information from these studies is at low risk of bias and unlikely to seriously alter the results. In two trials[24,27] the risk of bias was judged to be unclear and that plausible bias raises some doubt about the results (see table 3).

Table 3 Summary of trial quality - TMLR

Trial	Randomisation	Allocation Concealment	Blinding	Intention to Treat	Incomplete outcome data reporting	Funding source	Risk of bias
Aaberge '00[26]	yes block randomised	Allocation number and sealed envelopes	Operators were blinded to patient information	no	no	Gov	LOW
Allen '99[19]	yes block randomisation	NR	Blind assessment of ischemic changes, perfusion defects at rest and delayed perfusion	Yes	Controls crossed over. >50% missing outcomes in final values in both groups	Laser manufacturer	HIGH

			defects				
Allen '00[20]	Computer generated Stratified by sex and LVEF	Yes	Patients blinded for 1 year after surgery	Yes	>25% missing data from exercise tolerance in both groups	NR	LOW
Burkhoff '99[21]	Randomisation by a central coordinating centre by telephone Block randomised	Centre confirmed eligibility criteria before it provided a randomisation assignment.	Unmasked assessment of angina class. Exercise-tolerance tests, chocardiography, dipyridamole thallium stress test were assessed blind.	No Excluded patients who withdrew from the study	I) 20% missing data, C) 45% missing data for exercise tolerance	Laser manufacturer	HIGH
Frazier '99[22]	• Randomised 1:1	NR	Angina scores by an independent evaluator	NR	Cross over from control – >50% missing from outcome assessment	Laser manufacturer	HIGH
Galińanes '04[10]	Yes	Simple sealed envelope method to receive either treatment	Two blinded independent observers graded angina	NR	no	NR	LOW
Jones '99*[2][23]	Yes	Randomized to 2 study groups by an independent data management group	Caregiver and analyst blinded Blinding of data analyst	No	no	Laser manufacturer	LOW
Loubani '03[24]	yes	No	None	No	10% missing data from exercise tolerance	NR	unclear
Schofield '99[25]	Randomisation list generated and held by trial's statistician	Consecutively sealed opaque numbers	All scans processed by 1 investigator blinded to patient identity and treatment assignment	yes	13% missing data form perfusion scanning and exercise test. Same loss from both groups	gov	LOW
Van der Sloot[27]	Yes Randomised in pairs	NR	NR	NR	no	charity	unclear

NR: not reported

4.3 Description of Observational Studies -TMLR

4.3.1 Participants

For this section, baseline information will be summarised from the six TMLR case series studies and two non-randomised comparative studies. The number of participants in each study ranged form 28 to 967 with a total of 1987 patients. A description of their baseline characteristics are summarised in table 4. Four studies were conducted in America[21,32,33,34], two

in Germany[35,36,], one in India[37] and one in both Europe and Asia[38]. The mean age of the included participants ranged from 57 to 65 years. The majority of the participants were male, ranging from 64 to 2% (median 84% male, but one study not reported). Diabetes was reported in three studies[38,35,32] and the prevalence ranged from 14 to 35% in these studies. The number of participants who had undergone previous CABG was reported in all studies with a range from 6.3 to 90%. Hypertension was reported in five studies[37,38,35,32,33] and ranged from 50 to76%.

Table 4 Summary of patient characteristics- nonrandomised studies - TMLR

Trial	Year	Total Number	Setting	Age	% Male	Hypertension (%)	Previous CABG (%)	Diabetes (%)
Case Series								
Agarwal[37]	1999	102	India	56.7	92.1	50	12.7	NR
Burkoff[21]	1999	132	USA	61.1	82.6	NR	84.1	NR
Burns[38]	1999	967	Europe and Asia	62	84	59	70	14
Krabatsch[35]	2002	134	Germany	63.4	84.3	59.7	89.6	30.6
Horvath[32]	1997	200	USA	63	78	67	82	35
Stamou[33]	2002	169	USA	62.6	70	76	51	NR
Non-randomised Comparative								
Diegeler[36]	1998	28	Germany	64.5	64.3	NR	64.3	NR
Wehberg[34]	2003	255	USA	65.1	NR	NR	6.3	NR

NR: not reported

4.3.2 TMLR Intervention

Eight non-randomised studies have been included in this review. Six studies were case series[37,21,38,35,32,33,] and two were non-randomised comparative studies.[36,34] Five studies used the CO2 laser in their procedure[37,21,38,35,32] while two utilized the Holmium YAG laser.[36,34] One study took a hybrid approach and adopted both lasers in their study. [33] Only two studies[37,32] reported the wattage of their CO2 laser (800 and 850 watts), and the remaining studies were unreported. The average number of channels varied slightly between the studies and range was between 17 and 30 average channels. Similar to the PMR observational studies, funding was not reported.

Table 5 Summary of TMLR Intervention

Trial	Year	Funding	Laser Type	Wattage	Mean Channels n (sd)
Agarwal[37]	1999	NR	C02 Laser	800	23 (8)
Burkoff[21]	1999	NR	C02 Laser	NR	NR
Burns[38]	1998	NR	C02 Laser	NR	28.6 (12.2)
Krabatsch[35]	2002	NR	C02 Laser	NR	30 (9)
Horvath[32]	1997	NR	C02 Laser	850	NR
Stamou[33]	2002	NR	C02/YAG	NR	24 (NR)
Non-randomised Comparative					
Diegeler[36]	1998	NR	Holmium:YAG (Ho:YAG)	NR	Group A: 26 (6) Group B: 17 (5)
Wehberg[34]	2003	NR	Holmium:YAG (Ho:YAG)	NR	NR

NR= not reported

4.4 Outcomes - Effectiveness

4.4.1 Mortality

Mortality data was assessed at two time points in this analysis, perioperative (deaths within 30 days of intervention) and total deaths during the study period. All trials were followed for a minimum of 12 months, one for 42 months[10] where there were no deaths (N=20) and one for 36 months[24], where one death occurred at 11 months. Perioperative mortality rates will be described in the analysis of safety.

There was no statistically significant difference between intervention and control groups in mortality rates at 12 months (odds ratio 0.7 2%CI 0.4 to 1.2) (fig. 2). Nor was there any difference between groups when the data was analysed without the two studies where both intervention and control had CABG [20,24], (odds ratio 0.83 95% CI 0.49 to 1.41) (fig. 3).

Figure 2 Meta-analysis of mortality data at 12 months follow-up

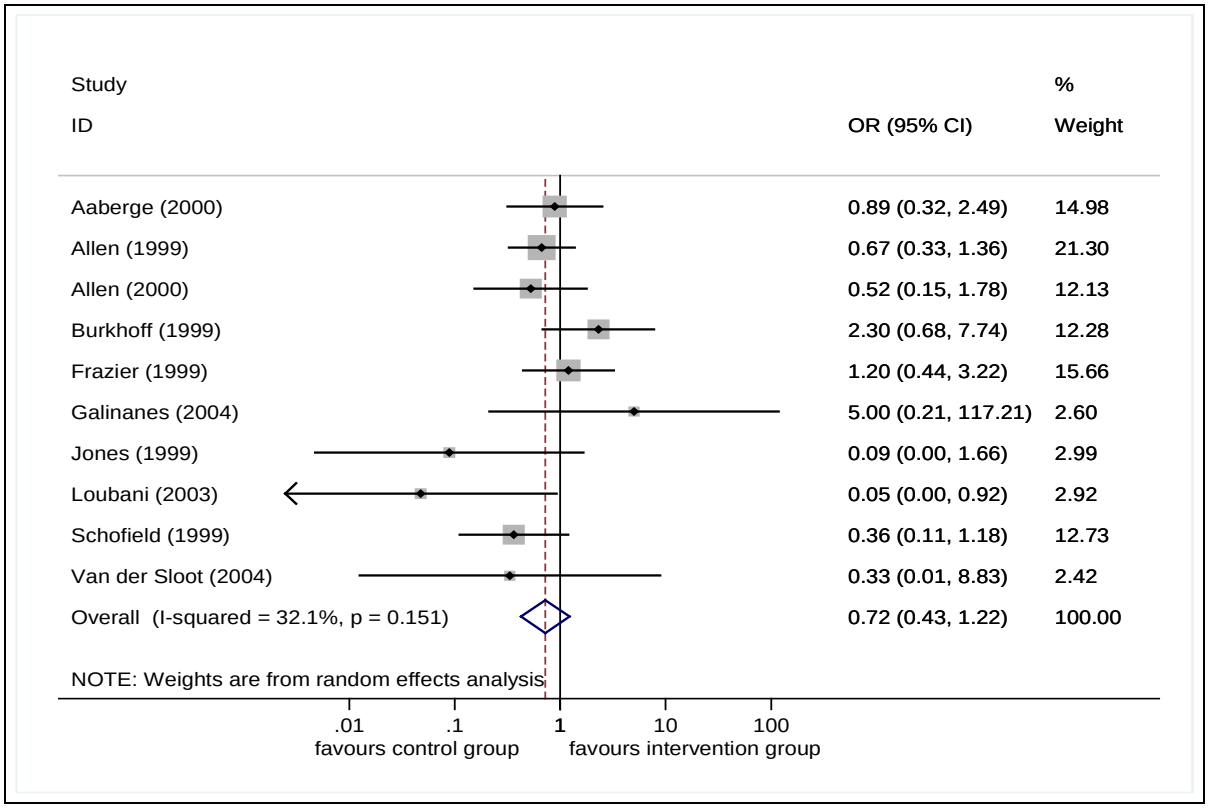
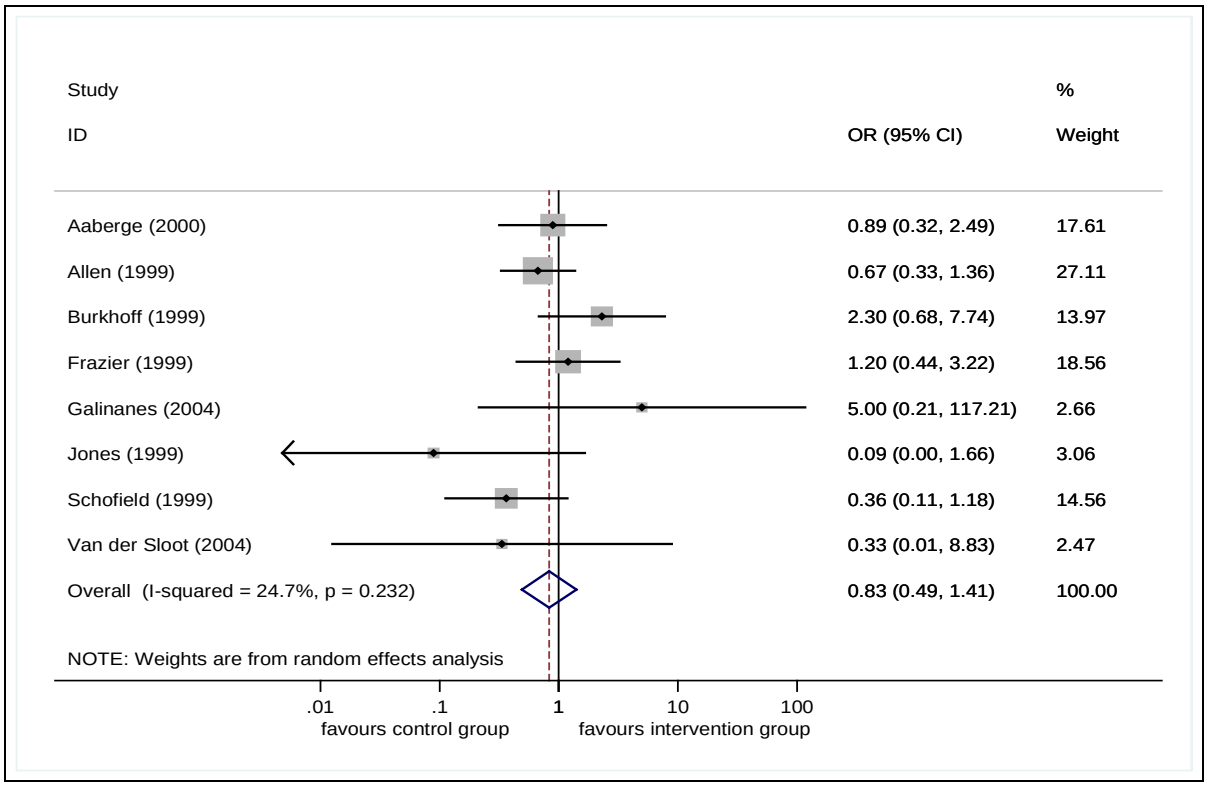


Figure 3 Mortality - TMLR - excluding CABG control trials



4.4.2 Myocardial Perfusion Tests

Eight of the trials measured myocardial perfusion; however, the heterogeneity in terms of the methods used to measure perfusion and the outcomes reported precludes meta-analysis of this outcome. (See table 6 for a summary of the tests and their outcomes). Stress was induced using dobutamine, dipyridamole-thallium, adenosine or exercise. Outcomes described included the number of nonviable segments, ventricular wall motion and percentage of myocardium with ischaemia and infarction. One study[26] found significant differences which favoured the control showing a worsening in wall motion abnormalities and an increase in the number of non-viable segments. One study[27] showed a small but significant decrease in reversible wall motion abnormality, favouring TMLR, but also a significant increase in fixed wall motion abnormality, favouring control. Myocardial perfusion was also assessed in this study using myocardial perfusion scintigraphy and no significant differences were found between the intervention and control groups. The other six trials found no significant difference in myocardial perfusion following TMLR.[26,19,21,10,23,25]

Table 6 Myocardial perfusion tests - TMLR

Trial	Method	Quantitative Summary	Narrative summary
Aaberge '00[26]	Dobutamine stress echocardiography and SPECT scan	Number of nonviable segments BL 12m N I: 52% 89% 44 C: 45% 62% 42 **P<0.01** Favours control WMSI – peak stress BL 12m N I: 1.99 (0.42) 1.93 (0.39) 44 C: 1.90 (0.40) 1.90 (0.36) 42 P=0.09 WMSI – rest BL 12m N I: 1.47 (0.40) 1.49 (0.44) 44 C: 1.47 (0.36) 1.56 (0.47) 42 **P=<0.05** P= significance both between groups during follow-up and within groups compared to baseline.	Following TMLR resting wall motion abnormalities worsened, wall motion abnormalities during dobutamine stimulation remained unchanged and the number of non-viable segments increased. Bold – favours control
Allen '99[19]	Dipyridamole-thallium stress testing and scanning	Changes from baseline to 12 months Ischemia m sd N I: -0.9% NR 30? C: -0.6% NR 31? P=0.90 Defects at rest m sd N I: 1.6% NR 30? C: 2.2% NR 31? P=0.84 Data only available for 61 patients – unclear how many are in each group. No significant difference between groups with respect to delayed defects also	No significant differences between the groups with respect to changes in ischemia, defects in perfusion at rest, or delayed defects. No correlation was noted between improvement in angina and the results of thallium scanning. Nor any differences in fixed defects
Allen '00[20]	NM		

Burkhoff '99[21]	Dipyridamole-thallium stress testing echocardiography and electrocardiography	Changes from baseline to 12 months Myocardium with Ischemia m: I: 11.5%, C: 12% range: 0 to 65, 0 to 50 N: 66, 65 NS Myocardium with infarction m: 11%, 11% range: 0 to 63, 0 to 39 N: 66, 66 NS	TMLR did not influence myocardial perfusion as assessed by this technique.
Frazier '99[22]	NM		
Galińanes '04[10]	Measured using MRI scanning, stress induced by infusion of adenosine	Stress perfusion data – unidirectional transfer constant for gadodiamide at 6 m follow-up Baseline: m / sd / N I: 46.5 / 17.9 / 9 C: 59.2 / 32.9 / 8 NS 6 months: m / sd / N I: 50.2 / 17.9 / 9 C: 71.6 / 38.4 / 8	No diff between the groups and also between baseline and final value within each group. No improvements in the distribution (transmural vs subendocardial or nature (reversible vs fixed) of any preoperative perfusion deficits were identified in either group
Jones '99*[23]	Dipyridamole-thallium stress testing and scanning	Results not reported	Thallium scans showed not improvement in the TMLR group when compared to the control group
Loubani '03[24]	Stress echocardiography using dobutamine. Digital images using quad- loop format on an Agilent 5500 system. No significant improvement in wall motion index. (lower result suggests improved wall motion and improved contractility of the lased areas)	WMSI (wall motion score index). Final value at 18 m follow-up WMSI at peak dose: I: 1.27, C: 1.50 P=0.43 SD: 0.45, 0.80 N: 8, 9	Wall motion score index after 18 months was not significantly different
Schofield	Perfusion scanning – using Tc-99m MIBI perfusion scans.	Myocardial sites with reversible ischaemia – between groups OR: 0.99 (0.82-1.20) p=0.975	The number of sites with reversible ischaemia decreased and the number with irreversible ischaemia increased. The overall number of sites with reversible ischaemia did not differ

<table>
<tr>
<td>‘99[25]</td>
<td>Patients were exercised using the modified Bruce protocol. Radionuclide scanning.</td>
<td>Myocardial sites with irreversible ischaemia among TMLR patients:
OR 1.27 (1.00-1.61) p=0.046</td>
<td>significantly between groups but there was a small excess of sites with irreversible ischaemia in TMLR patients.</td>
</tr>
<tr>
<td>Van der Sloot[27]</td>
<td>Myocardial Perfusion Scintigraphy
Stress induced by exercise or pharmacologically.
Images obtained using SPECT</td>
<td>Mean summed difference score – generated from the summed stress score and summed rest score
<table>
<tr><th></th><th colspan="3">Base line</th><th colspan="3">12 months</th></tr>
<tr><th></th><th>m</th><th>sd</th><th>N</th><th>m</th><th>sd</th><th>N</th></tr>
<tr><td>I</td><td>13.9</td><td>7.8</td><td>15</td><td>11.7</td><td>5.2</td><td>14</td></tr>
<tr><td>C</td><td>10.9</td><td>5.7</td><td>15</td><td>9.4</td><td>7.4</td><td>15</td></tr>
<tr><td></td><td></td><td></td><td></td><td>NS</td><td></td><td></td></tr>
</table>
In contrast to myocardial perfusion scintigraphy the results after TMLR stress echocardiography showed a small but significant decrease in reversible wall motion abnormality as well as an increase in fixed wall motion abnormality. The explanations for the differences in test results are unclear.</td>
<td>Improved myocardial perfusion was not indicated.</td>
</tr>
</table>

SPECT: Single photon emission computed tomography
BL – baseline
WMSI: wall motion score index
Reversible perfusion defect (ischaemia)
Abnormal perfusion at rest = fixed perfusion defect (scar)

4.4.3 Left Ventricular Ejection Fraction (LVEF) - TMLR

Three trials[26,21,25] reported left ventricular ejection fraction. One trial [21] measured the outcome at three months while the other two were measured at 12 months.[26,25] All three trials reported no statistically significant difference between the intervention and control groups (see table 7).

Table 7 Summary of LVEF - TMLR

		Baseline			Follow up		
Trial	**Group**	**m**	**sd**	**N**	**m**	**sd**	**N**
Aaberge[26]	I	48.9	11.9	49	47.4	14	43
	C	49.6	11.9	50	51	11.8	46
Schofield[25]	I	48	9.4	94	46	12.3	94
	C	49	10.6	94	48	11.7	94
Burkhoff[21]	I	50 (median)	31 to 68	92	0 (change from BL)	-25 to 20	Unclear
	C	45 (median)	31 to 68	90	-3 (change from BL)	-28 to 20	Unclear

BL: baseline, m: mean, sd: standard deviation, N: total number in each group

4.4.4 Exercise tolerance tests - TMLR

Nine trials reported the results of exercise tolerance tests.[26,20,21,22,10,23,24,25,27] The tests were all conducted using a modified Bruce exercise treadmill test and total exercise time in seconds was extracted from the papers. One trial was excluded from the meta-analyses because of methodological weakness.[22] Loubani '03 [24] only reported data at 6 months and is not included in the 0-12 month analyses. Four trials[26 20,21,10] did not report the outcome at 6 months so are not included in the 0-6 month analysis.

Including data from four trials[23,24,25, 27] the pooled mean difference between treatment groups at 6 months was 111.2 seconds (95% CI 32.5 to 190.0) (see fig. 4). This result showed statistically significant heterogeneity ($p<0.001$). When the trials[23,25,27] with the same comparator were combined (i.e. TMLR vs medical management) the result remained statistically significant 120.1 seconds (95% CI 4.5 to 235.7), however in the trial[24], where TMLR is combined with CABG and controlled against CABG only, there is no statistical significance between groups (96 seconds 95%CI -139.5 to 331.5).

Including data from seven trials[10,26,20,21,23, 25,27] the pooled mean difference at 12 months follow-up showed an improvement of 81.9 seconds (95% CI 26.7 to 137.3) (fig. 5). When the trials with the same comparator (i.e. medical management) were combined the result

remained significant. In two trials, however, where the comparators were different[20,10], there was not a significant difference in exercise tolerance between groups.

We undertook a sensitivity analysis to explore the effects of blinding and funding source on exercise tolerance at 12 months. In one trial[20] where patients were blinded to treatment there was no statistically significant difference between control and intervention groups (30.6 seconds 95% CI (-21.1 to 80.1)). Removing two trials[21,23] which reported that they were funded by laser manufacturers, from the pooled meta-analysis caused a reduction in effect size to 30.2 seconds (95% CI 22.4 to 37.9).

Fig.4 Exercise Tolerance Tests at 6 months Follow-up - TMLR

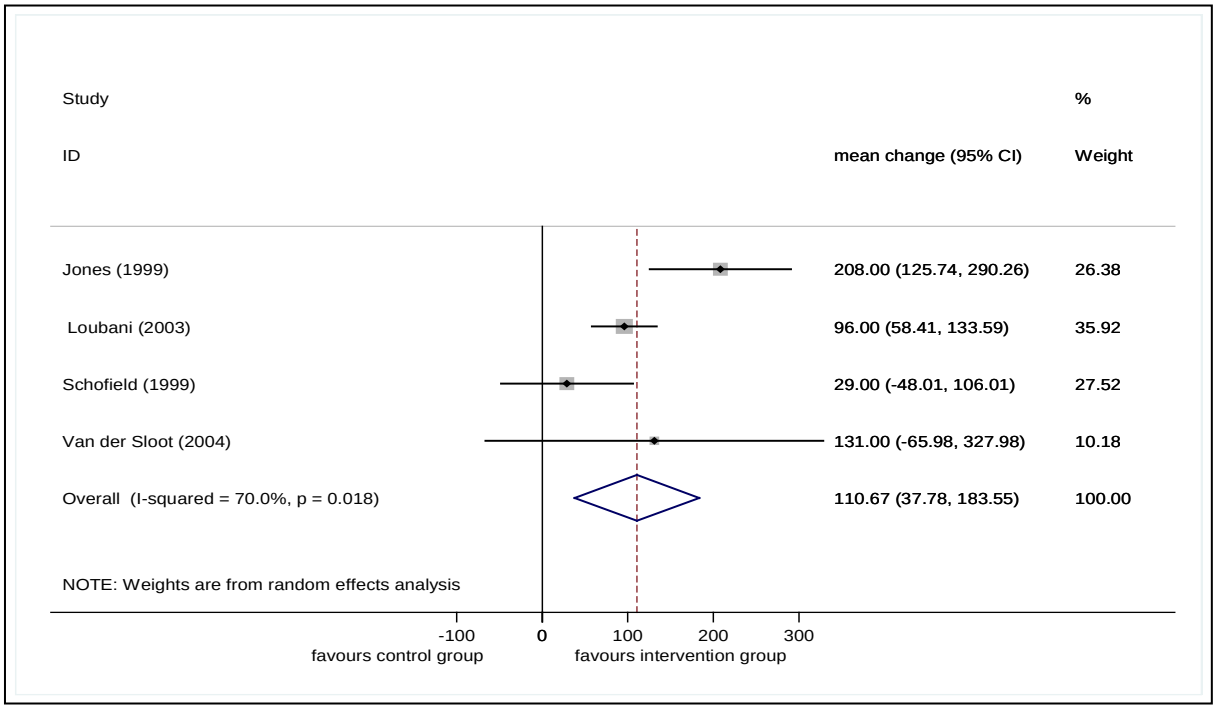
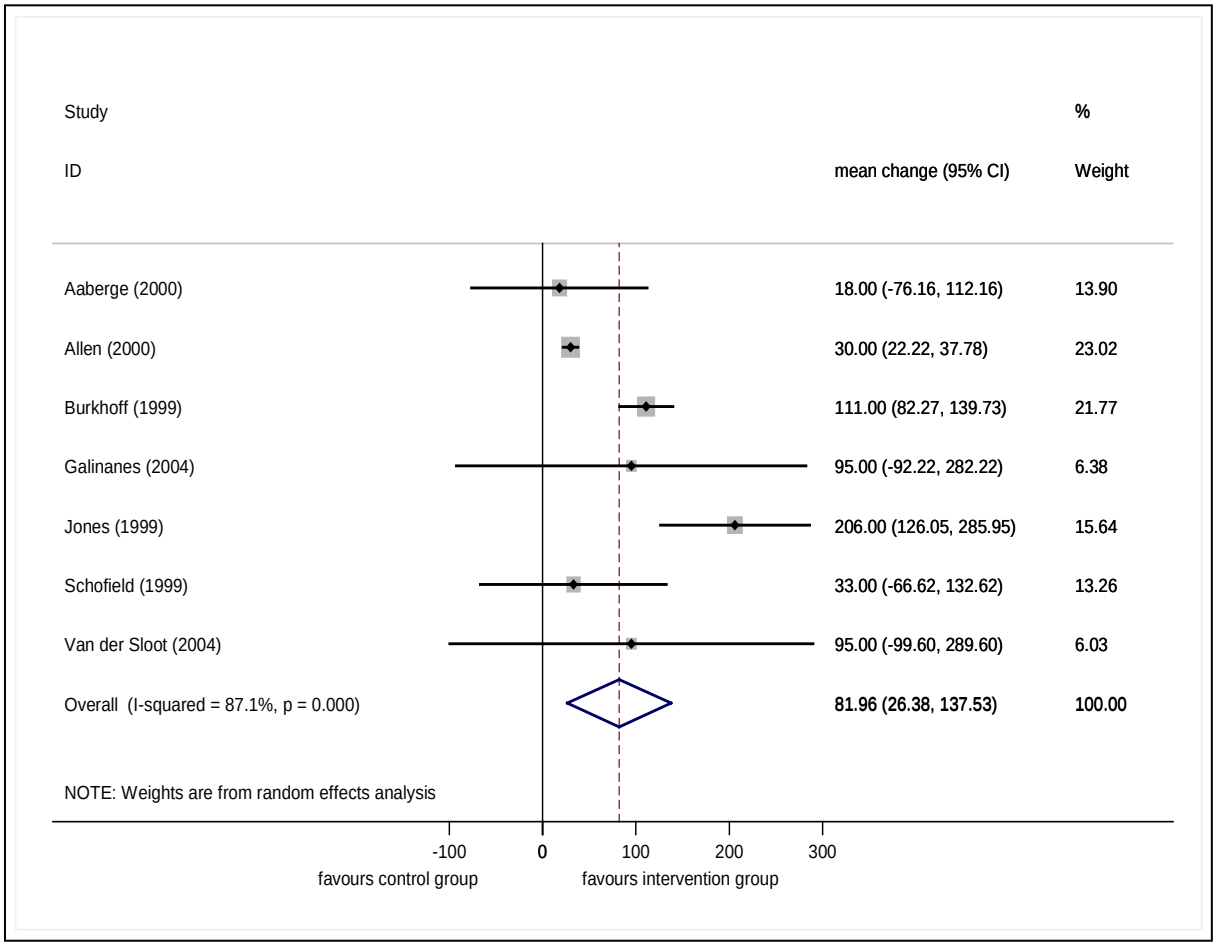


Fig.5 Exercise Tolerance Tests at 12 months Follow-up - TMLR



4.4.5 Angina Score

In nine trials the angina score was measured using the Canadian Cardiovascular Society Angina Score (CCSA) and in one[26] the New York Heart Association Score (NYHA) score was used. Both scoring systems are summarised (see glossary of terms). In five trials[26,20 10,23, 24,27] this outcome is reported as a continuous variable giving a mean final value or mean change from baseline. In four trials[19,21,22,25] it is presented as a dichotomous outcome, reporting the number of patients who reduced two or more CCSA classes (one trial [27] reports both).

The meta-analyses of angina score shows a significant improvement in patients who were treated with TMLR. Three of the five continuous outcome trials reported mean angina score at 6 months [10,23,27] and when pooled show a mean difference in angina score of -1.8 classes (95% CI -2.4 to -1.1) (see fig 6). All five trials reported mean angina score at 12 months, with a mean difference of -1 angina class (95% CI -1.7 to -0.3) (see fig 7). There is significant heterogeneity in these meta-analyses.

For trials reporting dichotomous outcomes with improvement defined as a reduction of 2 or more angina classes, the improvement in angina score in patients receiving TMLR is also significant (odds ratio 2.78 (95% CI 1.07 to 7.18). There was also significant heterogeneity in this meta-analysis (see fig. 8).

One trial[20] blinded patients for one year after surgery as to whether they received adjunctive TMLR following CABG. In this trial at 12 months follow-up the angina score was similar between groups.

Fig. 6 Angina Score at 6 months Follow-up – mean change from baseline - TMLR

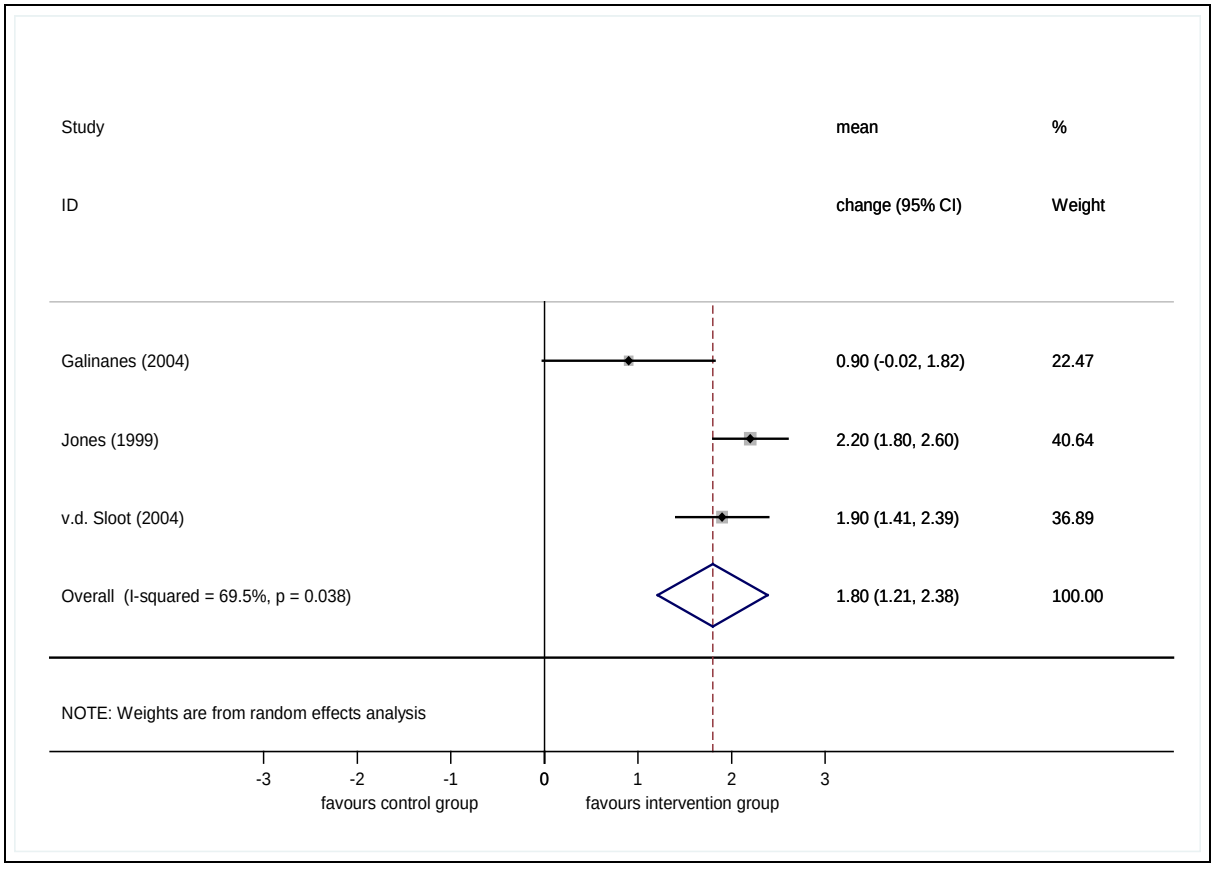


Fig. 7 Angina Score at 12 months – mean change from baseline – TMLR

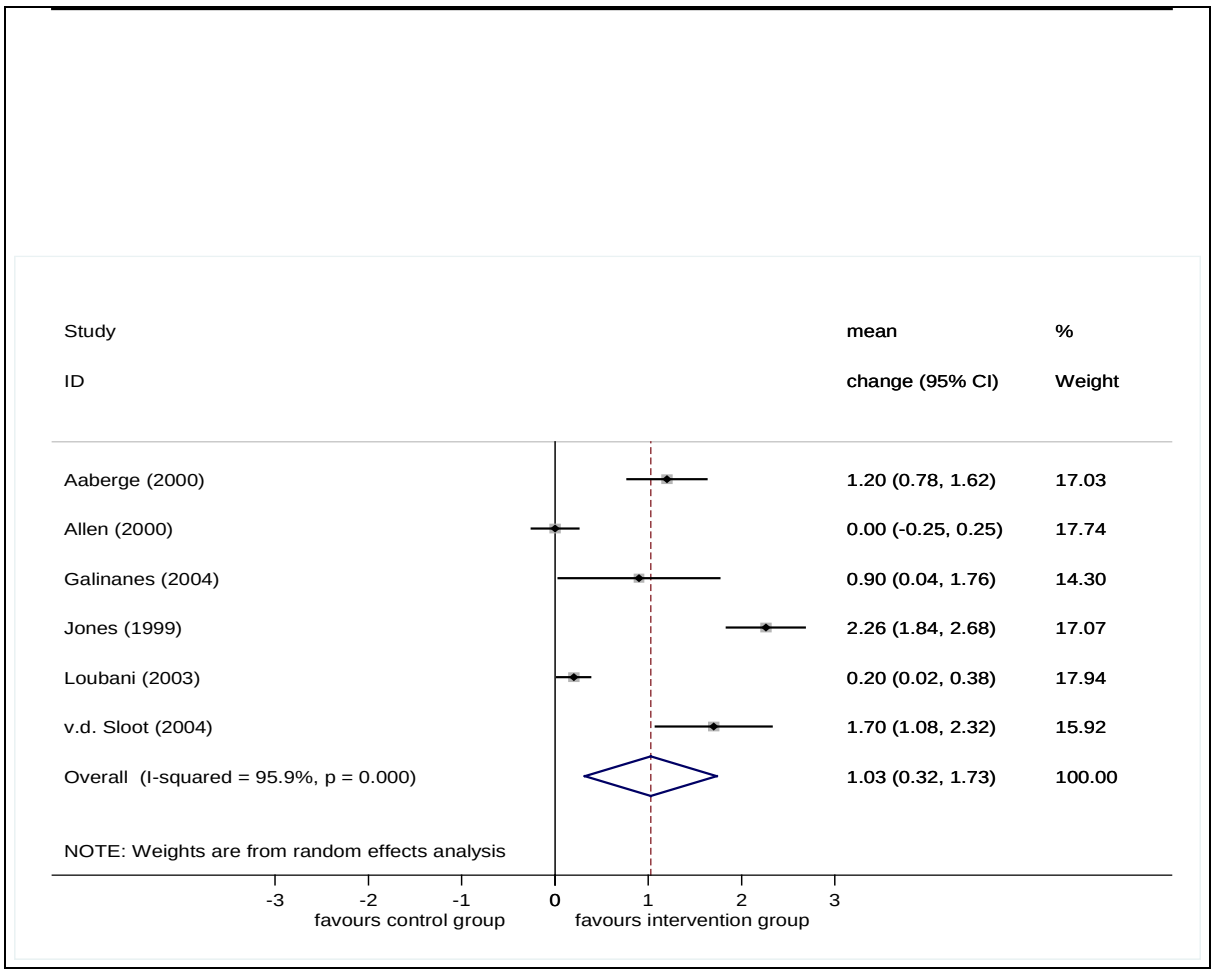
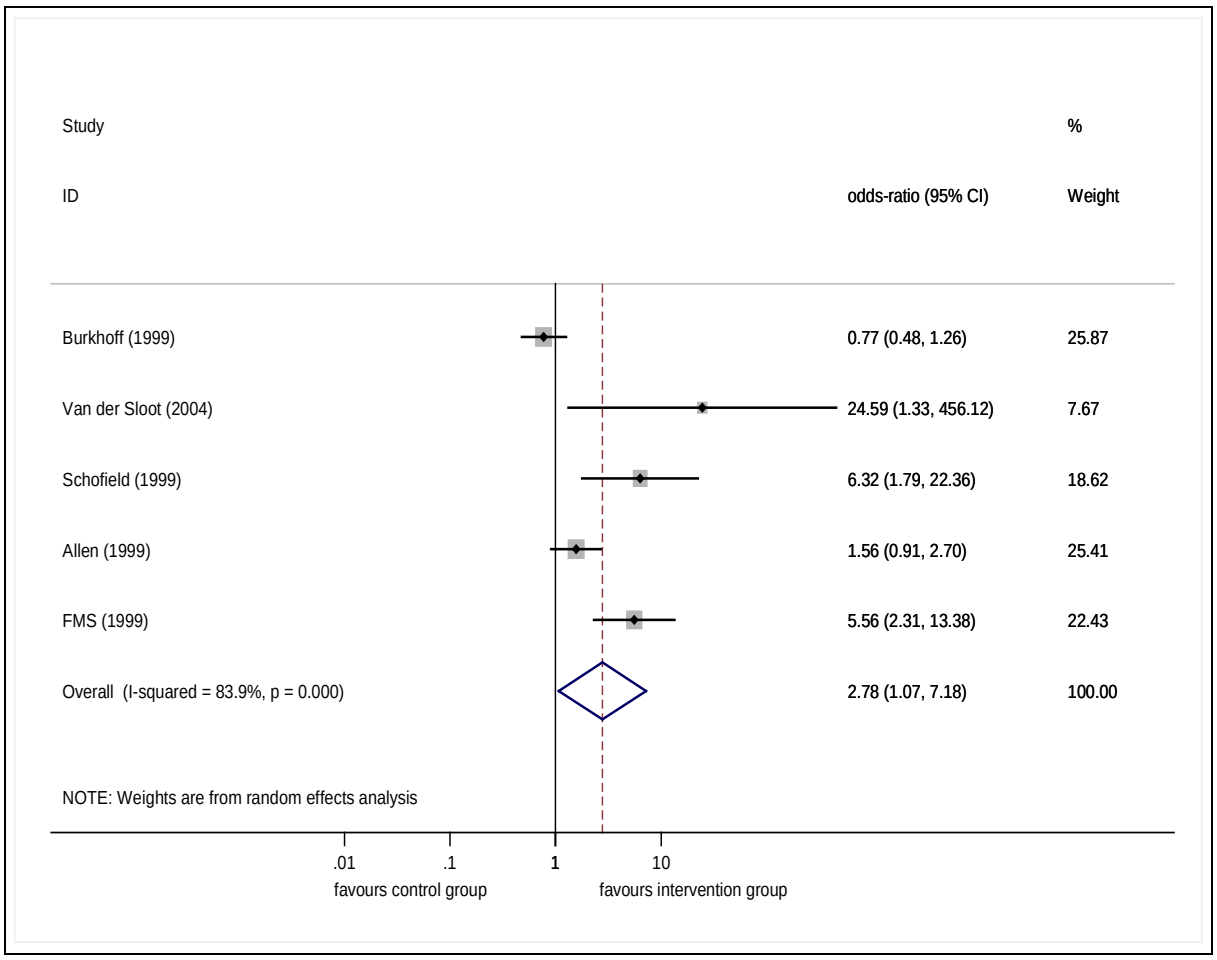


Fig. 8 Angina Score – improvement in 2 or more angina classes at 12 months - TMLR



4.4.6 Quality of Life

Five trials[26,21,22,10,27] measured quality of life. Different instruments were used including the Duke Activity Status Index, Seattle Angina Questionnaire, SF 30 and EuroQol questionnaire. Only one[10] showed a non-significant difference with treatment. Aaberge ’00, Burkhoff ’99, Frazier ’99 and van der Sloot’ 04[26,21,22,27] all found a statistically significant improvement in reported quality of life for patients receiving TMLR. There was no blinding of patients to treatment group in any of these studies.

4.5 Outcomes – Safety

4.5.1 Postoperative mortality

All included trials reported postoperative mortality rates. The pooled data showed no significant difference between intervention and control groups (odds ratio 0.78 05% CI 0.34 to 1.7). The mortality rate was, however, significantly greater in the TMLR group when those

trials comparing TMLR with concomitant CABG vs. CABG[20,24] were excluded (odds ratio 0.35 95% CI 0.13 to 0.93) (see figs 9 and 10).

Figure 9 Postoperative mortality (all included trials) - TMLR

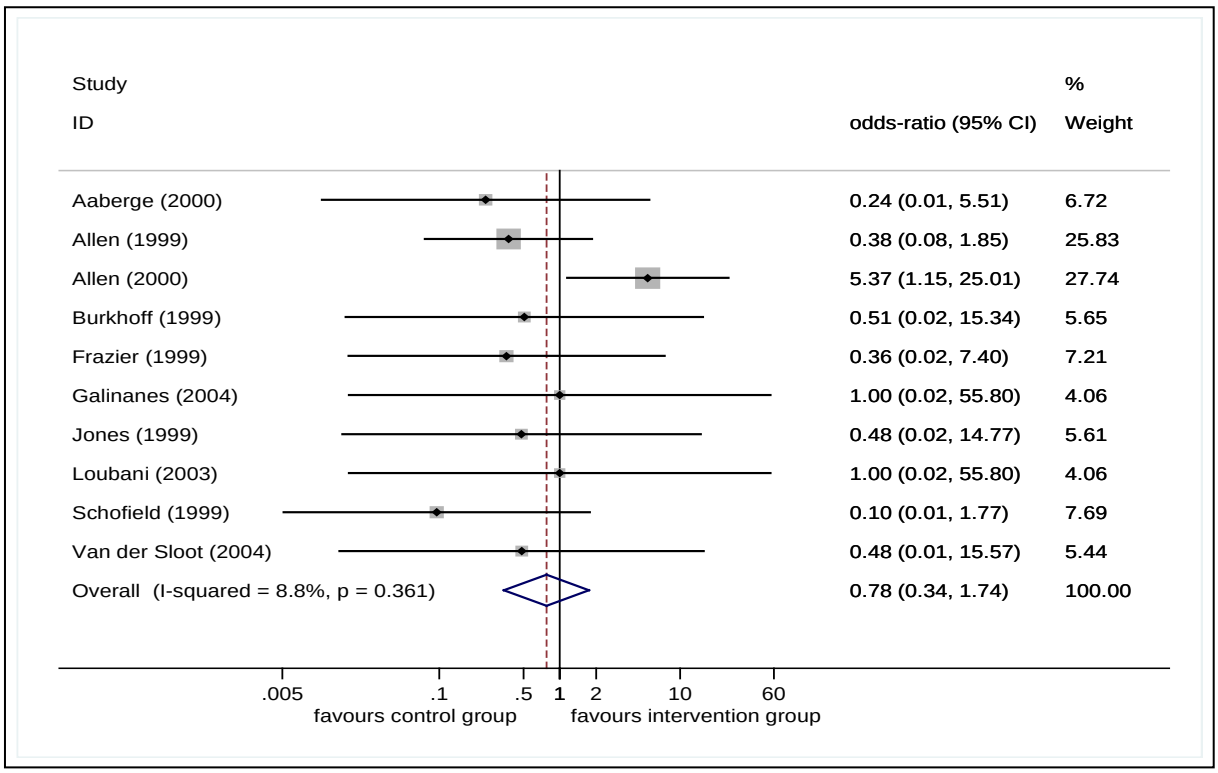


Figure 10 Postoperative mortality (CABG trials excluded) - TMLR

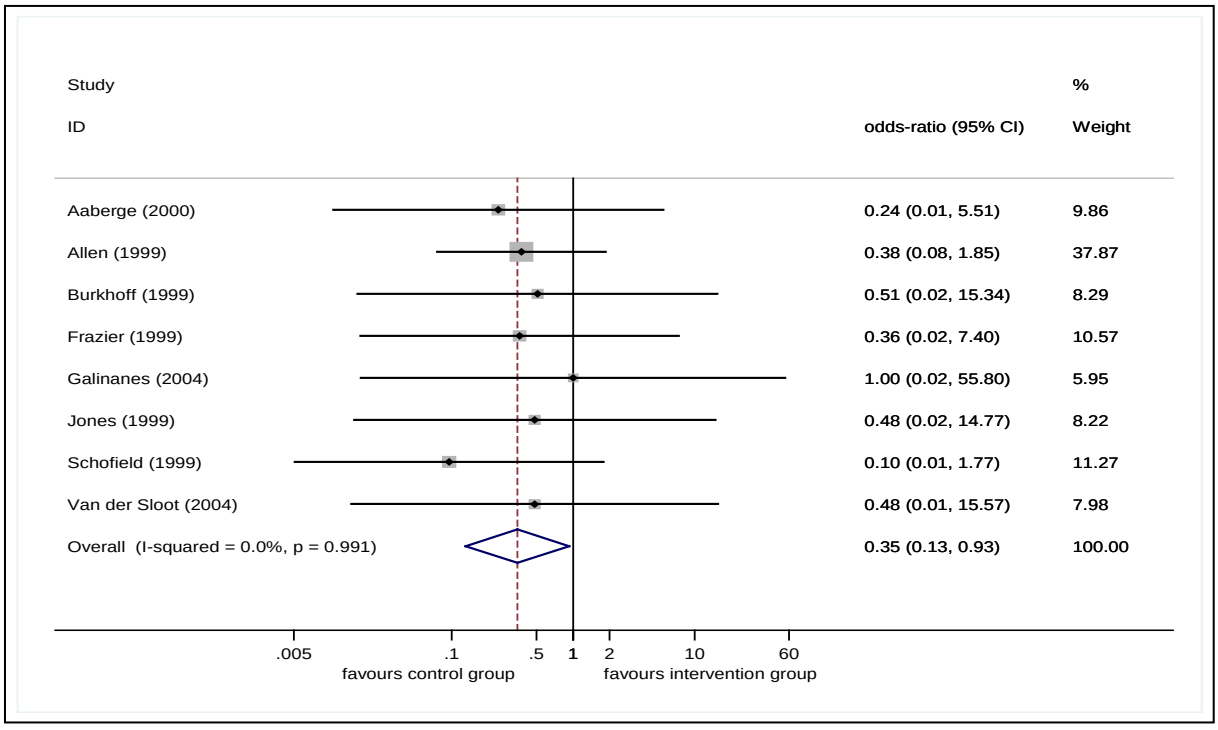


Table 8 Reported adverse events - TMLR
RCTs: number of events/number of patients

Event	Aaberge 2000		Allen 1999		Allen 2000		Burkhoff 1999		Frazier 1999		Galinanes 2004		Jones 1999		Loubani 2003		Schofield 1999		Van der Sloot 2004		Totals	
Cardiac	**I**	**C**	**I**	**C**	**I****	**C**	**I**	**C**	**I**	**C**	**I**	**C**	**I**	**C**	**I**	**C**	**I**	**C**	**I**	**C**	**I**	**C**
MI	4/50	0/50	7/132	0/142	3/132	2/131	14/92	8/90	6/91	0/101			2/42	0/43			5/94	1/94			**41/633 (6.5%)**	**11/651 (1.7%)**
Atrial Arrhythmias					24/132	21/131															**24/132 (18.1%)**	**21/131 (16%)**
Heart Failure	17/50*	0/50	5/132						10/91												**32/273 (11.7%)**	
Hypotension			13/132																		**13/132 (9.8%)**	
Atrial/ventricular fibrillation					5/132	3/131			7/91		2/10										**12/223 (5.4%)**	
Respiratory insufficiency/failure							5/92	1/90													**5/92 (5.4%)**	**1/90 (1.1%)**
Other																						
Thromboembolic disorder							9/92	3/90													**9/92 (9.8%)**	**3/90 (3.3%)**
Pneumonia							5/92	1/90													**5/92 (5.4%)**	**1/90 (1.11%)**
Phrenic-nerve paresis							3/92	0/90					4/42								**7/134 (5.2%)**	
Cellutitis							4/92	0/90													**4/92 (4.3%)**	
Reoperation for bleeding					4/132	1/131															**4/132 (3.03%)**	**1/131 (0.76%)**
Cerebral vascular accident					1/132	3/131															**1/132 (0.75%)**	**3/131 (2.3%)**

4.5.2 Adverse Effects - TMLR

Adverse event data was retrieved from all the included RCT studies, non-randomised comparative studies and case series studies. The data is presented in tables 8, 9 and 10. The type of event, the numbers of events in each study, and the total number of patients in each arm are shown. The data is presented in a narrative format.

These results need to be viewed cautiously as frequency of reporting may be a poor indication of the occurrence of an event. If the event it is not a predefined outcome trialists may not measure or report them.

The number of adverse events reported is greater in the TMLR group than in the controls. One hundred and seventy events were reported in the TMLR group compared with only 41 reported in the control group. The most frequently occurring adverse event in both groups are atrial arrhythmias. These also occurred frequently in patients in both the case series and comparative studies. Hypotension and heart failure also occurred in the TMLR groups but not in the controls. Myocardial infarction was the most likely to be reported and was often a prespecified endpoint. In the trials these appeared to occur more frequently in the treatment group than in the control group (6.5% of patients had an MI in the TMLR groups compared to 1.7% in the control group). One trial found a higher rate of thromboembolic disorders in the treated group than in the control.[21]

One case series study[33] reported 23 (13.6%) patients receiving TMLR suffered acute non-inflammatory pericarditis. Observational studies identified other outcomes not reported in the randomised studies including mitral regurgitation (5%) and cardiac tamponade (0.5%).

Phrenic- nerve paresis and neurological complications were reported as direct results of the surgical intervention. Bleeding requiring re-operation were also described in the treatment groups and only occurred in the control groups where the control also had a surgical procedure.

Table 9 Case Series - TMLR

Event	Agarwal 1999	Burkhoff 1999	Burns 1998	Krabatsch 2002	Horwath 1997	Stamou 2002	Totals
Cardiac							
Atrial Arrhythmias			81/932		0/20		**81/932 (8.7%)**
Ventricle dysfunction			70/932				**70/932 (7.5%)**
Atrial/ventricular fibrillation						40/169	**40/169 (23.7%)**
Acute non-						23/169	**23/169**

inflammatory pericarditis							**(13.6%)**
MI			30/932		4/20	1/169	**5/189 (2.64%)**
Tamponade			5/932				**5/932 (0.5%)**
Mitral regurgitation					1/20		**1/20 (5%)**
Other							
Infection			35/932		1/20		**36/952 (3.8%)**
Prolonged Ventilation						15/169	**15/169 (8.9%)**
Pneumonia					5/20		**5/20 (25%)**
Bleeding (reoperation)					2/20	7/169	**9/189 (4.8%)**
Stroke						2/169	**2/169 (1.2%)**

Table 10 Comparative Studies - TMLR

Event	**Diegeler 1998**		**Wehberg 2003**		**Totals**		
Cardiac	**TMLR**	**TMLR + CABG**	**TMLR + CABG**	**CABG**	**TMLR**	**TMLR + CABG**	**CABG**
Atrial/ventricular fibrillation			6/36	81/219		**6/36 (16.7)**	**81/219 (37%)**
Atrial Arrhythmias	2/14	0/14			**2/14 (14.3%)**		
MI	0/14	1/14				**1/14 (7.1%)**	
Other							
Re-admit 30 days			1/36	17/219		**1/36 (2.8%)**	**17/219 (7.8%)**
Bleeding (re-operation)	0/14	0/14	1/36	15/219		**1/36 (2.8%)**	**15/219 (6.8%)**
Respiratory failure			0/36	8/219			**8/219 (3.7%)**
Renal failure			0/36	6/219			**6/219 (2.7%)**
Neurological complications			1/36	3/219		**1/36 (2.8%)**	**3/219 (1.4%)**
Pneumothorax	1/14	1/14			**1/14**	**1/14 (7.1%)**	

4.6 Description of RCTs - PMR

4.6.1 Participants

The number of participants in each trial ranged from 68 to 275 with a total of 1040. A description of their baseline characteristics is summarised in table 11. Three trials[39,40,41] were conducted in the USA, one[42] in the UK, one in centres in both the USA and UK[43] and one[44] in Norway. The mean age of the included participants ranged form 62 to 65.5 years. The majority of the participants were male ranging from 75.7% to 91.5%. The proportion of patients with hypertension ranged from 55.9% to 73.5%. The prevalence of diabetes ranged from 15.9% to 47.8% and was reported in five of the trials. A high proportion of patients in all six trials (proportions ranging from 82% to 94.1%)[39,45,43,44,40,46] had undergone a previous coronary artery bypass graft.

Table 11 Summary of patient characteristics - PMR

Trial	Total Number	Setting	Age	% Male	Hypertension (%)	Previous CABG (%)	Diabetes (%)
Leon '05[39],	298	USA	62.9	77	73.5	88.3	43.9
McNab '06[45],	68	UK	63.6	88.2	NR	94.1	NR
Oesterle '00[43],	221	USA/UK	62	86	71.9	84.2	44.8
Salem '04[44],	82	Norway	65.5	91.5	47.6	89	15.9
Stone '02[40],	141	USA	65	79.7	68.5	83.5	41.7
Whitlow '03[46]	230	USA	63	75.7	55.9	82	47.8

4.6.2 Intervention

Three of the trials compared percutaneous laser revascularisation with continued medical management.[43,40,46] Two[39,44] compared the treatment with a sham control ensuring patients were blinded to their intervention. One trial[42] compared the intervention to spinal cord stimulation which is technique that used in the treatment of chronic pain. All of the trials used the Holmium: YAG laser and the number of channels created ranged from 8 to 34. One study [39] separated the intervention into low dose (10 to 15 laser pulses) or high dose (20 to 25 laser pulses) (table 12).

Table 12 Summary of interventions - PMR

Trial	Laser Type	Mean Channels n (sd)	Control intervention
Leon '05[39]	Holmium:YAG	Low dose:21 (8) high dose 34 (11)	Sham therapy
McNab '06 [45]	Holmium:YAG	9-12 (range)	Spinal cord stimulation
Oesterle '00[43]	Holmium:YAG	15 (range 8-35)	Medical management
Salem '04[44]	Holmium:YAG	NR	Sham therapy
Stone '02[40]	Holmium:YAG	20 (median)	Medical management
Whitlow '03[46]	Holmium:YAG	8-30 channels	Medical treatment

4.6.3 Study characteristics

All six trials were described as randomised and the method was described in five.[45,43,44,40,46] In one trial[40] the method of randomisation was inadequate and in another[39] it was not described, introducing a risk of allocation bias and weakening confidence in the results. Three trials[39,45,46] did not report using a system of allocation concealment which increases the risk of potential bias.[29] Three trials[39,44,40] blinded patients and data collectors to the treatment allocated. In the context of this study where the placebo effect is considered a powerful influence in patients' perception of symptoms[6] these studies have been considered at low risk of bias. Three trials[45,43,46] described an intention to treat analysis. None of trials had significant missing data in the final outcome assessment. Three trials[45,43,40] were funded by industry, two[39,46] did not describe their funding source and one was funded by a charity[44,] (table 13).

Table 13 Summary of Study Characteristics - PMR

Trial	Randomisation	Allocation Concealment	Blinding	Intention to Treat	Loss to Follow Up	Funding source	Risk of Bias
Leon '05[39]	Yes Method unclear	Not described	Patients and data collectors blind to treatment	NR	NR	NR	low
McNab '06[45]	In blocks of size 6 and 8 Computer generated list	NR	No	Yes	I:1 refused treatment 3 withdrew after treatment C: 2 refused treatment 1 withdrew 1 died	Manufacturers of SCS implantation equipment	unclear
Oesterle '00[43]	Randomised within blocks Data coordinating centre	Randomisation assignments were retained only at the data-coordinating centre	Angina class assessed by masked evaluators Patient sedation	Yes	11 patients died •19 withdrew	Laser manufacturer	low
Salem '04[44]	Randomised 1:1	Sealed coded envelopes Data management centre	Patient and evaluator blinded Placebo controlled Laser technician unblinded	NR	All patients except for 3 were available at 6 and 12 month follow up (2 deaths in control, 1 accident in intervention group)	charity	Low
Stone '02 [40]	Consecutive pairs	Inadequate method	Patients and follow up assessor Heavy sedation, dark goggles Blinding questionnaire	NR	NR	Laser manufacturer	low
Whitlow '03[46]	Blocked randomisation stratified to	NR	Blinded observes to assess angina	yes	None described	NR	unclear

	whether the patient could complete a stress test. Carried out by central computer		class				

4.7 Description of non-randomised Studies - PMR

4.7.1 Participants – non-randomised studies

The number of participants in each study ranged form 15 to 36 with a total of 121 patients. A description of their baseline characteristics are summarised in table 14. Two of the five[47,48] studies were based in the USA while the others were based in Italy[49], Germany[50]and Austria[51], with one trial in each county. The mean age of the included participants ranged from 60.7 to 66 years. The majority of the participants were male, ranging from 68 to 87% (median 81% male). Diabetes was reported in three studies [49,47,48] and the prevalence ranged from 37 to73% in these studies. The number of participants who had undergone previous CABG was reported in three studies with a range from 70 to 86%. Hypertension was reported in three studies [49,47,48] and ranged from 70 to 87%.

Table14 Summary of patient characteristics – non-randomised studies - PMR

Trial	Year	Total Number	Setting	Age	% Male	Hypertension (%)	Previous CABG (%)	Diabetes (%)
Galli[49]	1999	15	Italy	66	86.7	80	46.7	73
Kluge[50]	2000	36	Germany	64.3	80.6	NR	NR	NR
Laham[47]	2002	15	USA	64.1	73.3	86.7	14	46.7
Oesterle[48]	1998	30	USA	60.7	87	70	20	36.7
Strehblow[51]	2003	25	Austria	66	68	NR	44	NR

NR: not reported

4.7.2 Interventions – non-randomised studies

Of the five PMR studies, two used the Holmium YAG laser[47,48,] two used Eclipse[49,51] and one study made use of the Cardiogenesis laser system during the PMR procedure. [50] No studies reported the wattage of the laser employed; however, three studies[49,47,51] included the mean number of channels (range from 13-32 channels) as indicated by table 15. Indication of funding sources was not reported in all but one study that had support for research through a NIH grant.[47]

Table 15 Summary of PMR Intervention

Trial	Year	Funding	Laser Type	Wattage	Mean Channels n (sd)
Galli[49]	1999	NR	Eclipse laser	NR	13 (4)
Kluge[50]	2000	NR	Cardio genesis	NR	NR
Laham[47]	2002	NIH Grant	Holmium:YAG (Ho:YAG)	NR	32 (9)
Oesterle[48]	1998	NR	Holmium:YAG (Ho:YAG)	NR	NR
Strehblow[51]	2003	NR	Eclipse and biosense	NR	16 (5)

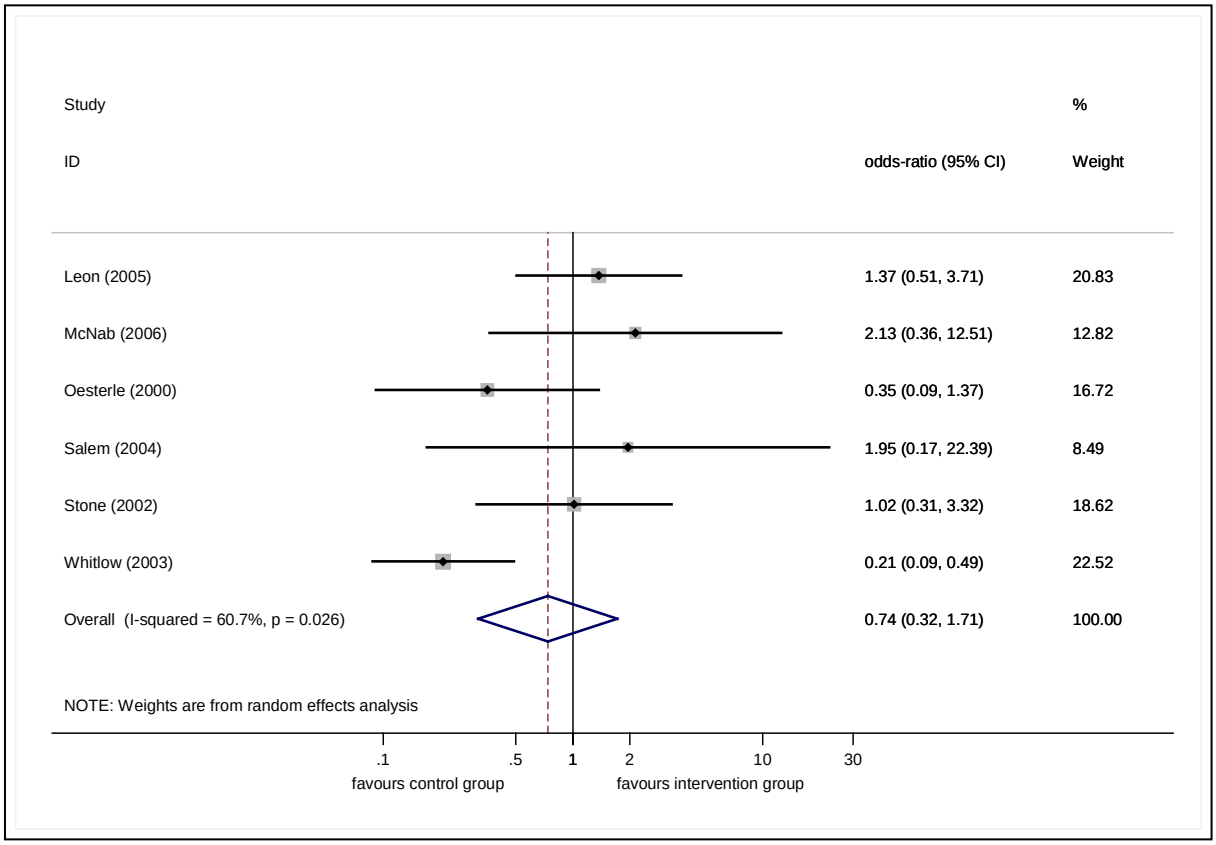
4.8 Effectiveness Outcomes (Based on RCT evidence) - PMR

4.8.1 Mortality

Mortality data was assessed at two time points in this analysis, perioperative (deaths within 30 days of intervention) and total deaths during the study period. All trials were followed for 12 months. Perioperative mortality rates will be described in the analysis of safety.

Deaths rates measured as total deaths during 12 months follow-up were not statistically different between intervention and control groups (Odds ratio 0.74 95% CI 0.32 to 1.7) (see figure 10). Additional analysis of PMR versus different control is provided in appendix 5.

Figure 11 PMR vs no PMR- Meta-analysis of mortality at 12 months



4.8.2 *Myocardial Perfusion Tests*

Only one trial[39], assessed myocardial perfusion. It used SPECT myocardial perfusion imaging following an adenosine infusion to induce cardiac stress. It found no significant difference when final values were compared with baseline values and between groups (see summary tables in appendix 3).

4.8.3 *Left Ventricular Ejection Fraction*

Two trials[43,44] measured left ventricular ejection fraction. Oesterle '00[43] measured change from baseline at 3 months follow-up and found no change between baseline or between intervention and control groups. Salem '04[44] also found no change between baseline or between intervention and control groups at 12 months follow-up.

4.8.4 Exercise Tolerance

All of the trials measured and reported exercise tolerance tests. These were carried out using a modified Bruce protocol and were reported as either final values at 12 months or change from baseline. One trial[46] reported the outcome as the number of patients who increased their exercise time by 60 or more seconds. They found a statistically significant benefit with treatment. We could not, however, incorporate the results of this trial in the meta-analysis as insufficient data was reported.

At 6 months follow-up a meta-analysis of three trials[39,45,43] found no difference in exercise tolerance times in those patients who had received PMR (see figure 12). At 12 months in a meta-analysis of five trials[45,43,39,40,44] the patients in the intervention group had a mean exercise time that was 17.7 seconds (95%CI 4.4 to 31.0) greater than those in the control groups - although this is unlikely to be considered a clinically significant improvement (figure 13). Three trials[39,40,44] blinded patients to the intervention they received, the results of these trials showed no significant difference between the intervention and control groups at either 6 months (18.3 seconds 95% CI -44.1 to 80.7) or at 12 months (11.0 seconds 95% CI -44 to 66.1) (see appendix 5).

Figure 12 Exercise Tolerance - 6 months Follow-up - PMR

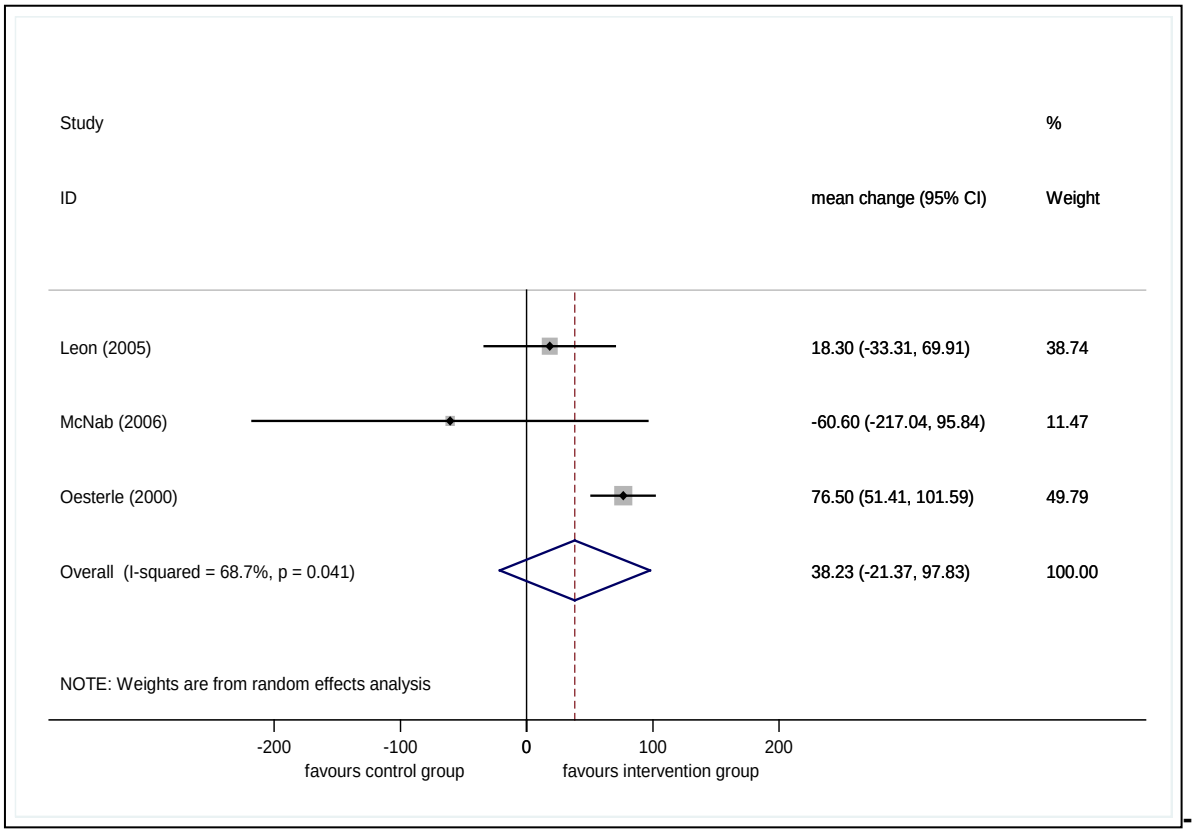
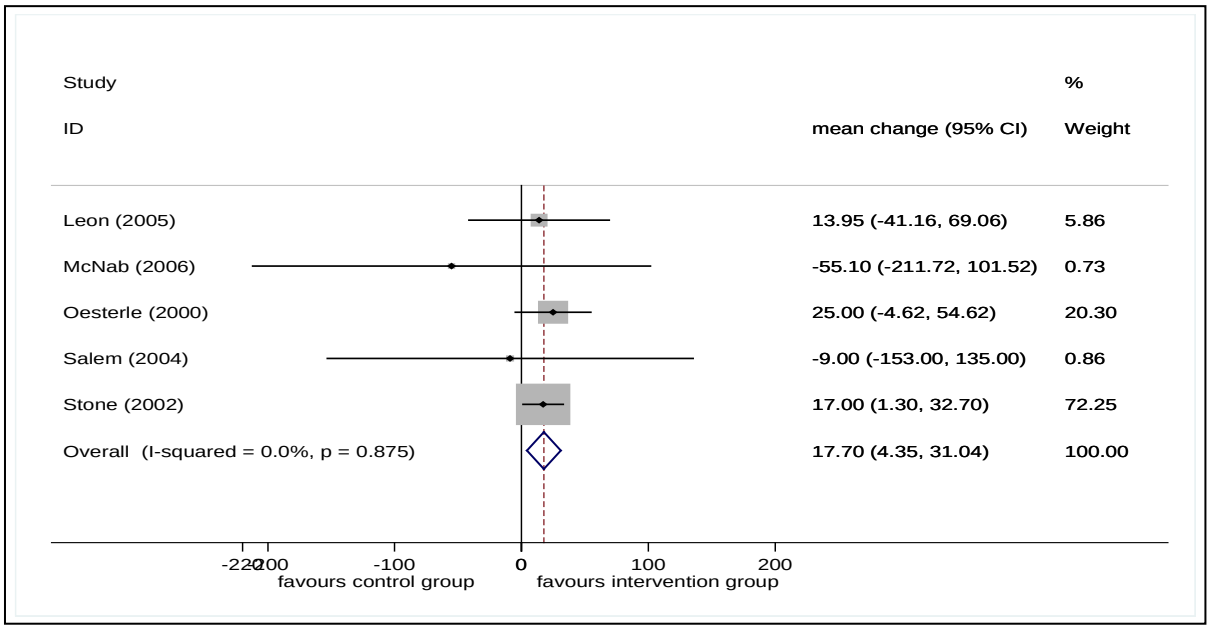


Figure 13 Exercise Tolerance - 12 months Follow-up - PMR



4.8.5 *Angina Score*

All of the trials measured CCSA angina score. This was reported as the number of patients who improved 2 or more angina classes. Three trials[44,46,39] also reported the mean final value or mean change from baseline. Three of the trials blinded patients to their treatment group, in two[40,39] the angina scores showed no significant difference between groups and in one[44] the results just achieved significance (p value= 0.04) (figures 13 and 14).

Figure 14 Angina Score - number of patients who improved 2 or more angina classes at 6 months - PMR

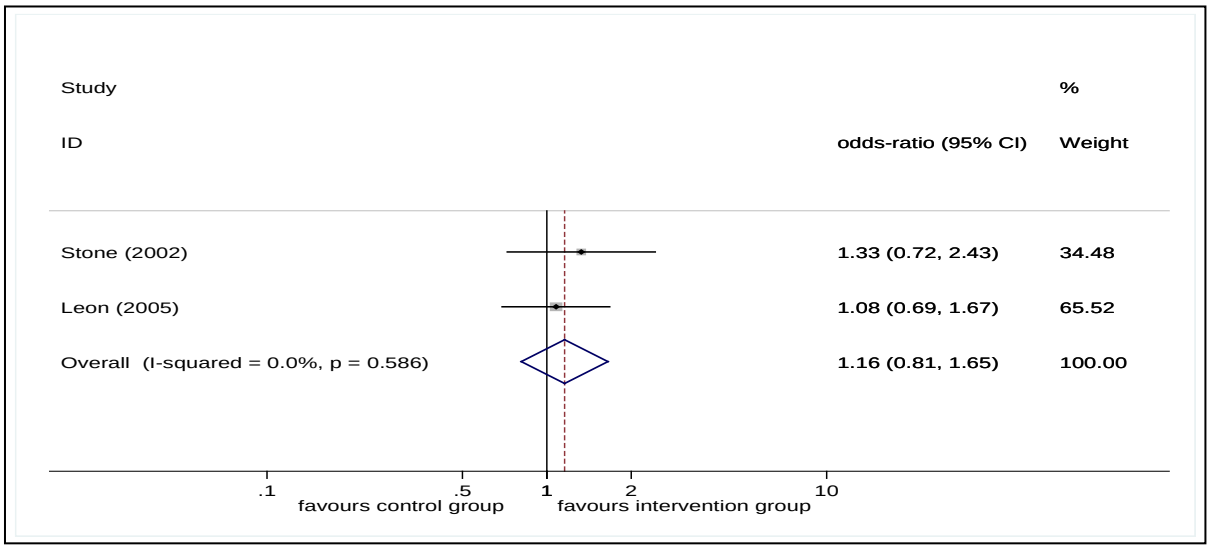
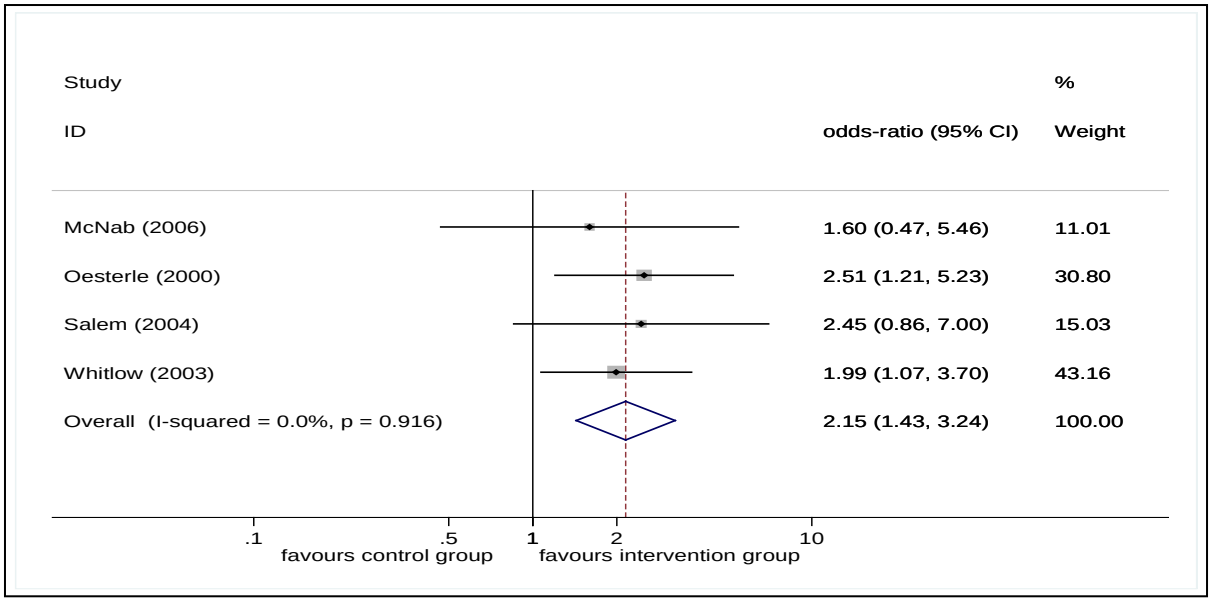


Figure 15 Angina Score - number of patients who improved 2 or more angina classes at 12 months - PMR



4.8.6 *Quality of Life*

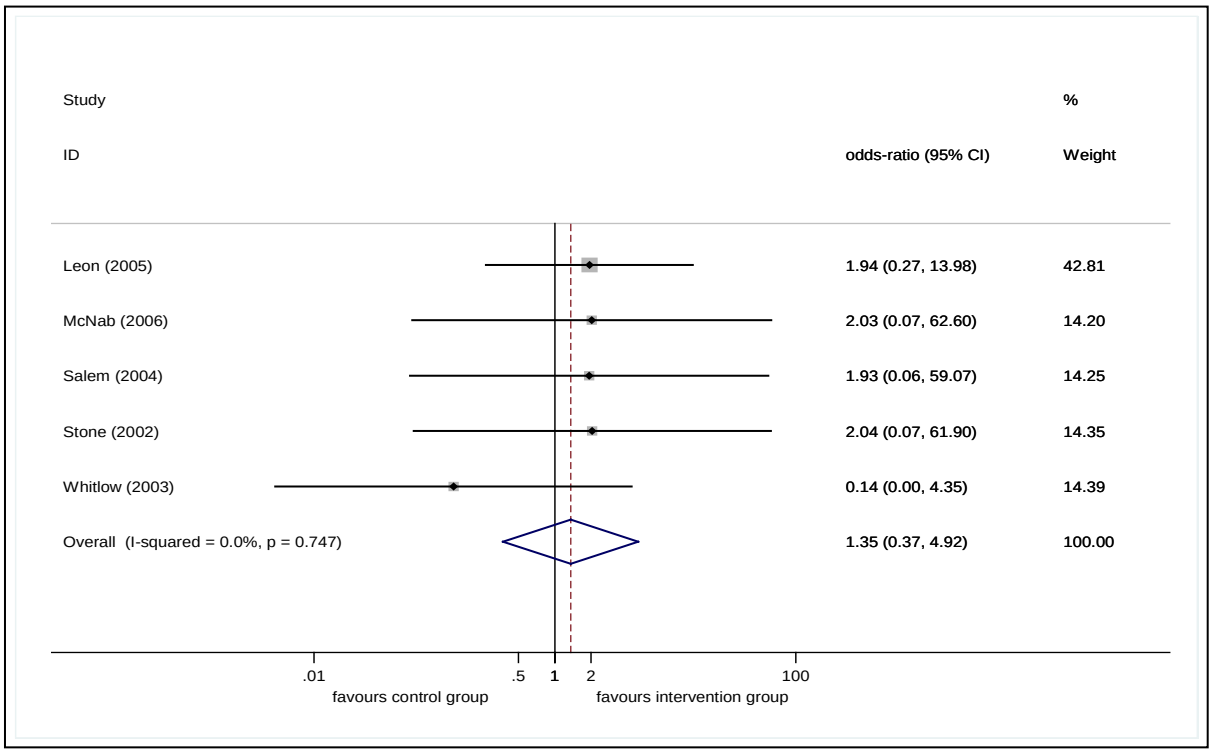
Quality of Life was measured and reported in five trials.[39,45,43,44,46] The instruments used included the SF12, SF36 and the Seattle Angina Score. No valid meta-analyses was considered possible due to the variety of instruments used. Only one trial[46] found a significant difference in quality of life which showed an improvement in the treatment group. The other four trials found no statistically significant difference between intervention and control group. This included two trials[44,39] where patients were blinded to treatment group.

4.9 Safety

4.9.1 *Postoperative mortality - PMR*

Five trials reported postoperative mortality.[39,45,44,40,46] The pooled estimate showed no significant difference between intervention and control groups (odds ratio 1.4, CI 0.4 to 4.9) (see fig 16).

Figure 16 Meta-analysis of Postoperative Mortality - PMR



4.9.2 Adverse effects – PMR

Adverse event data was retrieved from all the included RCT studies and non-randomised studies. The data is presented in tables 16 and 17. The type of adverse event, the numbers of events in each study and the total number of patients in each arm are shown. The data is presented in a narrative analysis.

In the randomised controlled studies the number of adverse events reported is greater in the intervention group (99 events vs 34 events)(see table 16). The most frequently occurring adverse event is myocardial infarction which occurs in both control and intervention groups and is an outcome reported by all the included trials. Adverse cardiac events occurring only in the intervention group include myocardial haematoma, dyspnoea, hypotension, LV perforation, pericardial effusion and tamponade.

The case series studies reported the following additional adverse events; myocardial perforation and nephropathy. Adverse vascular events also appear more commonly in the treatment groups than in the controls (23 events versus 8 events).

Table 16 Adverse effects table – PMR – RCTs

Event	Leon 2005		McNab 2006		Oesterle 2000		Salem 2004		Stone 2002*		Whitlow 2003		Totals	
Cardiac	**I**	**C**	**I**	**C**	**I**	**C**	**I**	**C**	**I**	**C**	**I**	**C**	**I**	**C**
MI	9/196	0/102	1/34	4/34	12/110	11/111	0/40	1/42	2/71	1/70	6/64	0/64	**34/515 (6.6%)**	**17/423 (4.0%)**
Myocardial Haematoma											5/64		**5/64 (7.8%)**	
Bradycardia					8/110	1/111							**8/110 (7.2%)**	**1/111 (0.9%)**
Atrial/ventricular fibrillation					4/110	4/111	0/40	1/42			1/64	0/64	**5/214 (2.3%)**	**6/217 (2.8%)**
Bundle-branch block					5/110	1/111							**5/110 (4.5%)**	**1/111 (0.9%)**
Cardioversion									3/71	0/70			**3/71 (4.2%)**	**0/70**
Dysponea							1/40						**1/40 (2.5%)**	
Hypotension											2/64		**2/64 (3.1%)**	
LV Perforation	2/196	0/102			3/110	0/111							**5/306 (1.6%)**	
Pericardial effusion					1/110	0/111							**1/110 (0.9%)**	**0/111**
Tamponade											5/64		**5/64 (7.8%)**	
Ventricular tachycardia					2/110	1/111							**2/110 (1.8%)**	**1/111 (0.9%)**
Peripheral														
Claudication							1/40						**1/40 (2.5%)**	
CVA or TIA					7/110	4/111	1/40	1/42	1/71	0/70	1/64	0/64	**10/285 (3.5%)**	**5/287 (1.7%)**
Femoral pseudoaneurysm			1/34	0/34									**1/34 (2.9%)**	**0/34**
Groin haematoma			2/34	1/34									**2/34 (5.9%)**	**1/34 (2.9%)**
Lower leg oedema							1/40	1/42					**1/40 (2.5%)**	**1/42 (2.4%)**
Peripheral vascular interventions							2/40	1/42					**2/40 (5%)**	**1/42 (2.4%)**
Vascular complications					6/110	0/111							**6/110 (5.5%)**	**0/111**
Total													**99**	**34**

Table 17 Adverse Effects – PMR – Case Series

Event	Galli 1999	Kluge 2000	Laham 2002	Oesterle 1998	Strehblow 2003	Totals
Cardiac						
Atrial/ventricular fibrillation				0/30		
Bundle branch block				1/30		**1/30 (3.3%)**
Intramyocardial hematoma					1/25	**1/25 (4%)**
MI			1/15	0/30	2/25	**3/40 (7.5%)**
Myocardial perforation	1/15				1/25	**2/40 (5%)**
Nephropathy				1/30		**1/30 (3.3%)**
Pacemaker implant					1/25	**1/25 (4%)**
Pericardial effusion				2/30		**2/30 (6.7%)**
Re-intervention					4/25	**4/25**
Tamponade				1/30		**1/30**
Ventricle dysfunction	2/15					**2/15**

5 DISCUSSION

The purpose of this review was to explore the safety and efficacy of TMLR and PMR used in the treatment of refractory angina pectoris.

5.1 Summary of main findings

In this review, we identified 29 studies for inclusion. There was a larger body of literature concerning TMLR and we identified 10 randomised controlled trials 2 non-randomised comparative studies and 6 case series (combined total of 4507 patients). We limited our inclusion of observational studies to include those with over 100 participants and with a minimum of 12 months follow-up. The literature for PMR was generally more recently published. We identified 6 randomised controlled trials (with a total of 1040 participants) and 5 case series. We did not limit our inclusion of observational studies for PMR. For both TMLR and PMR we used the observational data to explore adverse effects. The analysis of effectiveness used RCT data only.

5.2 TMLR

The ten included RCTs ranged in size from 20 to 275 participants with a total of 1359, the majority of whom were male. The intervention was carried out using either a Holmium: YAG laser or a carbon dioxide laser. Only one study used an excimer laser. The majority of the RCTs were undertaken in the USA. Seven trials compared TMLR with ongoing maximal medication, two combined TMLR with CABG and compared this with CABG alone. One trial compared TMLR with thoracic sympathectomy. Only one trial was able to blind patients to the intervention group. Two trials undermined the process of randomisation as control patients were able to cross over to the intervention group. Five were considered to be of low risk of bias and allowed greater confidence in their results.

Effectiveness

Mortality rates at 12 months following the intervention did not differ between groups (OR 0.89 95% CI 0.45 to 1.75). This remained unchanged in a sensitivity analysis exploring the effects of the two trials comparing TMLR with CABG vs CABG.

Myocardial perfusion tests were measured and reported very differently between studies precluding meta-analysis. Myocardial perfusion was measured in eight of the trials. None of the trials demonstrated a benefit sustained across all components of the test and two results suggested a worsening of myocardial perfusion following TMLR.

Left ventricular ejection fraction also provides information about heart functioning. It was measured in three trials, none of which found a statistically significant difference between the intervention and control groups.

Exercise tolerance tests were undertaken and reported in nine trials. At 6 months follow-up there was a statistically significant improvement in exercise tolerance in patients who had received TMLR (111.2 seconds (95% CI 32.5 to 190). At 12 months follow-up the mean difference was lower, but still significant showing a benefit in treatment (81.9 seconds (95% CI 26.7 to 137.3). In a sensitivity analysis exploring the effects of blinding on exercise tolerance the effect was lost and there was no difference between intervention and control groups (30.2 seconds (95% CI -21.1 to 80.1)).

Angina score was measured and reported in nine trials, most of which reported Canadian Cardiovascular Association scores (CCSA). However the different methods of reporting the outcome meant limited data was available for the meta-analsysis. An analysis of 6 of the trials showed a statistically significant improvement in angina score in patients who had received TMLR treatment at 6 and 12 months. At 12 months angina score showed a mean reduction in 1 class (95% CI 1.7 to 0.3).

Five trials measured quality of life, however the range of instruments used and the methods of reporting were so disparate that the data could not be pooled. Only one failed to show a favourable effect with treatment.

Safety

When TMLR is compared with medically managed controls and thoracic sympathectomy (1 trial) there is a statistically significant increase in the odds of peri-operative death (OR 0.35 95% CI 0.13 to 0.93). This result becomes non-significant when combined with trials where intervention and control both also have CABG (odds ratio 0.78 95% CI 0.34 to 1.7). In a narrative assessment of adverse events derived from the observational studies there appears to be a range of adverse events that are more likely to effect the intervention group, including myocardial infarction and heart failure.

5.3 PMR

The six included RCT ranged in size from 68 to 275 with a total of 1040 participants. The intervention was carried out using a Holmium: YAG laser. The majority of the participants were male and most of the studies were conducted in the USA. Three trials compared the laser intervention with ongoing maximal medical management, two with sham therapy and one with spinal cord stimulation. Three trials blinded patients and data collectors to the treatment group. Four trials were considered to be of lower risk of bias and to therefore allow greater confidence in the results.

Effectiveness

Mortality rates showed no statistically significant difference between intervention and control groups (odds ratio 0.74 95% CI 0.32 to 1.7).

One trial assessed myocardial perfusion using SPECT myocardial imaging following an adenosine infusion. It found no significant differences between intervention and control group.

Two trials measured left ventricular ejection fraction and found no difference between groups or from baseline.

Exercise tolerance was reported in all the trials. At 12 months there was a statistically significant increase of 17.7 seconds (95% CI 4.4 to 31.0) but this result is unlikely to be clinically significant. A sensitivity analysis adjusting for blinding of patients found that the results were non-significant at 12 months. Angina score was measured by all of the trials. At 12 months there was a significant improvement in the number of patients who had improved their angina score by 2 or more classes. This result was not significant at 6 months when the meta-analysis included the results from two trials where patients were blinded to treatment.

Quality of life was measured and reported in five trials. Only one trial found a statistically significant difference between intervention and control groups.

Safety

Postoperative mortality rate did not show any difference between treatment and intervention group (odds ratio 1.35 95% CI 0.37 to 4.92). There appears to be risks of experiencing a range of cardiovascular and vascular adverse events with treatment, including myocardial haematoma and bradycardia and bundle-branch block.

6 CONCLUSIONS

6.1 Implications for the NHS

TMLR and PMR are interventions with a poorly understood mechanism of effect. While theories are postulated, they remain unconfirmed. The patients studied in these trials had severe angina symptoms and had exhausted all forms of conventional therapy. They are likely to be motivated to want a novel therapy that might provide symptom relief.

This review has shown that for those outcomes where there is an objective measure of heart function, i.e. myocardial perfusion and left ventricular ejection fraction no effect is seen with treatment. This is despite a range of methods used to measure the outcomes as seen in the included trials.

Where measures become more subjective, such as exercise tolerance tests, angina score, and quality of life more of the trials see a statistically significant effect. This effect is however lost or much reduced where patients are blinded.

The concomitant postoperative mortality risk with TMLR and the associated risks of adverse effects raise concerns about the safety of these interventions.

The wider applicability of these findings must also be considered. The majority of participants in these trials were male and the majority of trials undertaken in the USA. There is no evidence to assume the benefits seen in subjective outcome measures would be the same in different patient populations.

6.2 Implications for future research

There are clearly real needs for patients with refractory angina who are perceived to have exhausted all forms of conventional therapy. Alternatives such as transcutaneous electrical nerve and external counterpulsation need to be explored and their effectiveness and safety tested. There is also a need to continue primary research in order to establish the most effective ways of both treating and preventing this condition.

Women are under-represented in these studies and primary research needs to ensure their findings will have external validity. Trials also need to ensure blinding of patients, assessors and care givers where possible to minimise bias.

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Appendix 1

Search Strategy

A comprehensive literature search was performed in July 2007. Searches were designed to retrieve:

- Papers describing the clinical effectiveness of laser surgery for angina
- Papers on the safety of laser surgery for angina.

The following electronic bibliographic databases were searched:

1. BIOSIS previews (Biological Abstracts)
2. British Nursing Index (BNI)
3. Cumulative index to nursing and allied health literature (CINAHL)
4. Cochrane Database of Systematic Reviews (CDSR)
5. Cochrane Central Register of Controlled Trials (CENTRAL)
6. Embase
7. Medline
8. Medline In-Process & Other Non-Indexed Citations
9. NHS Database of Abstracts of Reviews of Effects (DARE)
10. NHS Health Technology Assessment (HTA) Database
11. Science Citation Index (SCI)
12. Social Sciences Citation Index (SSCI)

To retrieve clinical effectiveness papers systematic review and randomised controlled trials filters were used where appropriate.

To retrieve papers on the safety of laser surgery for angina a list of terms related to safety were compiled and used in the search process where appropriate.

Attempts were also made to identify 'grey' literature by searching appropriate databases (e.g. Kings Fund, DH-Data) current research registers (e.g. National Research Register, Current Controlled Trials Register, ReFer Research Finding Register). A general internet search was also conducted using a standard search engine (Google) and a meta-search engine (Copernic). The reference lists of included studies and relevant review articles were also checked.

No date or language restrictions were applied to these searches.

Search strategies used in Medline (Ovid):

Database: Ovid MEDLINE(R) <1950 to June Week 3 2008>
Search Strategy:
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1. exp Angina Pectoris/
2. angina.tw.
3. Coronary Artery Disease/
4. (coronary adj3 arter$ adj3 (disease$ or insufficien$)).tw.
5. or/1-4
6. myocardial revascularization/ or angioplasty, transluminal, percutaneous coronary/
7. (transmyocardial adj3 revasculari?ation).tw.
8. (trans-myocardial adj3 revasculari?ation).tw.
9. (tmlr or tmr).tw.
10. percutaneous coronary intervention.tw.
11. pci.tw.

12. or/6-11
13. laser.tw.
14. laser therapy/ or angioplasty, laser/ or angioplasty, balloon, laser-assisted/
15. 13 or 14
16. 12 and 15
17. laser revasculari?ation.tw.
18. ((transmural or transmyocardial or subendocardial or perfusion$ or percutaneous) adj3 (channel$ or pathway$)).tw.
19. (percutaneous adj3 revasculari?ation).tw.
20. ((fiberoptic or fiber-optic or fibreoptic or fibre-optic) adj3 catheter).tw.
21. laser therapy/ or angioplasty, laser/ or angioplasty, balloon, laser-assisted/
22. or/16-21
23. 5 and 22

In the search above terms to describe angina (1-4) combined with terms to describe laser surgery (6-22). These terms were then combined with each of the filters below to retrieve literature on the clinical effectiveness and safety of laser surgery for angina

Systematic Review Filter

1. meta-analysis/
2. exp review literature/
3. (meta-analy$ or meta analy$ or metaanaly$).tw.
4. meta analysis.pt.
5. review academic.pt.
6. review literature.pt.
7. letter.pt.
8. review of reported cases.pt.
9. historical article.pt.
10. review multicase.pt.
11. or/1-6
12. or/7-10
13. 11 not 12

Randomised Controlled Trial Filter

1. randomized controlled trial.pt.
2. controlled clinical trial.pt.
3. randomized controlled trials/
4. random allocation/
5. double blind method/
6. single blind method/
7. clinical trial.pt.
8. exp clinical trials/
9. (clin$ adj25 trial$).ti,ab.
10. ((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ti,ab.
11. placebos/
12. placebos.ti,ab.
13. random.ti,ab.
14. research design/
15. or/1-14

Safety Filter

1. Safety/

2. patient safety.tw.
3. clinical safety.tw.
4. safe$.tw.
5. Medical Errors/
6. (reduc$ adj1 (risk$ or error$)).tw.
7. (minimis$ adj1 (risk$ or error$)).tw.
8. (minimiz$ adj1 (risk$ or error$)).tw.
9. (decreas$ adj1 (risk$ or error$)).tw.
10. clinical risk$.tw.
11. appropriate$.tw.
12. consequence$.tw.
13. operative mortalit$.tw.
14. post-operative mortailt$.tw.
15. Myocardial Infarction/
16. myocardial infarction$.tw.
17. repeat intervention$.tw.
18. heart failure.tw.
19. exp Pneumonia/
20. pneumonia.tw.
21. hemorrhage/ or blood loss, surgical/ or postoperative hemorrhage/
22. hemorrhage.tw.
23. bleeding.tw.
24. arrhythmia.tw.
25. mitral valve.tw.
26. rupture.tw.
27. 25 and 26
28. Infection
29. infection.tw.
30. (rupture adj3 mitral valve).tw.
31. or/1-30

The medicines reconciliation terms (1-13) were combined the with patient admission, discharge and transfer terms (15-18).

Cost effectiveness searches

To retrieve papers on cost-effectiveness and comparative costs of the different medicines reconciliation procedures searches were conducted in Medline, CINAHL, Embase, NHS Economic Evaluations Database (EED). The search terms given above were utilised. Search filters designed to retrieve economic evaluations, were applied to the Medline CINAHL and Embase searches. An example of the Medline (Ovid) search filter is provided below:

1. Economics/
2. exp "Costs and Cost Analysis"/
3. economic value of life/
4. exp economics hospital/
5. exp economics medical/
6. economics nursing/
7. exp models economic/
8. Economics, Pharmaceutical/
9. exp "Fees and Charges"/
10. exp budgets/
11. ec.fs.
12. (cost or costs or costed or costly or costing$).tw.
13. (economic$ or pharmacoeconomic$ or price$ or pricing$).tw.
14. quality adjusted life years/

15. (qaly or qaly$).af.
16. or/1-15

Terms related to medicines reconciliation (1-10) were combined with patient admission terms (12-14).

To retrieve cost effectiveness papers the above strategy was combined with search filters designed to retrieve economic evaluations as discussed above.

Appendix 2 Excluded Studies

Study	Reason for exclusion
Grauhan, O., Krabatsch, T., Lieback, E., and Hetzer, R. Transmyocardial laser revascularization in ischemic cardiomyopathy. *Journal of Heart and Lung Transplantation* 2001; **20** 687-691.	Trial participants did not have refractory angina
Lutter, G., Saurbier, B., Nitzsche, E., Kletzin, F., Martin, J., Schlensak, C., Lutz, C., and Beyersdorf, F. Transmyocardial laser revascularization (TMLR) in patients with unstable angina and low ejection fraction. *European Journal of Cardio-Thoracic Surgery* 1998; **13** 21-26.	Not all participants had refractory angina, procedure combined with perioperative use of an intraoaortic balloon pump
Epps, W. M. and Francalancia, N. Transmyocardial laser revascularization (TMR) and its role in the treatment of patients with coronary artery disease and angina. *Current Surgery* 2002; **59** 253-257.	Review article
Myers, J., Oesterle, S. N., Jones, J., and Burkhoff, D. Do transmyocardial and percutaneous laser revascularization induce silent ischemia? An assessment by exercise testing. *American Heart Journal* 2002; **143** 1052-1057.	Review article
Dixon, S. R., Schreiber, T. L., Rabah, M., Lee, D. T., Kelco, K. L., and O'Neill, W. W. Immediate effect of percutaneous myocardial laser revascularization on hemodynamics and left ventricular systolic function in severe angina pectoris. *American Journal of Cardiology* 1-3-2001; **87** 516-519.	Review article
Guleserian, K. J., Maniar, H. S., Camillo, C. J., Bailey, M. S., Damiano, R. J., Jr., and Moon, M. R. Quality of life and survival after transmyocardial laser revascularization with the holmium:YAG laser. *Annals of Thoracic Surgery* 2003; **75** 1842-1847.	Only a third of trial participants had refractory angina

Multiple Publications TMLR

Included Publication	**Multiple Publications of same trial (excluded)**
Aaberge, L.,et al. Transmyocardial revascularization with CO2 laser in patients with refractory angina pectoris - Clinical results from the Norwegian randomized trial. *Journal of the American College of Cardiology* 2000; **35** 1170-1177	▪ Aaberge, L.,et al Myocardial performance after transmyocardial revascularization with CO(2)laser. A dobutamine stress echocardiographic study. European Journal of Echocardiography 2001; 2 187-196. ▪ ▪ Aaberge, L.,et al. Effects of transmyocardial revascularization on myocardial perfusion and systolic function assessed by nuclear and magnetic resonance imaging methods. Scandinavian Cardiovascular Journal 2001; 35 8-13. ▪ ▪ Aaberge, L.,et al. Continued symptomatic improvement three to five years after transmyocardial revascularization with CO(2) laser: a late clinical follow-up of the Norwegian Randomized trial with transmyocardial revascularization. Journal of the American College of Cardiology 15-5-2002; 39 1588-1593[52,53]
▪ Allen, K. B., et al. Comparison of transmyocardial revascularization with medical therapy in patients with refractory angina. New England Journal of Medicine 1999; 341 1029-1036.	▪ Allen, K. et al. Transmyocardial revascularization: 5-year follow-up of a prospective, randomized multicenter trial. Annals of Thoracic Surgery 2004; 77 1228-1234

▪ Allen, K. B et al. Transmyocardial laser revascularization combined with coronary artery bypass grafting: a multicenter, blinded, prospective, randomized, controlled trial.[see comment]. Journal of Thoracic & Cardiovascular Surgery 2000; 119 540-549.	▪ Allen, K. B., et al Transmyocardial laser revascularization combined with coronary artery bypass grafting: a multicenter, blinded, prospective, randomized, controlled trial.[see comment]. Journal of Thoracic & Cardiovascular Surgery 2000; 119 540-549.
▪ Schofield, P. M., Sharples, L. D., Caine, N., Burns, S., Tait, S., Wistow, T., Buxton, M., and Wallwork, J. Transmyocardial laser revascularisation in patients with refractory angina: a randomised controlled trial.[see comment][erratum appears in Lancet 1999 May 15;353(9165):1714]. Lancet 13-2-1999; 353 519-524.	▪ Burns, S. M., Brown, S., White, C. A., Tait, S., Sharples, L., and Schofield, P. M. Quantitative analysis of myocardial perfusion changes with transmyocardial laser revascularization. American Journal of Cardiology 1-4-2001; 87 861-867.
▪ Salem, M., Rotevatn, S., Stavnes, S., Brekke, M., Vollset, S. E., and Nordrehaug, J. E. Usefulness and safety of percutaneous myocardial laser revascularization for refractory angina pectoris. American Journal of Cardiology 1-5-2004; 93 1086-1091.	▪ Salem, M., Rotevatn, S., Stavnes, S., Brekke, M., Pettersen, R., Kuiper, K., Ulvik, R., and Nordrehaug, J. E. Release of cardiac biochemical markers after percutaneous myocardial laser or sham procedures. International Journal of Cardiology 30-9-2005; 104 144-151.
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Excluded Non-randomised Studies

TMLR Less Than 100 Patients

Agarwal R, Ajit M, Kurian VM, Rajan S, Arumugam SB, Cherian KA. Transmyocardial laser revascularization for diffuse coronary artery disease: Early results. *Current Science* 1999;**77**(7):904-7.

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APPENDIX 3

TMLR – RCTs

<table>
<tr><th>Study Details</th><th>Participant characteristics</th><th>Intervention Characteristics</th><th>Results</th><th>Comments</th></tr>
<tr>
<td>Aaberge (2000)[26]

Study design: RCT

Location: Norway

Source of funding: Norwegian ministry of Health and Social Affairs

QUALITY
Randomisation: Randomized 1:1 using block randomization into two comparable groups
Allocation Concealment: Consecutively numbered sealed envelopes with allocation numbers and treatment inside.
Blinding: no
Intention to Treat Analysis: no
Loss to follow-up: 1 patient excluded from TMR group as given CABG while undergoing thoracotomy</td>
<td>Number of patients: 100
Mean Age: 62.5 yrs (SD 3.2)
Male: 86%
Hypertension: 95%
Diabetes Mellitus: 25%
Current Smoker: 18%
Previous CABG: NR
Mean LVEF: 49%
Baseline comparability: No - the double product at maximal exercise was higher in the TMR group than in the control group.

Inclusion Criteria:
▪ Patients suffering from angina pectoris NYHA functional class II or IV despite optimal medical treatment.
▪ Not candidates for percutaneous transluminal coronary angioplasty or coronary artery bypass grafting because or peripheral obstructions in the coronary arteries

Exclusion Criteria:
▪ age > 75 years</td>
<td>Intervention (laser type, wattage):
Left anterior thoracotomy laser treatment. Same surgeon. 800 W CO_2 laser. About one channel/ cm^2 of presumed ischemic an viable myocardium was made. Average of 48(SD7) channels made.

Control:
Medical management</td>
<td>EFFECTIVENESS
Mortality
<table>
<tr><th></th><th colspan="3">< 30 days</th><th colspan="3">> 30 days</th><th colspan="3">total</th></tr>
<tr><th></th><th>n</th><th>N</th><th>%</th><th>n</th><th>N</th><th>%</th><th>n</th><th>N</th><th>%</th></tr>
<tr><td>I:</td><td>2</td><td>50</td><td>4</td><td>7</td><td>48</td><td>14.6</td><td>9</td><td>50</td><td>18</td></tr>
<tr><td>C:</td><td>0</td><td>50</td><td>0</td><td>8</td><td>50</td><td>16</td><td>8</td><td>50</td><td>16</td></tr>
</table>
Angina Score (NYHA)
<table>
<tr><th></th><th colspan="3">Baseline</th><th colspan="3">3 m</th><th colspan="3">12 m</th></tr>
<tr><th></th><th>m</th><th>sd</th><th>n</th><th>m</th><th>sd</th><th>n</th><th>m</th><th>sd</th><th>n</th></tr>
<tr><td>I:</td><td>3.3</td><td></td><td>49</td><td>2.3</td><td></td><td>46</td><td>2.0</td><td></td><td>43</td></tr>
<tr><td>C:</td><td>3.2</td><td></td><td>50</td><td>3.1</td><td></td><td>48</td><td>3.1</td><td></td><td>46</td></tr>
</table>
P=0.01

Exercise tolerance
(total exercise time)
<table>
<tr><th></th><th colspan="3">Baseline</th><th colspan="3">3 m</th><th colspan="3">12 m</th></tr>
<tr><th></th><th>m</th><th>sd</th><th>n</th><th>m</th><th>sd</th><th>n</th><th>m</th><th>sd</th><th>n</th></tr>
<tr><td>I:</td><td>542</td><td>157</td><td>49</td><td>538</td><td>148</td><td>46</td><td>550</td><td>152</td><td>43</td></tr>
<tr><td>C:</td><td>570</td><td>163</td><td>50</td><td>570</td><td>176</td><td>48</td><td>560</td><td>184</td><td>46</td></tr>
</table>
Non significant

(time to chest pain)
<table>
<tr><th></th><th colspan="3">Base</th><th colspan="3">3 m</th><th colspan="3">12 m</th></tr>
<tr><th></th><th>m</th><th>sd</th><th>n</th><th>m</th><th>sd</th><th>n</th><th>m</th><th>sd</th><th>n</th></tr>
<tr><td>I:</td><td>409</td><td>122</td><td>49</td><td>487</td><td>152</td><td>46</td><td>475</td><td>150</td><td>43</td></tr>
<tr><td>C:</td><td>437</td><td>155</td><td>50</td><td>453</td><td>156</td><td>48</td><td>434</td><td>166</td><td>46</td></tr>
</table>
(time to 1 mm ST segment)
<table>
<tr><th></th><th colspan="3">Base</th><th colspan="3">3 m</th><th colspan="3">12 m</th></tr>
<tr><th></th><th>m</th><th>sd</th><th>n</th><th>m</th><th>sd</th><th>n</th><th>m</th><th>sd</th><th>n</th></tr>
<tr><td>I:</td><td>419</td><td>178</td><td>49</td><td>430</td><td>165</td><td>46</td><td>457</td><td>152</td><td>43</td></tr>
<tr><td>C:</td><td>455</td><td>204</td><td>50</td><td>466</td><td>212</td><td>48</td><td>444</td><td>191</td><td>46</td></tr>
</table>
QOL - NM</td>
<td>Other references of this study:

Aaberge (2002) 491
Aaberge (2001) 6239
Aaberge (2001) 2145</td>
</tr>
</table>

<table>
<tr>
<td></td>
<td>

left ventricular ejection fraction < 30%
non-demonstrated reversible ischemia
overt heart failure
inability to undergo study tests and condition precluding thoracic surgery

</td>
<td></td>
<td>
LVEF %
<table>
<tr><th></th><th colspan="3">Base</th><th colspan="3">3 m</th><th colspan="3">12 m</th></tr>
<tr><th></th><th>m</th><th>sd</th><th>n</th><th>m</th><th>sd</th><th>n</th><th>m</th><th>sd</th><th>n</th></tr>
<tr><td>I:</td><td>48.9</td><td>11.9</td><td>49</td><td>47</td><td>13.2</td><td>46</td><td>47.4</td><td>14</td><td>43</td></tr>
<tr><td>C:</td><td>49.6</td><td>11.9</td><td>50</td><td>52.3</td><td>11.5</td><td>48</td><td>51.0</td><td>11.8</td><td>46</td></tr>
</table>
Non significant

Medication usage:
An increased use of ACE inhibitors and diuretics and a reduced use of aspirin was observed in the TMR group during follow-up. The changes were not statistically significant (p> 0.08)

Dobutamine Stress Echocardiography and SPECT (Aaberge2001)
Resting wall motion abnormalities worsened, wall motion abnormalities during dobutamine stimulation remained unchanged and the number of probably non-viable segments increased.

SAFETY
<table>
<tr><th>Adverse Event</th><th>I</th><th>C</th></tr>
<tr><td>MI</td><td>4</td><td>0</td></tr>
<tr><td>perioperative heart failure</td><td>17</td><td>0</td></tr>
<tr><td>Temporary respiratory support</td><td>2</td><td>0</td></tr>
</table>
</td>
<td></td>
</tr>
<tr>
<td>Allen (1999) [19]

Study design: RCT

Location: USA 18 centres

Source of funding: Eclipse Surgical Technologies

QUALITY
Randomisation:
Randomisation was performed by each centre on a 1:1 basis with block size of 6 patients per centre
Allocation Concealment:
Not described
Blinding:</td>
<td>Number of patients: 275

Mean Age: 60 years

Male: 75.3%

Hypertension: 70.5%

Diabetes: 42.4%

Smoker: 72%

Previous CABG: 86.1%

Mean LVEF: 47%

Baseline comparability:
yes</td>
<td>Intervention (laser type, wattage):
Holmium: YAG laser (Eclipse Surgical Technologies)
Limited left anterior thoracotomy. A 20-W holmium laser was used to create channels. Delivered 6 to 8 W per pulse and energy was delivered at the rate of five pulses per second through a flexible 1-mm optical fiber. Channels were placed every square centimetre throughout the distal two thirds of the left ventricle. Three to five channels were placed. Mean 39 (SD= 11)</td>
<td>
EFFECTIVENESS
Mortality
< 30 days
<table>
<tr><th></th><th colspan="3"><30 days</th><th>30 days-1 year</th><th colspan="3">total</th></tr>
<tr><th></th><th>n</th><th>N</th><th>%</th><th>n</th><th>n</th><th>N</th><th>%</th></tr>
<tr><td>I:</td><td>7</td><td>132</td><td>5.3</td><td>14</td><td>21</td><td>132</td><td>16</td></tr>
<tr><td>C:</td><td>2</td><td>142</td><td>1.4</td><td>14</td><td>16</td><td>142</td><td>11.2</td></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td colspan="3">P=0.23</td></tr>
</table>
Angina Score
A reduction of two or more CCS classes % of patients
NR
<table>
<tr><th></th><th colspan="3">3 m</th><th colspan="3">6 m</th><th colspan="3">12 m</th></tr>
<tr><th></th><th>n</th><th>N</th><th>%</th><th>n</th><th>N</th><th>%</th><th>n</th><th>N</th><th>%</th></tr>
<tr><td>I:</td><td>95</td><td>115</td><td></td><td>86</td><td>98</td><td></td><td>76</td><td>76</td><td></td></tr>
<tr><td>C:</td><td>13</td><td>98</td><td></td><td>20</td><td>74</td><td></td><td>32</td><td>50</td><td></td></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td colspan="3">p<0.001</td></tr>
</table>
Myocardial perfusion
Using dipyridamolethallium stress testing. Changes from baseline to 12 months.
</td>
<td>CROSS-OVER
46 patients from the control group were transferred to a cross over group which received treatment. Consequently the control group may be different and the purpose of randomisation is lost.

Other refs
Allen (2004) 913</td>
</tr>
</table>

Blind assessment of ischemic changes, perfusion defects at rest and delayed perfusion defects **ITT:** yes **Loss to follow-up: n/total – deaths (%)** angina score I: 35/111 (31.5%) C:30/80 (37%) NB cross overs myocardial perfusion 61/178 (34%)	**Inclusion Criteria:** ▪ refractory class IV angina that was not amenable to coronary-artery bypass grafting or percutaneous transluminal coronary angioplasty, ▪ reversible ischemia ▪ left ventricular ejection fraction >25% **Exclusion Criteria:** ▪ Contraindication to general anaesthesia, ▪ severe chronic obstructive pulmonary disease ▪ need for continued use of intravenous antiangina medication ▪ inability to undergo dipyridamole-thallium stress scintigraphy ▪ non-Q-wave myocardial infarction within the previous two weeks or a Q-wave myocardial infarction within the previous three weeks ▪ long-term anticoagulant therapy ▪ presence of a ventricular mural thrombus, severe arrhythmias ▪ decompensated congestive heart failure.	channels were created per patient. ***Control:*** Medical treatment alone	Ischemia / Defects at rest m sd n m sd n I: -0.9% NR 30? 1.6% NR 30? C: -0.6% NR 31? 2.2% NR 31? P=0.90 P=0.84 Data only available for 61 patients – unclear how many are in each group. No significant difference between groups with respect to delayed defects also, data available for only 48 participants. **Quality of Life** 12 m m sd n I: 21 14 ? C: 12 11 ? P=0.003 Masked quality of life score using the Duke Activity Status Index. Based on a scale from 0 t0 58 with higher scores indicating greater functional capacity. N=112 Unclear if this result is a change from baseline. P value may be difference in final value and not change from baseline – unclear if they are similar at baseline. Insufficient reporting of data **SAFETY** Perioperative complications in TMLR group – Number of patients (%) Atrial arrhythmias 13 (10) Hypotension 13(10) Ventricular arrhythmia 16 (12) Non-Q-wave myocardial infarction 6(5) Q-wave myocardial infarction 1(1) Congestive heart failure 5(4) Respiratory insufficiency 4(3) transfusion due to blood loss from TMLR 0	

Allen (2000)[20]

Study design: RCT

Location: USA

Source of funding: NR

QUALITY
Randomisation:
Computer generated and stratified by sex and ejection fraction (≤40% >40%)
Allocation
Concealment: no
Blinding: Patients blinded for 1 year after surgery as to whether they received adjunctive TMR
Intention to Treat analysis:
After randomisation 3 patients were excluded for protocol violations (2 control, 1 treatment).
1 treatment withdrew.
ITT:no
Loss to follow-up: n/total – deaths (%)
Missing outcome data for the following

angina score	204/241 (16)
Exercise tolerance	135/243 (55.5%)

Number of patients: 266

Mean Age: 63.5 yrs

Male: 72% (n=190)

Hypertension: NR

Diabetes: 44%(n=116)
% previous CABG:

Mean LVEF: NR

Baseline comparability:
Yes

Inclusion Criteria:
- Isolated coronary artery disease with one or more major vessels or branches not by-passable for anatomic reasons
- presence of viable myocardium surrounding the non by-passable vessels.

Exclusion Criteria:
- severe chronic COAD (forced expiratory volume in 1 second < 55% of predicted value)
- non-Q-wave or Q-wave MI within 2 or 3 weeks of enrolment
- severe arrhythmia uncontrolled by a device or medication
- decompensated cardiac failure.

Intervention
CABG or suitable vessels plus TMR of areas not suitable to grafting

Laser energy was delivered with a flexible 1 – mm optical fibre. Delivered 6-8 W of laser energy at 5 pulses/s. TMR was performed either on an arrested heart before placement of grafts (n=19) or after the completion of grafts (n 112). An average of 25 (SD=10) channels were created.

Control:
CABG alone

EFFECTIVENESS
Mortality

	perioperative			total		
	n	N	%	n	N	%
I:	2	132	1.5	8	132	6.06
C:	10	131	7.6	14	131	10.7

Angina Score
12 month angina assessment score complete on 84% (204/243) of patients – unclear from which group.

	Base			3 m (change)			12 m (change)		
	m	sd	n	m	sd	n	m	sd	n
I:	2.8			0.4			0.5		
C:	2.9			0.4			0.6		

Exercise tolerance
(change from baseline) Bruce protocol

	Base			12 m		
	m	sd	n	m	sd	n
I:			132	366	324	?
C:			131	336	408	?
				P=0.7		

Only 55% (135/243) of patients available for comparison. Unclear which group.

Net change in **MET from baseline**:
Patients unable to perform a baseline exercise treadmill test because of angina (n=83) were assigned values of 0 minutes and 1 metabolic equivalent (MET)

	Base			12 m		
	m	sd	n	m	sd	n
I:			?	3.9	3.4	?
C:			?	3.6	3.7	?
				P=0.9		

QOL- NM

SAFETY

	TMLR + CABG n (%)	CABG	P=
Atrial arrhythmia	24 (18)	21 (16)	0.7
Ventricular fibrillation	5(4)	3(2)	0.7
Cerebral vascular accident	1(1)	3(2)	0.4

Unclear what the end point in exercise time is being measured.

			Reoperation for bleeding: 4(3) / 1(1) / 0.4 Q wave MI: 2(2) / 0(0) / 0.5 Non-Q wave MI: 1(1) / 2(2) / 0.6	
Burkhoff 1999 [21] **Study design:** RCT **Location:** USA 16 centres **Source of funding:** CardioGenesis Corporation **QUALITY** **Randomisation:** Block randomisation **Allocation concealment:** Randomisation was done by a central coordinating centre by telephone. The centre confirmed eligibility criteria before it provided a randomisation assignment. **Blinding:** Unmasked assessment of angina class. Exercise-tolerance tests, echocardiography, dipyridamole thallium stress test were assessed blind. **Intention to Treat analysis:** Excluded patients who withdrew from the study **Loss to follow-up:** Withdrawals	**Number of patients:** 182 **Mean Age:** 64 years **Male:** 90.7% (discrepancy between table and text) **Hypertension:** 80.8% **Previous CABG*:*** 36.8% **% smokers:** 82.4% (history of smoking) **Baseline comparability:** No – significantly more patients in control group with hypertension and hyperlipidaemia. **Inclusion Criteria:** ▪ CCSA scores of III or IV, despite maximum tolerated doses of at least two antianginal drugs. ▪ left-ventricular ejection fraction of 30% or more ▪ reversible perfusion defects on dipyridamole thallium stress test. ▪ two consecutive	**Intervention** TMR with continued medication. Left thoracotomy and transmyocardial laser channels were created in and around previously identified areas of reversible ischaemia with a density of about one channel per 1.0-1.5 cm^2 A median of 18 (range 9-42) channels were created with a holmium: YAG (CardioGenesis Corp). **Control:** Continued medication with current treatment regimen	**Mortality** perioperative: n / N / % — total: n / N / % I: 1 / 92 / 1 — 5 / 92 / 5.3 C: 0 / 90 / 0 — 9 / 90 / 10 **Angina Score** Decrease in two or more CCSA classes at 12 months 12 m: n / N / % I: 47 / 77 / 61 C: 8 / 72 / 11 **Exercise tolerance** Median (IQR range) change in exercise duration from baseline Base line: m / range / N — 6 m (change): m / range / N — 12 m (change): m / range / N 364 / 105-981 / 92 — 100 / 200-0 / ? — 65 / -25-180 / 74 381 / 89-747 / 90 — -20 / 60- -100 / ? — -46 / P=<0.0001 / 67 **QOL-Seattle angina questionnaire – Disease perception** Median and range scores reported. Change from baseline med / IQR range / N I: 50 / 20 to 60 / 78 C: 10 / 0 to 20 / 74 Scores of each QOL index rose significantly more in the TMLR group. The reported QOL was therefore higher in the TMLR group. **Ejection Fraction%** Median (range) change from baseline baseline: med / IQR range / n — Change at 3 m: med / IQR range / n I: 50 / 31-68 / 92 — 0 / -25 to 20 / NR C: 45 / 31-68 / 90 — -3 / -28 to 20 / NR NS	Left-ventricular fraction did not change significantly. May be an improvement in perfusion undetectable by this technique. Thallium scans showed no improvement in blood flow.

<table>
<tr>
<td>I: 9
C: 7
(data not lost for mortality data but not recorded for assessment of angina and exercise-tolerance test.
I: 18/92
C: 23/90</td>
<td>exercise-tolerance tests (of a maximum of 4 tests) and the test could be limited by symptoms or ischaemic changes on electrocardiography, but typical angina occurring during at least one test
▪ one region of protected myocardium.

Exclusion Criteria:
▪ Patients who had been admitted to hospital for unstable angina, substantial change in angina pattern or change in antianginal drugs were not included until 21 days after the last event.
▪ Patients who had had myocardial infarction within 3 months
▪ severe symptomatic heart failure
▪ history of clinically important ventricular arrhythmias
▪ cardiac transplant
▪ poor surgical candidates.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frazier 1999[22]

Study design: RCT

Location: USA- 12 US</td>
<td>Number of patients:192

Mean Age: 61

Male: 79.8%

Hypertension: 64.6%</td>
<td>Intervention:
Transmural channels approximately 1 mm in diameter were created with a single pulse of the carbon dioxide laser (peak power 850 W) (The Heart Laser</td>
<td>EFFECTIVENESS
Mortality
<table>
<tr><th></th><th colspan="3">< 30 days</th><th colspan="3">total</th></tr>
<tr><th></th><th>n</th><th>N</th><th>%</th><th>n</th><th>N</th><th>%</th></tr>
<tr><td>I:</td><td>3</td><td>91</td><td>3.3</td><td>13</td><td>91</td><td>14.3</td></tr>
<tr><td>C:</td><td>0</td><td>101</td><td>0</td><td>7</td><td>41</td><td>17.1</td></tr>
<tr><td colspan="4">Cross over – had TMR</td><td>15</td><td>60</td><td>25</td></tr>
</table></td>
<td>Crossover from medical treatment to TMLR was allowed if a patient had unstable angina that necessitated IV antianginal therapy</td>
</tr>
</table>

centres

Source of funding:
PLC Medical Systems

QUALITY
CROSS OVER
Randomisation:
In a 1:1 ratio
Allocation concealment:
Not described
Blinding:
Blinded independent assessment of angina
ntention to Treat analysis:
Yes –in Spertus paper
Loss to follow-up: yes – see outcomes

Other papers reporting this trial:
Spertus 2001
March 1999

Previous CABG:
91.7%

Diabetes: 45.8%

Baseline comparability: yes

Inclusion Criteria:
- CCS class III or IV angina refractory to medical treatment
- reversible ischemia of the left ventricular free wall
- Coronary disease that was not amenable to coronary-artery bypass grafting or percutaneous transluminal coronary angioplasty.
- Patients whose coronary disease was severe and diffuse or who did not have a target vessel or conduit suitable for grafting.

Exclusion Criteria:

- Ejection fraction less than 20% or if they had a concurrent major illness.

System, PLC Medical Systems) through the left ventricle. Approximately on e channel was created per square centimetre of myocardial surface.

Control:
Medical treatment alone

Angina Score
Defined as an improvement in angina by at least two Canadian Cardiovascular Society classes from base line.

	3 m		6 m		12 m		
I:	78	68%	67	67%	44	61	72%
C:	77	20%	67	27%	23	54	43%
C/O			24	6%	3	20	13%
			P=0.001		P=0.001		

Exercise tolerance
SPECT with pharmacologic stress testing with dipyridamole.
Change in segments of reversible ischemia.

	12 m		
	m	sd	n
I:	-1.4		38
C:	+1.3		13
	P=0.002		

No ITT data given – so cross over data not included in the control group.
Also 58% (n=53) TMLR group and 87% (n=88) of control group data missing.
No change in number of fixed defects per patient

QOL
SF 36
% improvement from baseline

	3 m			6 m			12 m		
	m	sd	n	m	n	sd	m	sd	n
I:	38								
C:	6								
	P<0.001			P=0.01			P<0.001		

SAFETY

TMLR:
6 (7%) acute MI
10 (11%) had congestive heart failure
7 (8%) had ventricular tachycardia or ventricular fibrillation
1 (1%) had unstable angina
29 (31.9%) had complications

for 48 hours or more in an ITU. These patients were considered part of the medical-treatment group until crossover, after which they were followed separately.
Did perform ITT putting all crossed over patients in to the medication group.

Galinanes 2004 [10]

Study design: RCT

Location: UK

Source of funding: NR

QUALITY
Randomisation:
Not described
Allocation concealment:
Simple sealed envelopes
Blinding:
Blinded observers
Intention to Treat analysis: No
Loss to follow-up: No

Number of patients:
20

Mean Age: 65.1

Male: 80%

Hypertension: 65%

Diabetes: 30%

Previous CABG:75%

Baseline comparability: Yes

Inclusion Criteria:
- CCS score III or IV
- CAD not amenable to routine revascularisation
- LVEF > 3%
- No contraindications to adenosine stress MRI

Intervention:
TMLR via L aterolateral thoracotomy. Holmium: YAG laser. Channels distributed at 1 cm^2 throughout the lased area. An average 42 channels (SD 11)

Control:
Thoracic sympathectomy performed using a mediatinoscope introduced through a small anterior thoracotomy in the left second intercostal space.
Ablation of the sympathetic chain was achieved by diathermy skeletonization from the left border of the vertebral bodies and posterior thirds of the ribs.

EFFECTIVENESS
Mortality

	< 30 days			total		
	n	N	%	n	N	%
I:	0	10	0	0	10	0
C:	0	10	0	2	10	20%

Angina Score
CCCSA class

	Baseline			6 m			42 m		
	m	sd	n	m	n	sd	m	sd	n
I:	3.6	0.5	10	1.9	0.7	10	2.5	0.9	10
C:	3.4	0.5	10	2.6	1.1	10	3.2	0.7	8
				P=0.008 vs preop value			P=0.01 vs preop value		

Exercise tolerance
Bruce protocol. Indications for terminating the test were chest pain, ischemic changes on the ECG, limiting dyspnoea, or fatigue. (seconds)

	Baseline			6 m			12 m		
	m	sd	n	m	sd	n	m	sd	n
I:	281	161	8	352	110	8	NR		
C:	290	154	7	266	83	7	NR		
				NS					

Myocardial perfusion
Measured using MRI scanning – results for the treated areas under stress induced by infusion of adenosine

	Baselline			6 months		
	m	sd	N	m	sd	N
I:	46.5	17.9	9	50.2	17.9	9
C:	59.2	32.9	8	71.6	38.4	8
				NS		

No diff between the groups and also between baseline and final value within each group. No improvements in the distribution (transmural vs subendocardial or nature (reversible vs fixed) of any preoperative perfusion deficits were identified in either group

Quality of Life
SF 36 – physical functioning – also measured 8 other domains using SF36 including mental health.

	Baseline			6 m			42 m		
	m	sd	n	m	n	sd	m	sd	n
I:	36.5	25.6	10	64	30.2	10	48.7	29.2	10
C:	28	17.7	10	37	37	10	29.9	9.2	10

Also measured:
QOL using Seattle Angina Questionnaire

Also MRI scans for quantitative perfusion analysis

P=< 0.05 NS

SAFETY
Atrial fibrillation following surgery
I: 2/10 (20%)
C: 0

Jones[23]

Study design: RCT

Location: USA

Source of funding: Cardio-genesis Corporation

QUALITY
Randomisation: Yes (method not described)
Allocation concealment: yes
Blinding: Data analysts
Intention to Treat analysis: no

Loss to follow-up unclear

Number of patients: 85

Mean Age: 62.2 yrs

Male: 100%

Hypertension:73.3%

Previous CABG: 42%

Baseline comparability: Significantly more patients in the surgical group had hypertension (text and table give different results – table suggests more patients in control group have hypertension)

Inclusion Criteria:
- Disabling angina (Canadian Cardiovascular Society Angina CCSA class 3 or 4)
- not be candidates for conventional therapy
- be maintained on maximal tolerated doses of at least two cardiac medications and have
- areas of viable ischemic

Intervention:
Anterior thoracotomy. Holmium : YAG laser (CardioGenesis Corp)
Control:
Continued medical therapy

EFFECTIVENESS
Mortality

	< 30 days			total		
	n	N	%	n	N	%
I:	1	42	2.4	5	42	11.9
C:	0	43		0	43	

Angina Score
CCSA score

	Base			3 m			6 m			12 m		
	m	sd	n	m	sd	n	m	sd	n	m	sd	n
I:	3.8	0.4	42	1.9	1	39	1.7	1	39	1.71	1	37
C:	3.6	0.5	43	3.6	0.6	43	3.7	0.5	unclear	3.77	0.6	unclear

P< 0.0001 against preop value and also controls

Exercise tolerance
(Bruce Treadmill Scores)
Angina is the endpoint

	Base			3 m			6 m			12 m		
	m	sd	n	m	sd	n	m	sd	n	m	sd	n
I:	360	150	42	481	133	35	514	108	35	490	108	35
C:	370	150	43	334	154	43	316	126	43	294	108	43

P=0.0002 against preop values and also controls

(n – at follow- up Cautious about these figures)

Quality of Life: NM

Myocardial perfusion
Thallium scans showed no improvement in the TMR group when compared to the medication control group. Results not reported.

	▪ Coronary angiograms performed within 3 months of randomisation must show one area of adequate perfusion in the region of one of the major coronary arteries. ▪ Modified Bruce Protocol resulted in angina as an endpoint on at least one test. ▪ ejection fractions of all participants were 30% or greater. **Exclusion Criteria:** ▪ left main coronary artery lesions of greater than 70% without open bypasses to the anterior descending or circumflex arteries ▪ congestive heart failure ▪ Obstructive pulmonary disease was an exclusion criteria when it would affect exercise testing.		**SAFETY** Adverse event N=42 MI 2 Post op bleeding 0 Phrenic nerve paralysis 4 Chest wall pain 1	

Loubani 2003 [24]

Study design RCT

Location: UK

Source of funding*:* NR

QUALITY
Randomisation*:*
Yes – method not described
Allocation concealment:
no
Blinding:
none
Intention to Treat analysis:
no
Loss to follow-up:
2 lost to follow up from TMR group

Number of patients*:*
20

Mean Age*:* 64.3

male*:* 90%

hypertension*:*55%

previous CABG*:*NR

diabetes mellitus: 5%

Baseline comparability: yes

Inclusion Criteria:
- Patients who had elective coronary artery bypass operation with one or more non graftable dominant coronary arteries and normal left ventricular function with no previous myocardial infarction.

Exclusion Criteria:
None described

Intervention):
CABG in combination with TMLR (holmium yttrium-aluminum-garnet laser) laser. Channels distributed at 1/cm^2 throughout lased area. Mean number of channels created was 18.6 (4.2) per patient.

Control:
CABG alone (using cardiopulmonary bypass and intermittent cross-clamp fibrillation with mild hypothermia (32ºC) for myocardial protection.)

EFFECTIVENESS
Mortality

	< 30 days			Total		
	n	N	%	n	N	%
I:	0	10	0	1*	10	10
C:	0	10	0	0	10	0

*At 11 months post-op from metastatic colon cancer.

Angina Score
Change score reported CCS and NYHA (only extracting CCS)

	Base			6 m			18 m			36 m		
	m	sd	n	m	sd	m	sd	n	n	m	sd	n
I:				0.4	0.2	0.7	0.4	9	10	0.5	0.2	9
C:				0.2	0.2	0.8	0.5	10	10	0.5	0.3	10
				NS			NS			NS		

Exercise tolerance
Change score reported (Bruce protocol) Indications to terminate the test were chest pain, ischemic changes on electrocardiogram, limiting dyspnea or fatigue. The total exercise time was noted and the reason for stopping documented

	Base			6 m			18 m			36 m		
	m	sd	n	m	sd	n	m	sd	n	m	sd	n
I:				199.2	66.5	10	157	46.3	8	68.1	66.5	8
C:				46.8	20	10	61	39.2	9	57.2	42.1	9
							P=<0.05 vs control			NS		

Myocardial Perfusion
Stress echocardiography using dobutamine. Digital images using quad- loop format on an Agilent 5500 system. No significant improvement in wall motion index. (lower result suggests improved wall motion and improved contractility of the lased areas)
WMSI (wall motion score index)

	WMSI at peak dose	SD	n
I:	1.27	0.45	8
C:	1.50	0.80	9
	P=0.43		

QOL: NM

Also reported postoperative wall motion score index

Schofield 1999[25]

Burns 2001 (999)

Study design: RCT

Location: UK

Source of funding: MRC

QUALITY
Randomisation: Method not reported
Allocation Concealment: Method not reported
Blinding: All scans processed by 1 investigator blinded to patient identity and treatment assignment.
Intention to Treat analysis: no
Loss to follow-up 13% - evenly distributed between groups

Other refs to this study: Campbell 2001

Number of patients: 188

Mean Age: 60.5 yrs

Male: 89.9% (n=169)

Diabetes 17.6%

Hypertension:

Previous CABG: 92.6%

% current smoker: 3.7%

Baseline comparability: yes
Inclusion Criteria:
- Class III and IV angina
- Refractory angina, unsuitable for conventional revascularization, and had demonstrable reversible ischemia. (Measured by radionuclide multigated acquisition scan at assessment and at 12 months

Exclusion Criteria:
- If left ventricular ejection fraction was <30% measured by radionuclide multigated acquisition scan.
- .Unable to do treadmill test

Intervention
TMLR and medication . Small anterolateral thoracotomy. 1000w CO2 device delivers 850 W peak power to tissue.

Channels 1 mm in diameter and about 1 cm2 apart channels created – median 30 (range 6-75)

Control:
Continued medical management alone

EFFECTIVENESS
Mortality :

	< 30 days			total		
	n	N	%	n	N	%
I:	5	94	5.3	11	94	11.7
C:	0	94	0	4	94	4.2

Angina Score:
Reduction of 2 Canadian Cardiovascular Society score for angina at 12 m

	number of patients who reduced 2 CCSA classes	N	%
I	18	74	25
C	3	78	4
	P=<0.001		

Exercise tolerance
Modified Bruce protocol
Exercise testing intensity increased every 3 min. The treadmill test was symptom limited, in exceptional cases the test was stopped because of increased blood pressure or arrhythmia. Maximum exercise time was recorded as well as the reasons for stopping.

	Base			3 m			6 m			12 m		
	m	sd	n	m	sd	n	m	sd	n	m	sd	n
I:	435	223	94	495	153	85	520	170	79	510	211	76
C:	428	198	94	452	167	87	484	143	87	470	175	84

No significant difference

Myocardial perfusion scanning and exercise test
Perfusion scanning – using Tc-99m MIBI perfusion scans. Patients were exercised using the modified Bruce protocol.

	Base			3 m			6 m			12 m		
	m	sd	n	m	sd	n	m	sd	n	m	sd	n
I:				0.172	0.003	88	0.176	0.003		0.173	0.003	72
C:				0.161	0.003	88	0.162	0.003		0.166	0.003	76
				P=0.007 (worse in TMLR group)			P=0.001(worse in TMLR group)			NS		

Higher values indicate greater severity and extent of ischemia. A number of dimensionless quantities can be generated to quantify the relative amount of hypoperfusion. Severity and reversibility were determined for a given cardiac region.. The objective was to see if there were any changes in the same patient measured over time. Data here for stress.

Number of myocardial sites with reversible ischaemia

	Baseline			6m			12m		
	n	N	%	n	N	%	n	N	%
I	144	460	31	87	400	22	78	370	21
C	160	469	34	94	405	23	86	399	22

OR: 0.99 (0.82-1.20) p=0.975

Results showed an overall deterioration in myocardial perfusion in the areas lasered that is evident after 3 months and sustained throughout to 1 year after TMLR.

. also recorded angina on 11 point scale.

. use of nitrates reduced in TMLR patients

. sites of reversible ischemia reported

Ejection Fraction %

	Base			12 m		
	m	sd	n	m	sd	n
I:	48	9.4	88	48	11.7	72 (?)
C:	49	10.6	88	46	12.3	76 (?)
				NS		

QOL: NM

SAFETY
MI
I: 5/94 (5.3%) – 2 during first 3 months
C: 1/94 (1%)

Van der Sloot 2004 [27]

Study design:
RCT
Location:
The Netherlands – single centre
Source of funding:
Dutch Heart Foundation

QUALITY
Randomisation:
Randomised in pairs
Allocation concealment:
no
Blinding:
no
Intention to Treat analysis*:* yes

Loss to follow-up
no

Number of patients:
30

Mean Age: 60.4

Male: 90%

Hypertension:

Diabetes: 16.6%

Previous CABG:

Baseline comparability:
Yes

Inclusion Criteria:
- Inclusion:
- NYHA functional class III-IV/IIV angina pectoris despite maximal medication not amenable to PTCA or CABG (determined independently)
- Scintigraphically proven reversible perfusion defect
- Left ventricular

Intervention
I: excimer TMLR (via left lateral thoracotomy and without cardiopulmonary bypass. 46 (10) TM channels were created in the ischemic area of the left ventricular wall as assessed by perfusion scintigraphy. Approximately on e transmyocardial channel per cm^2 was created with a XeCl excimer laser. Preoperative medication was resumed within 24 hours.

Control:
continued maximal medication defined as maximally tolerable doses of β-blockers, Ca-antagonists and nitrates was continued.

This study show a relief of angina and improved QOL without evidence of

Effectiveness
Mortality

	< 30 days			total		
	n	N	%	n	N	%
I:	1	15	6.7	1	15	6.7
C:	0	15	0	0	15	0

Angina Score
Number reduced 2 classes at 12 months

	n	N	%
I:	11	14	78.6%
C:	0	15	0
	P=0.00000.1		

Mean angina class

	Base			3 m			6 m			12 m		
	m	sd	n	m	sd	n	m	n	sd	m	sd	n
I:	3.8	0.4	14	2.1	0.6	14	1.9	0.7	14	1.9	0.9	14
C:	3.9	0.3	14	3.7	0.5	15	3.9	0.4	15	3.7	0.6	15
										P=0.0000.1		

Exercise tolerance
Exercise tolerance was measured using a symptom limited treadmill test according to a modified Bruce protocol. Medication was continued during the test. Exercise time and the reason for stopping were recorded.

	Base			3 m			6 m			12 m		
	m	sd	n	m	sd	n	m	sd	n	m	sd	n
I:	465	167	14	542	154	14	525	145	14	519	157	14
C:	486	216	15	453	240	15	519	157	14	445	212	15
	P=0.16											

Change from base line to 12 m follow-up in TMLR compared to change

ejection fraction (LVEF) ≥35%
- Life expectancy ≥ 1 year

Exclusion Criteria
- Ventricular arrhythmias requiring treatment
- Clinically manifest heart failure
- Severe intrinsic haemorrhagic disorders
- Lack of informed consent

improved cardiac perfusion or function. Consequently TMLR is primarily a symptomatic treatment with results that are comparable with other approaches including revascularization processes.

in control

Stress Echocardiography
Images were obtained at baseline and with increasing dobutamine doses.
Reversible wall motion abnormality score was significantly decreased at 12 months in TMLR group.

	Base			12 m		
	m	sd	n	m	sd	n
I:	1.1	0.5	15	0.5	0.5	14
C:	1.1	0.6	15	1.2	0.8	15

P=0.005

Fixed wall abnormality was increased

	Base			12 m		
	m	sd	n	m	sd	n
I:	0.3	0.5		0.7	0.5	
C:	0.3	0.5		0.5	0.7	

P = 0.008

Data measured but not reported for effects on time to target heart rate or severe angina or ischemic ECG changes

Myocardial Perfusion Scintigraphy
Stress induced by exercise or pharmacologically. Images obtained using SPECT
Mean summed difference score – generated from the summed stress score and summed rest score

	Base line			12 months		
I	13.9	7.8	15	11.7	5.2	14
C	10.9	5.7	15	9.4	7.4	15
				NS		

Quality of Life
Visual analogue scale of the EuroQol questionnaire

	Base			3 m			6 m			12 m		
	m	sd	n	m	sd	n	m	n	sd	m	sd	n
I:	46	14	14	66	7	14	69	14	14	67	16	14
C:	48	16	15	48	16	15	43	13	15	48	17	15
											ITT p value= 0.004	

SAFETY

TMLR
1 died postoperatively due to MI

SPECT: single-photon emission computed tomography (myocardial perfusion scan) ITT: intention to treat analysis; NS: non significant statistically; NM: not measured

RCTs - PMR

<table>
<tr><th>Study Details</th><th>Participant characteristics</th><th>Intervention Characteristics</th><th>Results</th><th>Comments</th></tr>
<tr>
<td>Leon 2005[39],

Study design: RCT

Location: USA

Source of funding: NR

QUALITY
Randomisation:
Method unclear
Allocation concealment:
Not described
Blinding:
Patients and data collectors blind to treatment.
Intention to Treat analysis:

Loss to follow-up</td>
<td>Number of patients: 298

Mean Age: 62.9 (10.1)

Male: 77%

Hypertension: 73.5%

Previous CABG: 88.3%

Diabetes: 43.9%

Hyperlipidaemia: 83.2%

Mean Ejection Fraction: 49.3% (12%)

Baseline comparability:
yes
Inclusion Criteria:

▪ history of CAD with refractory angina (CCS class III or IV), despite optimal medical therapy.
▪ All patients were considered unacceptable candidates for percutaneous revascularization therapies or surgical revascularisation procedures.
▪ All patients were able to complete a minimum of 2 min but not more than 12 mins of an exercise test and had reversible ischaemia during dual isotope perfusion imaging studies.</td>
<td>Intervention

LV electromechanical mapping was performed and treatment zones were pre-specified suing the combination of a recent coronary angiogram, the SPECT imaging results and the diagnostic LV electromechanical map. Areas of previous infarction were carefully excluded as treatment zones. The direct myocardial revascularisation was performed in one or two designated treatment zones in each patient. Laser source was a pulsed Ho:YAG laser. Laser channels were created with either
I1: 20-25 high dose or
I2: 10-15 low dose laser pulses

Control: sham therapy laser turned on but no further procedure was performed.

Concurrent care:</td>
<td>EFFECTIVNESS
Mortality
<table>
<tr><th></th><th colspan="3">< 30 days</th><th colspan="3">Total</th></tr>
<tr><th></th><th>n</th><th>N</th><th>%</th><th>n</th><th>N</th><th>%</th></tr>
<tr><td>I:</td><td>2</td><td>196</td><td>1</td><td>10</td><td>196</td><td>5.1</td></tr>
<tr><td>C:</td><td>2</td><td>102</td><td>2</td><td>7</td><td>102</td><td>6.9</td></tr>
</table>
Angina Score
<table>
<tr><th></th><th colspan="3">Improvement of at least 2 CCSA classes (6 m)</th></tr>
<tr><th></th><th>n</th><th>N</th><th>%</th></tr>
<tr><td>I1:</td><td>40</td><td>98</td><td>41</td></tr>
<tr><td>I2:</td><td>47</td><td>98</td><td>48</td></tr>
<tr><td>C:</td><td>42</td><td>102</td><td>41</td></tr>
</table>
Exercise tolerance
Excise duration - treadmill
<table>
<tr><th></th><th colspan="3">Base</th><th colspan="3">6 m</th><th colspan="3">12 m</th></tr>
<tr><td>I1</td><td>393</td><td>154.2</td><td>98</td><td>421.4</td><td>156.6</td><td>98</td><td>431.2</td><td>175.4</td><td>98</td></tr>
<tr><td>I2</td><td>366</td><td>146.8</td><td>98</td><td>432.2</td><td>150.8</td><td>98</td><td>425.7</td><td>153.7</td><td>98</td></tr>
<tr><td>C</td><td>358.6</td><td>146.5</td><td>102</td><td>396.6</td><td>175.1</td><td>102</td><td>395.3</td><td>177.9</td><td>102</td></tr>
<tr><td></td><td></td><td></td><td></td><td colspan="3">P=0.348 between groups</td><td colspan="3">P=0.334 between groups</td></tr>
</table>
QOL
SF12 physical component
<table>
<tr><th></th><th colspan="3">Base</th><th colspan="3">12 m</th></tr>
<tr><th></th><th>m</th><th>sd</th><th>n</th><th>m</th><th>sd</th><th>n</th></tr>
<tr><td>I1:</td><td>26.7</td><td>6.6</td><td>98</td><td>32.8</td><td>10.2</td><td>98</td></tr>
<tr><td>I2:</td><td>26.6</td><td>7.1</td><td>98</td><td>33.5</td><td>10.5</td><td>98</td></tr>
<tr><td>C:</td><td>26.0</td><td>6.1</td><td>102</td><td>32.4</td><td>9.6</td><td>102</td></tr>
<tr><td></td><td></td><td></td><td></td><td colspan="3">P=0.800</td></tr>
</table>
Myocardial Perfusion
SPECT myocardial perfusion imaging following adenosine infusion. Summed scores of images were determined and compared with baseline values
Values during stress – no significant changes
<table>
<tr><th></th><th>m</th><th>sd</th><th>N</th></tr>
<tr><td>I1</td><td>17.7</td><td>8</td><td>98</td></tr>
<tr><td>I2</td><td>19.3</td><td>9.5</td><td>98</td></tr>
<tr><td>C</td><td>17.3</td><td>7.6</td><td>102</td></tr>
<tr><td></td><td colspan="3">P=0.345</td></tr>
</table>
</td>
<td></td>
</tr>
</table>

<table>
<tr>
<td></td>
<td>Exclusion Criteria:
▪ Severe left ventricular dysfunction (ejection fraction <30% assessed by echocardiography)
▪ Recent myocardial infarction (within 30 days of treatment)
▪ Braunwald class IIIb unstable angina, chronic atrial fibrillation, prosthetic valve or significant aortic valve pathology
▪ Myocardial wall thickness <9 mm (by transthoracic echocardiography)
▪ Left ventricular thrombus
▪ Major life-threatening comorbidity</td>
<td></td>
<td>Safety

<30 days
I:12/196(6.1%)
C: 2/102 (2.0%)

MACE (major adverse cardiac events ie cardiac death, acute Q-wave and non-Q-wave myocardial infarction, revascularization procedures for procedure-related complications or coronary ischemia, left ventricular perforation and stroke).

Acute MI (Q-wave and non-Q-wave)
<30 days
I: 9/196 (4.6%)
C: 0/102 (0%)

LV perforation
<30 days
I: 2/196 (1.0%)
C: 0/102 (0%)</td>
<td></td>
</tr>
<tr>
<td>McNab 2006[45]

Study design: RCT

Location: UK

Source of funding: Medtronic SA

QUALITY
Randomisation: Randomised using a computer-generated list. Randomisation was in blocks of size 6 and 8.
Allocation Concealment: Not described
Blinding: no
Intention to Treat analysis: yes
Loss to follow-up

PMR:1 refused the procedure, 3 withdrew</td>
<td>Number of patients: 68

Mean Age: 63.5

Male: 88.2%

Hypertension: NR

Previous CABG: 94.1%
Baseline comparability: yes

Inclusion Criteria:
▪ Limiting angina despite maximally tolerated anti-anginal medication
▪ Angiographically documented coronary disease unsuitable for conventional revascularisation
▪ Reversible ischaemia

Exclusion Criteria:
▪ Myocardial wall thickness</td>
<td>Intervention
Biplane ventriculography performed to provide landmarks for laser tip placement. A 9F Axcis guiding catheter was used to position the optical fibre attached to a Holmium:YAG laser. Each position was checked in two radiographic views to ensure placement of channels at least 1 cm apart and nine to 12 channels were created.

Control:
SCS implantation, Medtronic fully implantable Itrel 3 systems were used for this study. The lead was advanced via the epidural space to the high thoracic/low cervical spinal cord.

Subjects were trained pre and</td>
<td>EFFECTIVENESS
Mortality
<table>
<tr><th></th><th colspan="3">< 30 days</th><th colspan="3">total</th></tr>
<tr><th></th><th>n</th><th>N</th><th>%</th><th>n</th><th>N</th><th>%</th></tr>
<tr><td>I:</td><td>0</td><td>34</td><td>0</td><td>2</td><td>34</td><td>5.9%</td></tr>
<tr><td>C:</td><td>1</td><td>34</td><td>2.9%</td><td>4</td><td>34</td><td>11.8%</td></tr>
</table>

Angina Score
Change in CCS ≥ 2 classes – number of patients
<table>
<tr><th></th><th colspan="3">3 m</th><th colspan="3">12 m</th></tr>
<tr><th></th><th>n</th><th>N</th><th>%</th><th>n</th><th>N</th><th>%</th></tr>
<tr><td>I:</td><td>5</td><td>34</td><td>14.7</td><td>8</td><td>30</td><td>26.7</td></tr>
<tr><td>C:</td><td>12</td><td>32</td><td>37.5</td><td>5</td><td>30</td><td>16.7</td></tr>
<tr><td></td><td colspan="2">P=0.077</td><td></td><td colspan="2">P=0.166</td><td></td></tr>
</table>
</td>
<td></td>
</tr>
</table>

after their procedure but before the 12 month follow-up visit

SCS*:* 2 refused procedure (1 had PMR but analysis as ITT)
1 withdrew after device implantation, 1 died. 31 available at 12 months (1 could not complete exercise tolerance)

<8 mm in the areas to be treated by PMR, implanted pacemakers or defibrillators or co morbidity that was considered to be of greater significance than angina pectoris.

post implant to try and achieve maximum benefit. The stimulation regime advised was a minimum of three 1 h sessions in each 24 h period. In addition each patient was encouraged to use the device prior to carrying out activities known to cause angina symptoms and with each episode of angina for which sublingual nitrates would normally be used.

Exercise tolerance
Total exercise time on a modified Bruce protocol, all tests were terminated by the subject. minutes

				3 m			12 m		
	m	sd	n	m	sd	n	m	sd	n
I:	444.6	3.68	33	(441)	(227.4)	33	427.2	233.4	30
C:	382.8	3.45	32	(439.8)	(210.6)	32	420.5	220.2	30
Difference adjusted for baseline 95% CI				0.61 (-0.55 to 1.77)			0.59 (-1.02 to -2.20)		
				P=0.353			P=0.466		

Time to angina

	3 m			12 m		
	m	sem	n	m	sem	n
I:	6.26	0.65	33	7.30	0.90	30
C:	7.31	0.73	32	6.86	0.82	30
Difference adjusted for baseline 95% CI	1.84 (0.19 to 3.49)			1.23 (-0.61 to 3.07)		
	P=0.028			P=0.191		

QOL
SF36 and Seattle questionnaire
SF 36 in physical component score – mean difference adjusted for baseline scores. Values above zero favour SCS

	3 m			12 m		
	m	CI	n	m	sd	n
Mean difference – physical component	1	-5 to 7.5	32	4	-2 to 11	30
Mental component	1	-5 to 8	33	5	-2 to 12	30

SAFETY
SCS: one subject reported a change in distribution of a paraesthesis on the day following the implant procedure.

Adverse events in first year

Event	SCS	PMR
Unstable angina	18	12
MI	4	1
Worsening angina	6	3
Infection of SCS system	0	NA
Undesirable change in stimulation	18	NA
Pain at neurostimulator site	3	NA
Neurostimulator generator migration	2	NA
Lead migration	1	NA

			Femoral pseudoaneurysm 0 1 Groin haematoma 1 2 Other miscellaneous 2 7	
Oesterle (2000)[43] **Study design:** RCT **Location:** USA (12 centres) and UK (1 centre) **Source of funding:** Eclipse Surgical Technologies Inc. **QUALITY** **Randomisation:** Data-coordinating centre **Allocation Concealment:** *no* **Blinding:** Patients unmasked. Angina class assessed by masked evaluators. **Intention to Treat analysis:** yes **Loss to follow-up** For exercise tolerance	**Number of patients:** 221 **Mean Age:** median 62 range (38-90) **% male*:*** n=190 86.0% **% hypertension*:*** n=159 72.0% **% previous CABG**: n = 85 (84.2%) **current smoker**: n=28 12.6% **Diabetes:** n=99 (44.8%) **Baseline comparability:** No Higher proportions of patients with hyperlipidaemia, family history of CAD and previous cardiac interventions in the control group. Control had higher median score n the Seattle angina questionnaire. **Inclusion Criteria:** ▪ Angina class f III or IV on the Canadian Cardiovascular Society scale despite maximum tolerated doses of at least tow antianginal drugs ▪ A left ventricular ejection fraction of 30% or more ▪ Reversible perfusion defects on the thallium stress test	**Intervention** Holmium:YAG laser used. Optical fibre was capped with a 1,75 mm lens and four nitinol petal to retard advancement through the full thickness of the myocardium during laser activation. The position of each laser channel – created with four laser pulses of 2 J – was also marked on the acetate sheets to ensure that channels were placed at least 1 cm apart. Medium number of channels was 15 (range 8 to 35). **Control:** Medical management	**EFFECTIVENESS** ***Mortality*** < 30 days: n / N / %; > 30 days (during 12 months follow up): n / N / % I: 0 / 110 / 0 ; 8 / 110 / 7.3 C: 0 / 111 / 0 ; 3 / 111 / 2.7 ***Angina Score*** Assessors masked T: 28 had angina class II or lower/92 C: 12 had angina class II or lower/99 **Exercise tolerance** Calculated as exercise duration at 12 months minus that at baseline. Median increase reported 6 m: median / IQR / n; 12 m: median / IQR / n I: 89.0 / -15 to183 / 100 ; 60 / -15 to 185 / 85 C: 12.5 / -67 to 125 / 97 ; 35 / -60 to 140 / 90 P=0.06 Missing outcome data for I: 17/102 (16.7%) C: 18/108 (16.7%) **Quality of Life** Seattle angina score In all 5 indices had increased significantly more in the PTMR group than in the control group Disease perception **Ejection Fraction** Ejection fraction did not change from baseline to 3-month follow-up in either group: Base: median / IQR / n; 3 m: median / IQR / n I: 50% / 8-75 / 110 ; 51% / 10-70 / 110 C: 50% / 25-75 / 111 ; 50% / 22-70 / 111 NS	

	▪ 2 consecutive exercise-tolerance tests with durations within 15% of each other and typical angina during at least one of the qualifying tests. **Exclusion Criteria:** ▪ ejection fraction less than 30% ▪ exercise tolerance not limited by angina ▪ symptomatic heart failure ▪ treatment with more than 80 mg frusomide daily (or equivalent dose of another diuretic ▪ left-ventricular wall thickness less than 8 mm ▪ renal insufficiency ▪ aortic stenosis ▪ severe peripheral vascular disease ▪ evidence of left ventricular thrombus ▪ clinically significant ventricular arrhythmias ▪ unstable angina ▪ need for adjustment for antianginal medications within 2 weeks f screening ▪ transmural myocardial infarction within 3 months ▪ non-transmural infarction within 6 weeks of study entry		**SAFETY** Acute complications occurring within 24 hours included 3 episodes of bradycardia, one episode of ventricular tachycardia, three cases of myocardial perforation, one pericardial effusion, two cerebrovascular accidents, on TIA, one femoral pseudoaneurysm and one case of ischaemia for the right leg Adverse events during follow-up including periprocedural events	

Event	T:		C:	
	Number of patients	events	No of patients	events
Death	8	8	3	3
MI	11	12	7	11
Bradycardia	7	8	1	1
CVA or TIA	7	7	4	4
Vascular complications	6	6	0	0
Bundle-branch block	4	5	1	1
Atrial fibrillation	4	4	4	4
Myocardial perforation	3	3	0	0
Ventricular tachycardia	2	2	1	1
Pericardial effusion	1	1	0	0
Hospital admission for angina	34	79	52	103

Salem 2004 [44]

Other references to same study:
Salem (2005)

Study design: RCT

Location: Norway

Source of funding:
Bergen Heart Foundation

QUALITY
Randomisation:
Method not described
Allocation Concealment:
Sealed and coded randomisation envelopes
Blinding:
Patient and Independent assessor blind. Laser technician unblind
Intention to Treat analysis:
no

Loss to follow-up: no

Number of patients:82

Mean Age: 66.02

% male:91.4% n=75

% hypertension: 47.5% n=39

% previous CABG:
89% n=73

Diabetes: 15.9% n=13

Current smoker: 74.4% n=61

Baseline comparability:
yes
Inclusion Criteria:
- Stable CCS class III or IV angina refractory to maximally tolerated doses of ≥2 antianginal medication
- Evidence of reversible myocardial ischaemia on exercise testing or techmetium sestamibi stress myocardial perfusion scanning
- Ejection fraction ≥25% and wall thickness ≥ 8mm in the target region for PMLR by echocardiography.

Exclusion Criteria:
- Recent myocardial infarction
- Symptomatic heart failure with exercise limited by dyspnoea
- Significant ventricular arrhythmias requiring long-term therapy
- Ventricular thrombus
- Significant peripheral vascular disease

Intervention
CardioGenesis PMLR laser system. Laser catheter was placed in the left ventricle, At each targeted channel site the location of the catheter tip was checked using biplane fluoroscopy to ensure contact with the endocardium.

Control:
Sham therapy

EFFECTIVENESS
Mortality

	< 30 days			total		
	n	N	%	n	N	%
I:	0	40	0	1	40	2.5
C:	1	42	2.4	2	42	4.8

Angina Score
Mean CCS class

	Base			3 m			6 m			12 m		
	m	sd	n	m	sd	n	m	n	sd	m	sd	n
I:	3.1		40				2			2		39
C:	3.2		42				2.8			2.8		40

Number2 ≥CCSA classes from baseline at 12 m
T: 14/40 (35%)
I: 6/42 (14%)
P=0.04

Exercise tolerance

	Base			12 m		
	m	sd	n	m	sd	n
I:	610	222	40	620	245	39
C:	585	235	42	604	229	40
				P=>0.1		

QOL
Seattle Angina Questionnaire- Disease perception

	Base			3 m			6 m			12 m		
	m	sd	n	m	sd	n	m	n	sd	m	sd	n
I:	45		40							55		39
C:	40		42							45		40
										P=0.09		

For angina stability and frequency the scores were significantly better than sham therapy.

Ejection Fraction

	Base		12 months	
T:	64%	40	64%	39
C:	63%	42	63%	40
			NS	

Reported Kaplan-Meier cardiac event free survival to 12 months (p=0.29 log-rank test)

<table>
<tr>
<td></td>
<td>
▪ Aortic valve stenosis
▪ Mechanical aortic prosthesis
▪ Unstable angina requiring hospitalisation within 14 days before consent of necessitating a significant change in medication
</td>
<td></td>
<td>
SAFETY
T: 1 CVA, claudication, lower leg oedema, 2 peripheral vascular interventions and 3 angina hospitalisations
C: 1 MI, 1 TIA, 1 atrial fibrillation, 1 dyspnoea, 1 peripheral vascular intervention, 1 leg oedema/pain, 3 angina hospitalisations.
</td>
<td></td>
</tr>
<tr>
<td>
Stone 2002 [40]

Study design: RCT

Location: USA

Source of funding: Eclipse Surgical Technologies

QUALLITY
Randomisation:
Consecutive patients
Allocation Concealment:
Inadequate methods
Blinding:
Patients and follow-up assessor
Intention to Treat analysis:

Loss to follow-up: yes
</td>
<td>
Number of patients:141

Mean Age: median 65

% male :n=114 80.9%

% hypertension: n=96 68.1%

% previous CABG: 83.5%

Current smoker: n=18 12.8%

Baseline comparability: Yes

Inclusion Criteria:
▪ Canadian Heart Association class III or IV angina despite maximally tolerated anti-anginal medication
▪ Planned percutaneous coronary intervention.
▪ No other lesions present requiring percutaneous coronary intervention or CABG
▪ Myocardial viability in the distribution subtended by the by the chronic total occlusion
▪ Myocardial wall thickness
</td>
<td>
Intervention
PMTR plus maximal medical therapy.

Laser revascularisation was performed in the myocardial territories subtended by the chronic total occlusion using the Eclipse holmium/YAG laser with fluoroscopic guidance

Control:
Maximal medical therapy
</td>
<td>
EFFECTIVENESS
Mortality
<table>
<tr><th></th><th colspan="3">< 30 days</th><th colspan="3">> 30 days 6 months</th></tr>
<tr><th></th><th>n</th><th>N</th><th>%</th><th>n</th><th>N</th><th>%</th></tr>
<tr><td>I:</td><td>0</td><td>71</td><td></td><td>6</td><td>71</td><td>8.6</td></tr>
<tr><td>C:</td><td>1</td><td>70</td><td>1.4</td><td>6</td><td>70</td><td>8.6</td></tr>
</table>
Angina Score
Angina improved ≥ 2 or more classes at 6 months
I: 35/71 (49%)
C: 26/70 (37%
P=0.33
Assuming the total number in group is as randomised

Exercise tolerance
Modified Bruce exercise test – improvement from baseline
<table>
<tr><th></th><th colspan="2">Base</th><th></th><th colspan="2">6 m</th><th></th></tr>
<tr><th></th><th>m</th><th>sd</th><th>n</th><th>m</th><th>sd</th><th>n</th></tr>
<tr><td>I:</td><td></td><td></td><td>64</td><td>86</td><td>38</td><td>36</td></tr>
<tr><td>C:</td><td></td><td></td><td>65</td><td>69</td><td>29</td><td>35</td></tr>
<tr><td></td><td></td><td></td><td></td><td colspan="3">P=0.73</td></tr>
</table>
NB loss to F-U is 50%

Quality of Life: NM

SAFETY
In hospital
<table>
<tr><th></th><th>MI</th><th>TIA</th><th>Ventricular tachycardia or fibrillation</th><th>cardioversion</th></tr>
<tr><td>T:</td><td>2 (2.8%)</td><td>1</td><td>5 (7%)</td><td>3 (4.5%)</td></tr>
<tr><td>C:</td><td>1 (1.4%)</td><td>0</td><td>0</td><td>0</td></tr>
</table>
</td>
<td></td>
</tr>
</table>

	≥9 mm in the area intended for treatment by PTMR (ie. the nonrevascularizable region and surrounding margin) as measured by two-dimensional echocardiography ▪ Continued medical management if PCI was unsuccessful **Exclusion Criteria:** ▪ Left ventricular ejection fraction <30% ▪ Myocardial infarction within three months, left ventricular aneurysm or mural thrombus ▪ Aortic stenosis, aortic regurgitation or a prosthetic aortic valve ▪ Decompensated heart failure ▪ Ventricular tachycardia or fibrillation within one week ▪ The inability to perform a baseline modified Bruce exercise stress test for any reason other than severe angina, or if the electrocardiogram was uninterpretable for ischaemia ▪ A previous PCI was performed within the last six months ▪ A noncardiac condition with anticipated life expectancy <1 year ▪ Participation in other investigational drug or device studies ▪ The inability or unwillingness to comply with the follow-up procedures or provide informed consent.			

Whitlow 2003[46]

Study design: RCT

Location:20 centres in the USA

Source of funding: NR

QUALITY
Randomisation:
Blocked randomisation stratified to whether the patient could complete a stress test. Carried out by central computer.
Allocation Concealment:
NR
Blinding:
Blinded observer to assess angina class.
Intention to Treat analysis:
yes
Loss to follow-up: none described

Number of patients: 230

Mean Age: 63

Male: 75.7%

Hypertension: 55.9%

Diabetes Mellitus: 47.8%

Previous CABG: 82%

Current smoker: NR

Baseline comparability:
Yes

Inclusion Criteria:
- Medically refractory CCSA III or IV who were rejected for both coronary artery bypass grafting and percutaneous intervention
- LVEF ≥30%
- Wall thickness in the target area ≥9mm
- Angina during an exercise stress test.

Exclusion Criteria:

- Myocardial infarction within 3 weeks or if they had a co-morbid medical condition that prohibited exercising on the treadmill.
- Significant aortic stenosis
- Mechanical aortic valve
- Left ventricular thrombus

Intervention (laser type, wattage):

Medical treatment plus PMR
8 to 30 channels placed using fluoroscopic guidance after angiography was performed. Channels placed approximately 1 cm apart.

Control:
Medical treatment

Effectiveness
Mortality
< 30 days

	n	N	%	n	N	%
I:	1	64	1.6	13	64	20.3
C:	0	166	0	11	166	6.6

Angina Score

	Base			6 m P=0.003			12 m p=<0.001		
	m	sd	n	m	n	sd	m	sd	n
I:	3.3	0.5	64	2.2	1.5	63	1.9	1.5	58
C:	3.2	0.4	16 6	2.6	1	16 6	2.4	1	15 5

Improved 2 ≥ functional classes at 12 m. I: 38% C: 19% p value: 0.001

Exercise tolerance

	Baseline			Number who ≥60 secs from baseline		
	m	sd	n	n	N	%
I:	382	246	64	37	51	58
C:	415	260	219	72	208	33

P=0.001
Naughton protocol stress test
NB: W/D not described

QOL
Change from baseline

	Baseline			12 m P=0.005		
	m	sd	n	m	sd	n
I:	5.2	5.3	64	10	12.9	51
C:	5.6	5.5	219	5.7	10.3	208

Measured using the DASI score (Duke Activity Status Index)

Safety

Procedural adverse events	I: N=64
Tamponade	5
Stroke	1
Q-wave myocardial infarction	0
Non-Q-wave myocardial infarction	6
Ventricular fibrillation	1
Atrial fibrillation	2
Hypotension	2
Myocardial hematoma	5

			Revascularization procedures during FU: I / C Bypass surgery: 2 / 6 Surgical TMR: 0 / 4 Cardiac transplantation: 2 / 0 PCI: 10 / 19 PMR: 0 / 11	

TMLR - Observational Studies

Case Series

Study Details	Participant characteristics: n (%)	Intervention Characteristics	Results	Comments
Author, year Agarwal[37] **Study design:** Case series prospective **Location:** India **Source of funding:** not described **Length of follow-up:** 12 months	**Number of patients:**102 **Mean Age:** 56.7 **% male:** 92.1 **% hypertension:** 51 (50%) **Smoking:** 20 (19.6) **Previous CABG:** 13 (12.7%) **Mean ejection fraction:** 44.7% (SD 10.5%) **Inclusion Criteria:** ▪ Severe angina refractory to maximal medical therapy ▪ Not amenable to PTCA or CABG **Exclusion Criteria:** ▪ Ejection fraction < 30% ▪ Scant evidence of reversible ischaemia	**INTERVENTION** TMLR **Laser:** 800 W CO_2. Pulse duration was 25 ms. **Channels:** 23 (SD 8)	**EFFECTIVENESS – summary** Baseline: n=102 / 1 year FUP=: n=41 attrition 24/102 (23.5%) Angina Class: m (sd) 2.56 (0.7); m (sd) 0.8 (0.9); P value NR Exercise TT(m): 5.5 (3); 9.7 (4); p<0.008 LVEF: 44.7 (10.5); 42 (11.7); NR **SAFETY** **Post operative outcome** **Operative mortality**: 15/102 (14.7%) **Late Clinical outcome** **Deaths**: 2/87 (2.3%)	

<table>
<tr>
<td>Author, year
Burkoff[21]

Study design: case series, retrospective
Location: USA

Source of funding:
CardioGenesis Corp

Length of follow-up: 12 months</td>
<td>Number of patients: 132

Mean Age: 61.1 (SD11.3)

% male: 82.6%
% hypertension: NR

Smoking: NR

Previous CABG: 84.1%

Mean ejection fraction: 44 (SD12)

Inclusion Criteria:
▪ Medically refractory class III and IV angina
Exclusion Criteria: NR</td>
<td>INTERVENTION
TMLR

Laser: CO_2 laser (The Heart Laser PLC Systems)</td>
<td>EFFECTIVENESS
Not measured

SAFETY
Perioperative
Deaths 16/132 (12.1%)

30 days – 1 year
Deaths: 13/116 (11.2%)

Total 1 year mortality 22%</td>
<td></td>
</tr>
<tr>
<td>Author, year
Burns[38]

Study design: case series – prospective
Location: 21 European and Asian centres

Source of funding: not described

Length of follow-up: 12 months

Loss to follow-up: 35</td>
<td>Number of patients: 967

Mean Age: 62 (SD 8.7 yrs) % male: 781 (84%)

% hypertension: 339/578 (59%)

Smoking: 105/692 (15%)

% diabetes: 111/777 (14%)

Previous CABG: 500/712 (70%)

Mean ejection fraction: 49% (SD 14.9%)

Inclusion Criteria:
Exclusion Criteria:
▪</td>
<td>INTERVENTION
TMLR

Laser: CO_2 (PLC Medical Systems)
Channels: mean 28.6 (SD 12.2)</td>
<td>EFFECTIVENESS - summary

<table>
<tr><td></td><td>Baseline</td><td>1 year FU p=</td></tr>
<tr><td>attrition</td><td>N=243</td><td>N=103</td></tr>
<tr><td>Angina Class CCSA Improvement of 2+ classes</td><td></td><td>3(3%) N=64</td></tr>
<tr><td>LVEF (change)</td><td>48%(11.6%)</td><td>N=64
-4.43 p=<0.01</td></tr>
<tr><td>Exercise TT</td><td>6.06</td><td>N=63
+1.83 <0.001</td></tr>
</table>

SAFETY
Post operative outcome
Operative mortality: 90/932 (9.7%)
Bleeding 97.6%)
Infection 35 (4.1%)
LV dysfunction : 70 (8.2%)
Arrhythmia: 81 *8.6%)
MI 30 (3.5%)
Cardiac tamponade 5 (0.6%)
Others 82 (9.7%)
Late Clinical outcome
Deaths: 9%</td>
<td></td>
</tr>
</table>

<table>
<tr>
<td>Author, year
Krabatsch[35]

Study design: case series, prospective
Location: Germany

Source of funding: NR
Length of follow-up: 1 year</td>
<td>Number of patients: 134
Mean Age: 63.4
Male: 84.3%
Hypertension: 59.7%
Diabetes: 30.6%
Smoking: NR
Previous CABG: 89.6%

Mean ejection fraction
Inclusion Criteria:
▪ Patient not amenable to PRCA or CABG
▪ CCSA III or IV angina despite maximum antianginal therapy
▪ Proof of viable but ischemic myocardium
Exclusion Criteria:
NR</td>
<td>INTERVENTION
TMLR

Laser: CO_2 Heart Laser (PLC Medical Systems)

Channels: created 1 cm apart. Mean 30 (SD 9) channels were created.</td>
<td>EFFECTIVENESS - NM
SAFETY
1 Year mortality: 18/134 17%</td>
<td></td>
</tr>
<tr>
<td>Author, year
Horvath[32]

Study design: case series, prospective

Location: USA

Source of funding: NR

Length of follow-up: 10 (SD 3) months</td>
<td>Number of patients: 200

Mean Age: 63 (SD 10)

Male: 78%

Hypertension: 67%

Diabetes: 35%

Smoking: NR

Previous CABG: 82%

Mean ejection fraction: 45 (10)

Inclusion Criteria:
▪ Severe angina refractory to medical therapy
▪ Reversible ischemia
▪ Contraindications to percutaneous transluminal coronary angioplasty or CABG or transplantation
Exclusion Criteria: NR</td>
<td>INTERVENTION
TMLR

Laser: 1000 W CO_2 devise (The Heart Laser, PLC Medical Systems) that delivers 850 watts. Average pulse energy of 42 (10) joules.</td>
<td>EFFECTIVENESS
<table><tr><td></td><td>B/L
n=200</td><td>1 yr</td><td>p=</td></tr><tr><td>CCSA reduction in 2+ classes</td><td></td><td>70/95</td><td>0.001 (attrition 47.8%)</td></tr></table>
Medication usage: 56% of the patients had decreased their usage of cardioactive medications and 19% had increased their usage.
Perfusion scans: decrease in number of perfusion defects in treated left ventricular free wall (statistically significant).

SAFETY
Arrhythmias: 0
MI: 4 (18%)
Acute mitral regurgitation: 1
Bleeding: 2 (1%)
Intraortic balloon pump assistance: 7 (4%)
Wound infection:1
Pneumonia: 5 (2.5%)
Mortality: 18 (9%) – majority were cardiac in nature.

30 days – 1 year
Mortality: 17 (9%)
Additional procedures: 13</td>
<td></td>
</tr>
</table>

<table>
<tr>
<td>Author, year
Stamou[33]

Study design: Case series prospective

Location: USA

Source of funding: not described

Length of follow-up: 12 months</td>
<td>Number of patients: 169

Mean Age: 62.6

% male: 119 (70%)

% hypertension: 129 (76%)

% smoker: 149 (88%)

% previous CABG: 86 (51)

Inclusion Criteria:
▪ Intractable angina and ≥major vessel or branch not amenable to surgical revascularization due to diffuse disease or vessel diameter <1 mm
▪ Presence of viable myocardium surrounding the non-graftable arteries.

Exclusion Criteria:
▪ Recent myocardial infarction
▪ Severe arrhythmias
▪ Decompensated heart failure</td>
<td>INTERVENTION
TMLR and CABG
Laser: CO_2 Heart Laser or the Holmium Laser system
Channels: mean 24 placed 1/cm^2</td>
<td>EFFECTIVENESS- summary
<table>
<tr><td></td><td>B/L</td><td>1 yr</td><td>P=</td></tr>
<tr><td></td><td>n=166</td><td></td><td>0.001</td></tr>
<tr><td>CCSA III and IV</td><td>152/166 (90%)</td><td>7/166 (4.2)</td><td></td></tr>
<tr><td>Cardioactive meds use</td><td>91%</td><td>56%</td><td>0.003</td></tr>
</table>
SAFETY
Post operative outcome

Reoperation due to bleeding: 7 (4%) only 1 was attributed to laser channels.

Stroke: 2 (1%)

Prolonged ventilation: 15 (9%)

New-onset atrial fibrillation 40 (24%)

Acute noninflammatory Pericarditis 23 (14%)

MI 1(1%)

Operative mortality 14 (8%)

Late Clinical outcome

Deaths: 10 (6.6%)</td>
<td></td>
</tr>
</table>

S: described as significant but p value not reported. Exercise TT: exercise tolerance test. NM: not measured

Comparative Studies- TMLR

Study Details	Participant characteristics: n (%)	Intervention Characteristics	Results	Comments
Author, year	**Number of patients:** 28	**GROUP A**	**EFFECTIVENESS – summary**	n=9

<table>
<tr>
<td>Diegeler[36]

Study design: non-randomised, comparative, prospective study.

Location: Germany

Source of funding: NR

Length of follow-up:1 year</td>
<td>Mean Age: 64.5 (SD 10.3)
Male:64.3%
Hypertension: NR
Diabetes: NR
Smoking: NR
Previous CABG:64.3%
Mean ejection fraction: 52 (SD 13.1)
Inclusion Criteria:
▪ Demonstrable ischemic reaction in an area of vial myocardium under stress proved by thallium scan
Exclusion Criteria:
▪ NR</td>
<td>TMLR

Laser: Holmium YAG Laser.

Operation: left anterior lateral or left posterior lateral thoracotomy

Channels:
Created 1 – 1.5 cm^2 to each other. Mean 26 (6)

GROUP B
CABG plus TMLR
Channels Mean 17 (5)
Grafts: 1.4 (SD 0.2)</td>
<td>Group A
B/L n=14 1 YR p=
CCS- class 3.5 (0.4) 1.9 (0.3) 0.01
ET (6 months) 37.9 (10.3) 64.4(14.7) 0.05
EF NR 64.4(14.7) NS
Thalium scan NS
Reduction of nitrates 12/14(85.7%)

Group B

SAFETY
Periopertive
<table>
<tr><th></th><th>Group A</th><th>Group B</th></tr>
<tr><td>Mortality</td><td>0</td><td>0</td></tr>
<tr><td>MI</td><td>0</td><td>1</td></tr>
<tr><td>Atrial arrhythmia</td><td>1</td><td>0</td></tr>
<tr><td>Ventricular arrhythmia</td><td>1</td><td>0</td></tr>
<tr><td>Bleeding</td><td>0</td><td>0</td></tr>
<tr><td>Pneumothorax</td><td>1</td><td>1</td></tr>
</table>
30 days – 1 year
<table>
<tr><th></th><th>Group A</th><th>Group B</th></tr>
<tr><td>Mortality</td><td>2</td><td>0</td></tr>
</table></td>
<td>1.2(0.2)</td>
</tr>
<tr>
<td>Wehberg[34]

Study design: non-randomised, controlled study, retrospective.

Location: USA
Source of funding: NR</td>
<td>Number of patients:255
Mean age: 65.1
Previous CABG: 6.3%
Baseline comparability: no
Inclusion criteria
▪ CCSA III or IV
▪ Severe – 3 vessel coronary artery disease
Exclusion criteria:
▪ If both a bypass graft and TMR were used in the same region of the ventricle.
▪ Ejection fraction ≥30%
▪ Patients who required an emergency revascularization procedure within 12 hours
▪ Acute myocardial infarction within 72 hours</td>
<td>Group A: TMLR plus CABG (n=36)
Holmium YAG laser
Group B: CABG (n=219)</td>
<td>EFFECTIVENESS
NR for 12 m

Safety
Group A Group B P=
Mortality 0 6/255 2.3% .80

Major adverse outcomes
<table>
<tr><th></th><th>Group A</th><th>Group B</th></tr>
<tr><td>Atrial fibrillation</td><td>6/36 (16.7%)</td><td>81/219 (37.4%)</td></tr>
<tr><td>Reoperative bleeding</td><td>1/36</td><td>15/219 (6.8)</td></tr>
<tr><td>Respiratory failure</td><td>0</td><td>8/219 (3.6%)</td></tr>
<tr><td>Renal failure</td><td>0</td><td>6/219 (2.7%)</td></tr>
<tr><td>Neurologic complications</td><td>1/36 (2.8%)</td><td>3/219 (1.4)</td></tr>
</table></td>
<td></td>
</tr>
</table>

	▪ Patients who developed persistent unstable angina despite continuous intravenous infusions of nitrates and antiplatelet medications		Readmit 30 d 1/36(2.8%) 17/219 (7.8%)	

PMR Observational Case Series

Study Details	Participant characteristics: n (%)	Intervention Characteristics	Results	Comments
Author, year Galli[49] **Study design:** Case series **Location:** Italy **Source of funding:** **Length of follow-up:** 5.3 months (4.2)	**Number of patients:** 15 **Mean Age:** 66 (8) **% male:** 86.7 **% hypertension:** 80 **Smoking:** NR **Diabetes:** 73 **Previous CABG:** 46.7 **Mean ejection fraction:** 42 (7.5) **Inclusion Criteria:** ▪ CCS III-IV ▪ Not amendable to PTCA or CABG ▪ Ischemia or myocardial viability in the regions that need to be treated ▪ EF greater than 25% ▪ Wall thickness of greater than 9mm in treatment target **Exclusion Criteria:** ▪ Hemodynamic instability due to left ventricle disease or more severe arrhythmia ▪ Recent acute MI ▪ Endoventricular	**INTERVENTION** PMR **Laser:** PMR, Eclipse laser **Channels:** 13 (4)	**EFFECTIVENESS – summary** Outcome | B/L n= 15 | FU n= 13 | P value Angina CCS class | 3.3 (0.4) | 1.2 (NR) | NR Exercise TT(m) | NR | NR | NR LVEF | 42 (7.5) | NR | NR **SAFETY** **Post operative outcome** **Operative mortality**: 0/15 Myocardial perforation: 1/15 (0.07%) Hospitalisation for angina symptoms 1/15 (0.07%) Severe left ventricle dysfunction 2/15 (13%) **Late Clinical outcome** No major clinical events **Deaths**: 0/15	

<table>
<tr>
<td></td>
<td>thrombosis
▪ Aortic valve affected by severe pathology and/or severe peripheral artery disease
▪ severe co-morbidities</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Author, year
Kluge[50]

Study design: Case series

Location: Germany

Source of funding: NR

Length of follow-up: 12 months</td>
<td>Number of patients: 36

Mean Age: 64.3 (7.5)

% male: 80.6

% hypertension: NR

Smoking: NR

Diabetes: NR

Previous CABG: NR

Mean ejection fraction: 59.1 (11.8)

Inclusion Criteria:
▪ CCS III-IV refractory to medical therapy, maximum tolerated dose of two angina medications
▪ Non amendable CAD
Exclusion Criteria:
▪ LVEF less than 35%
▪ Unbypassed left main artery stenosis greater than 50%
▪ Unstable angina pr MI in last 3 months
▪ Wall thickness in target region of less than 8mm
▪ Absence of stress induced myocardial perfusion defects on thallium-201 scintigraphy</td>
<td>INTERVENTION
PMR

Laser: Cardio Genesis

Channels: NR</td>
<td>EFFECTIVENESS – summary

<table>
<tr><td>Outcome</td><td>B/L n= 36</td><td>FU n= NR</td><td>P value</td></tr>
<tr><td>Angina CCS class</td><td>3.22 (.42)</td><td>1.41 (.93)</td><td>.008</td></tr>
<tr><td>Exercise TT(m)</td><td>359 (126)</td><td>430 (166)</td><td>.007 NS</td></tr>
<tr><td>LVEF</td><td>59.1 (11.8)</td><td>59.3 (14.6)</td><td>NS</td></tr>
</table>
SAFETY

Post operative outcome
Operative mortality: NR

Late Clinical outcome

Deaths: NR</td>
<td></td>
</tr>
<tr>
<td>Laham[47]

Study design: case series, prospective</td>
<td>Number of patients: 15

Mean Age: 64.1

male: 73.3%</td>
<td>INTERVENTION

Laser:
LMR using Biosense guidance. Holmium:</td>
<td>EFFECTIVENESS – summary

<table>
<tr><td></td><td>N=15</td><td></td><td></td></tr>
<tr><td>CCSA class</td><td>3.4 (0.6)</td><td>2.5 (1.4)</td><td>P=0.054</td></tr>
</table></td>
<td></td>
</tr>
</table>

Location: USA **Source of funding:** NIH grants **Length of follow-up:** 6m	**% hypertension:** 86.7% **Current smoking:** 26.7% **Previous CABG:** 14% **Mean ejection fraction:** 47.4%(14) **Diabetes mellitus:** 46.7% **Inclusion Criteria:** ▪ Area of myocardium supplied by a major coronary artery with advanced disease not amenable to bypass grafting or percutaneous intervention ▪ Corresponding area of inducible ischemia (fully or partially reversible defect on a nuclear perfusion scan **Exclusion Criteria:** ▪ Unstable angina ▪ Recent MI ▪ Recent (3m) coronary angioplasty ▪ Ejection fraction <30% ▪ Aortic stenosis or sclerosis or a prosthetic valve ▪ Severe peripheral vascular disease ▪ Cardiac pacemakers ▪ Frequent atrial or ventricular arrhythmias ▪ Cerebral metal implant and ▪ Sever claustrophobia	YAG laser pulses 2J to the ischemic area indicated on the baseline NOGA map. 15 to 25 laser channels are performed in each ischemic area up to a maximum of two zones. Mean number of channels 32 (SD9)	<table><tr><td>Exercise time</td><td>298 (97)</td><td>365 (79)</td><td>P=0.02</td></tr><tr><td>LV</td><td>48.8 (11.4)</td><td>56.1 (12.7)</td><td>P=0.25</td></tr><tr><td colspan="4">MRI Left Ventricular function assessment</td></tr><tr><td>Resting baseline thickening of normal wall</td><td>45.3 (11.5)</td><td></td><td>NS</td></tr><tr><td>Normal wall systolic radial motion</td><td>22.8 (9.4%)</td><td>30.8 (3.9%)</td><td>P=0.02</td></tr><tr><td>Resting radial motion and thickening of the target wall</td><td></td><td></td><td>P=< 0.001</td></tr><tr><td>Target wall thickening</td><td>30.6 (11.7%)</td><td>44.2 (11.9%)</td><td>P=0.003</td></tr><tr><td>Target wall motion</td><td>16.3 (9.2%)</td><td>25.3 (7.3%)</td><td>P=0.006</td></tr><tr><td colspan="4">MRI Myocardial perfusion/ contrast</td></tr><tr><td>Mean size of myocardial area demonstrating delayed contrast arrival</td><td></td><td>Reduced from baseline 7.7 (3.7%)</td><td>P=0.001</td></tr></table>	
Oesterle 1998 Oesterle[48] **Study design:** case series, pilot study, prospective	**Number of patients:**30 **Mean Age:** 60.7 **male:** 87% **% hypertension:** 70%	**INTERVENTION** **Laser:** Holmium: YAG laser. Delivered 2J/pulses to create channels, 1-2 mm_2	**EFFECTIVENESS – summary** <table><tr><td></td><td colspan="3">B/L</td><td colspan="3">6m</td></tr><tr><td></td><td>M</td><td>SD</td><td>n</td><td>M</td><td>sd</td><td>n</td></tr><tr><td>Angina</td><td>3.2</td><td>0.41</td><td>30</td><td>1.4</td><td>0.8</td><td>17</td></tr></table>	

<table>
<tr>
<td>Location: USA

Source of funding: NR

Length of follow-up: 6 m</td>
<td>Smoking: NR

Diabetes: 36.7%

Previous CABG: 20%

Mean ejection fraction:

Inclusion Criteria:
▪ Multivessel coronary artery disease viewed as untreatable by surgery or conventional catheter- based intervention
▪ Resting LVEF of > 30%
▪ Class III or IV angina while receiving at least 2 antianginal medications a the maximum tolerable dosage
Exclusion Criteria:
Ventricular wall thickness < 8mm</td>
<td></td>
<td>
<table>
<tr><td>score</td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Exercise tolerance</td><td>15553.73</td><td>7570.3</td><td>30</td><td>22494.1</td><td>11330.4</td><td>17</td></tr>
</table>
SAFETY

Post operative outcome
Operative mortality: 15/102 (14.7%)

Late Clinical outcome
Deaths: 2/87 (2.3%)

<table>
<tr><td></td><td></td></tr>
<tr><td>Pericardial tamponade</td><td>1</td></tr>
<tr><td>Bundle branch block</td><td>1</td></tr>
<tr><td>Pericardial effusion</td><td>2</td></tr>
<tr><td>nephropathy</td><td>1</td></tr>
<tr><td>Ventricular fibrillation</td><td>0</td></tr>
<tr><td>Vascular complications</td><td>0</td></tr>
<tr><td>MI</td><td>0</td></tr>
</table>
</td>
<td></td>
</tr>
<tr>
<td>Author, year
Strehblow[51]

Study design: Case series

Location: Austria

Source of funding: NR

Length of follow-up: 6 months</td>
<td>Number of patients: n=25
15 Eclipse laser
10 10 Biosense laser

Mean Age:
66 (7)

% male:
68

% hypertension: NR

Smoking: NR

Diabetes: NR

Previous CABG: 44

Mean ejection fraction:
61.3 (17.1)

Inclusion Criteria:
▪ CCS Class III- IV</td>
<td>INTERVENTION
PMR

Laser: Eclipse and Biosense lasers

Channels:: 16 (5)</td>
<td>EFFECTIVENESS – summary

<table>
<tr><td>Outcome</td><td>B/L n= 25</td><td>FU n= 25</td><td>P value</td></tr>
<tr><td>Angina</td><td>3.3 (0.5)</td><td>1.8 (1.2)</td><td>.001</td></tr>
<tr><td>Exercise TT(m)</td><td>290 (60)</td><td>320 (58)</td><td>.066</td></tr>
<tr><td>LVEF</td><td>61.3 (17.1)</td><td>54.7 (14.5)</td><td>.055</td></tr>
</table>
SAFETY

Post operative outcome
Intramyocardial hematoma 1/25 (4%)
Myocardial perforation 1/25 (4%)
Pacemaker implantation 1/25 (4%)
MI 2/25 (8%)
Re-intervention (PTCA or CABG) 4/25 (16%)
Operative mortality: 0/25

Late Clinical outcome

Deaths:
Deaths 2/25 (8%)</td>
<td></td>
</tr>
</table>

	▪ Myocardial ischemia proven by perfusion scintigraphy ▪ End-diastolic wall thickness of at least 8mm **Exclusion Criteria:** ▪ Left ventricle thrombus ▪ MI within 3 weeks ▪ Unstable angina ▪ LVEF less than 30 Aortic valve disease			

APPENDIX 4 Checklist of quality assessment of non-randomised studies

Criteria	Yes	No	Unclear	Comments
1. Were participants a representative sample selected from a relevant patient population, e.g. randomly selected from those seeking for treatment despite of age, duration of disease, primary or secondary disease, and severity of disease?				
2. Were the inclusion/exclusion criteria of participants clearly described?				
3. Were participants entering the study at a similar point in their disease progression, i.e. severity of disease?				
4. Was selection of patients consecutive?				
5. Was data collection undertaken prospectively?				
6. Were the groups comparable on demographic characteristics and clinical features?				
7. Was the intervention (and comparison) clearly defined?				
8. Was the intervention undertaken by someone experienced at performing the procedure?[1]				
9. Were the staff, place, and facilities where the patients were treated appropriate for performing the procedure? (E.g. access to back-up facilities in hospital or special clinic)				
10. Were all the important outcomes considered?				
11. Were objective (valid and reliable) outcome measures used, including satisfaction scale?				
12. Was the assessment of main outcomes blind?				
13. Was follow-up long enough (≥1y) to detect important effects on outcomes of interest?				
14. Was information provided on non-respondents, dropouts?[2]				
15. Were the withdrawals/drop-outs having similar characteristics as those completed the study and therefore unlikely to cause bias?[3]				
16. Was length of follow-up similar between comparison groups				
17. Were all the important prognostic factors identified, e.g. age, duration of disease, disease severity?[4]				
18. Were the analyses adjusted for confounding factors?				

The same form was adapted to assess the quality of case series after taking out question 6, 12, 16 and 18.

Note:

1. 'Yes' if the practitioner received training on conducting the procedure before or conducted same kind of procedure before, i.e. no learning curve.
2. 'No' if participants were from those whose follow up records were available (retrospective)
3. 'Yes' if no withdrawal/drop out; 'No' if drop-out rate ≥30% or differential drop-out, e.g. those having most severe disease died during follow up but the death was not due to treatment; no description of those lost.
4. 'Yes' if two or more than two factors were similar.

Appendix 5 Meta-analysis

Cardiac perfusion intervention trials summary cross-sectional and change data - results of meta-analyses

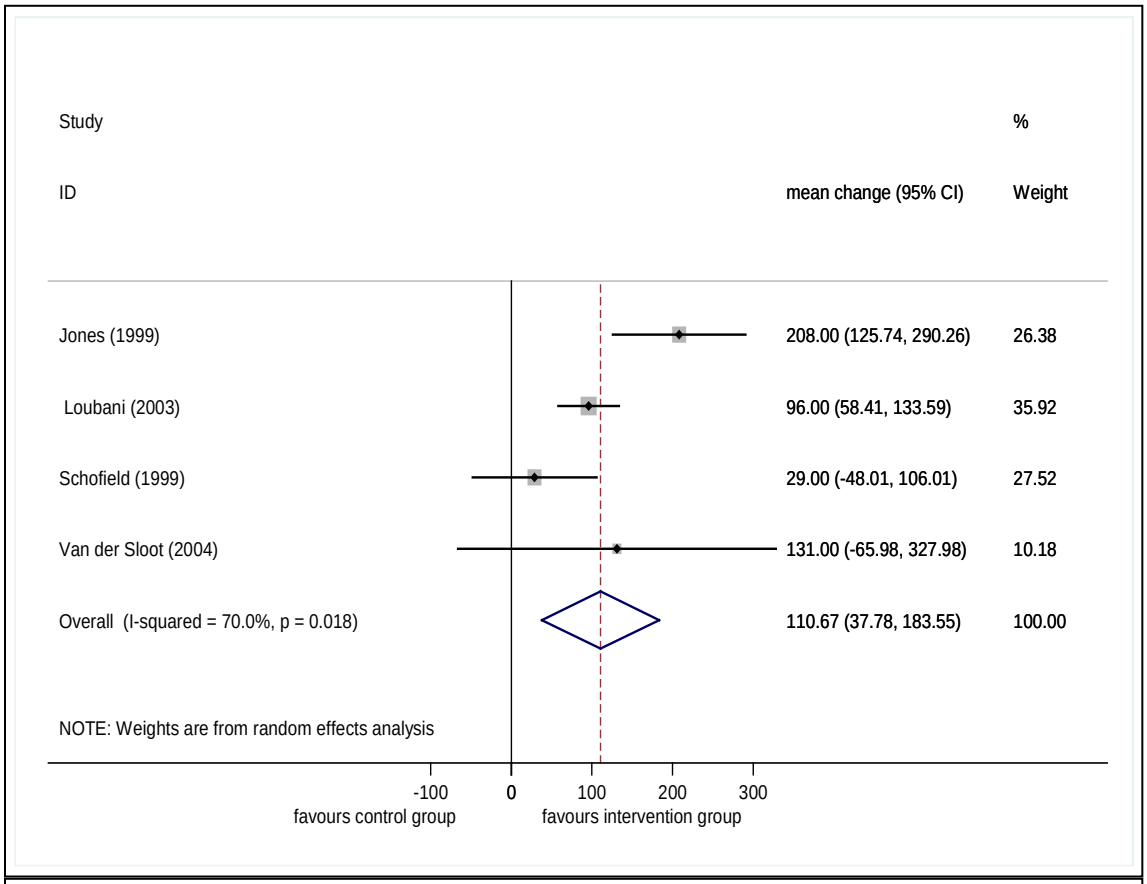
1. Continuous outcomes

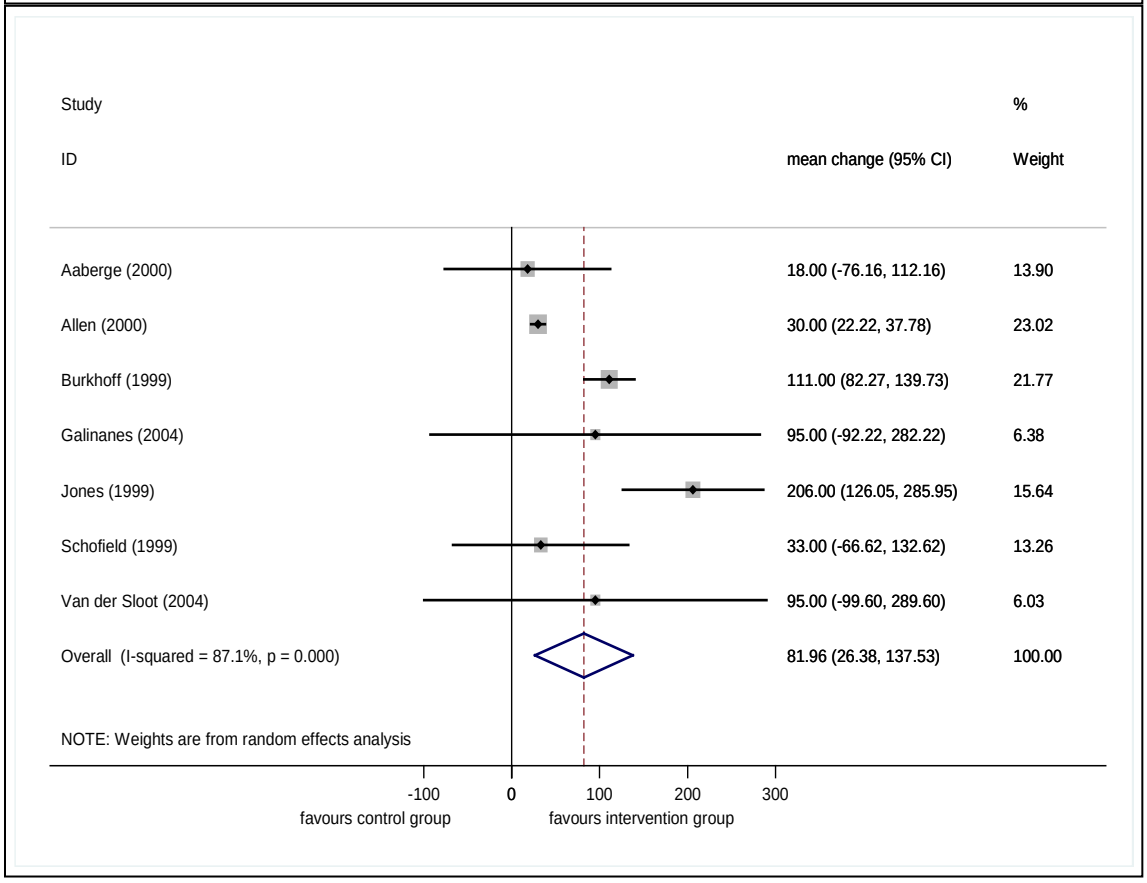
Outcome	measure	adjusted*	level	study	diff **	95% CI	p ***
exercise tolerance	TMLR			**0 – 6 months**			
				Jones	208	125.7, 290.3	
				Loubani	96	58.4, 133.6	
				Schofield	29	-48.0, 106.0	
				v.d. Sloot	131	-65.4, 327.4	
					Pooled		
		none			111.2	32.5, 190.0	< 0.001
		comparator	tmlr+med		120.1	4.5, 235.7	
			tmlr+cabg		96.0	-139.5, 331.5	
				0 – 12 months			
				Aaberge	18	-76.2, 112.2	
				Allen	30	22.2, 37.8	
				Burkhoff	111	82.3, 139.7	
				Galinanes	95	-92.2, 282.2	
				Jones	206	126.1, 286.0	
				Schofield	33	-66.6, 132.6	
				v.d. Sloot	95	-99.6, 289.6	
					Pooled		
		none			81.9	26.7, 137.3	0.018
		comparator	tmlr+med		108.6	83.6, 133.5	
			tmlr+cabg		30.6	-21.1, 80.1	
			sympathect.		95.6	-118.0, 308.8	
		blinding	no		108.3	83.6, 133.1	
			yes		30.6	-21.1, 80.1	
		industry	no		30.2	22.4, 37.9	
			yes		121.7	92.7, 151.0	

* mean difference adjusted for covariates

** mean difference between treatment groups over time interval

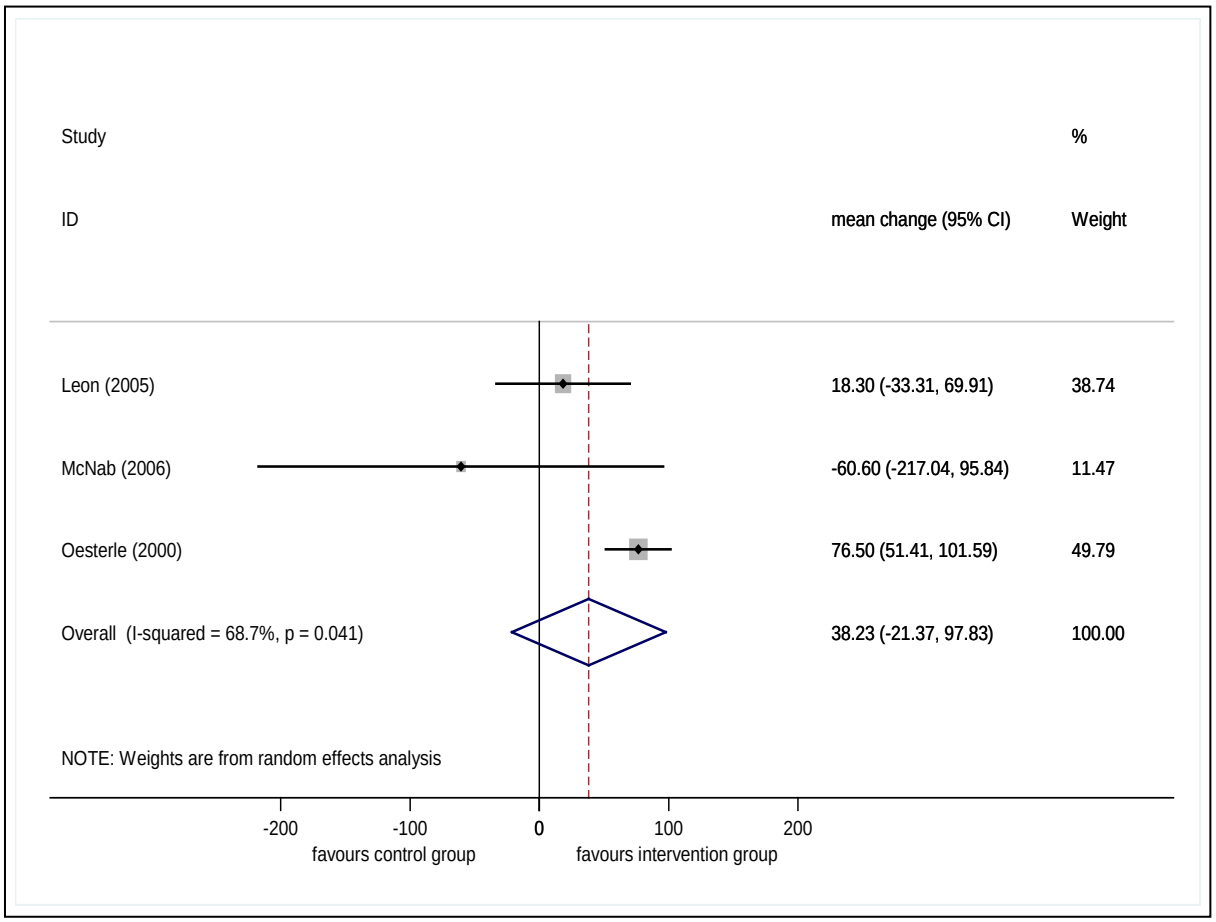
**** p-value for heterogeneity statistic (Q)

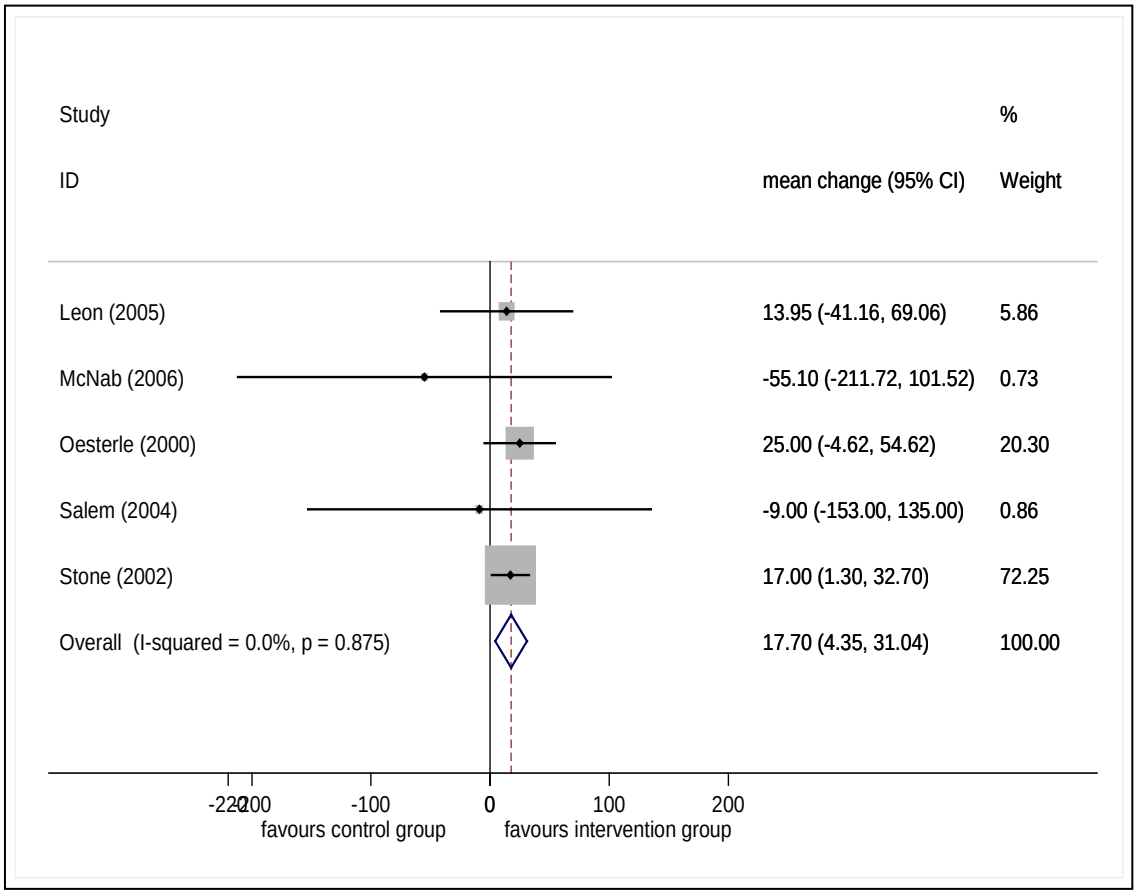

Study
ID
mean change (95% CI)
%
Weight
Jones (1999)
208.00 (125.74, 290.26)
26.38
Loubani (2003)
96.00 (58.41, 133.59)
35.92
Schofield (1999)
29.00 (-48.01, 106.01)
27.52
Van der Sloot (2004)
131.00 (-65.98, 327.98)
10.18
Overall (I-squared = 70.0%, p = 0.018)
110.67 (37.78, 183.55)
100.00
NOTE: Weights are from random effects analysis
-100
0
100
200
300
favours control group
favours intervention group


Study
ID
mean change (95% CI)
%
Weight
Aaberge (2000)
18.00 (-76.16, 112.16)
13.90
Allen (2000)
30.00 (22.22, 37.78)
23.02
Burkhoff (1999)
111.00 (82.27, 139.73)
21.77
Galinanes (2004)
95.00 (-92.22, 282.22)
6.38
Jones (1999)
206.00 (126.05, 285.95)
15.64
Schofield (1999)
33.00 (-66.62, 132.62)
13.26
Van der Sloot (2004)
95.00 (-99.60, 289.60)
6.03
Overall (I-squared = 87.1%, p = 0.000)
81.96 (26.38, 137.53)
100.00
NOTE: Weights are from random effects analysis
-100
0
100
200
300
favours control group
favours intervention group

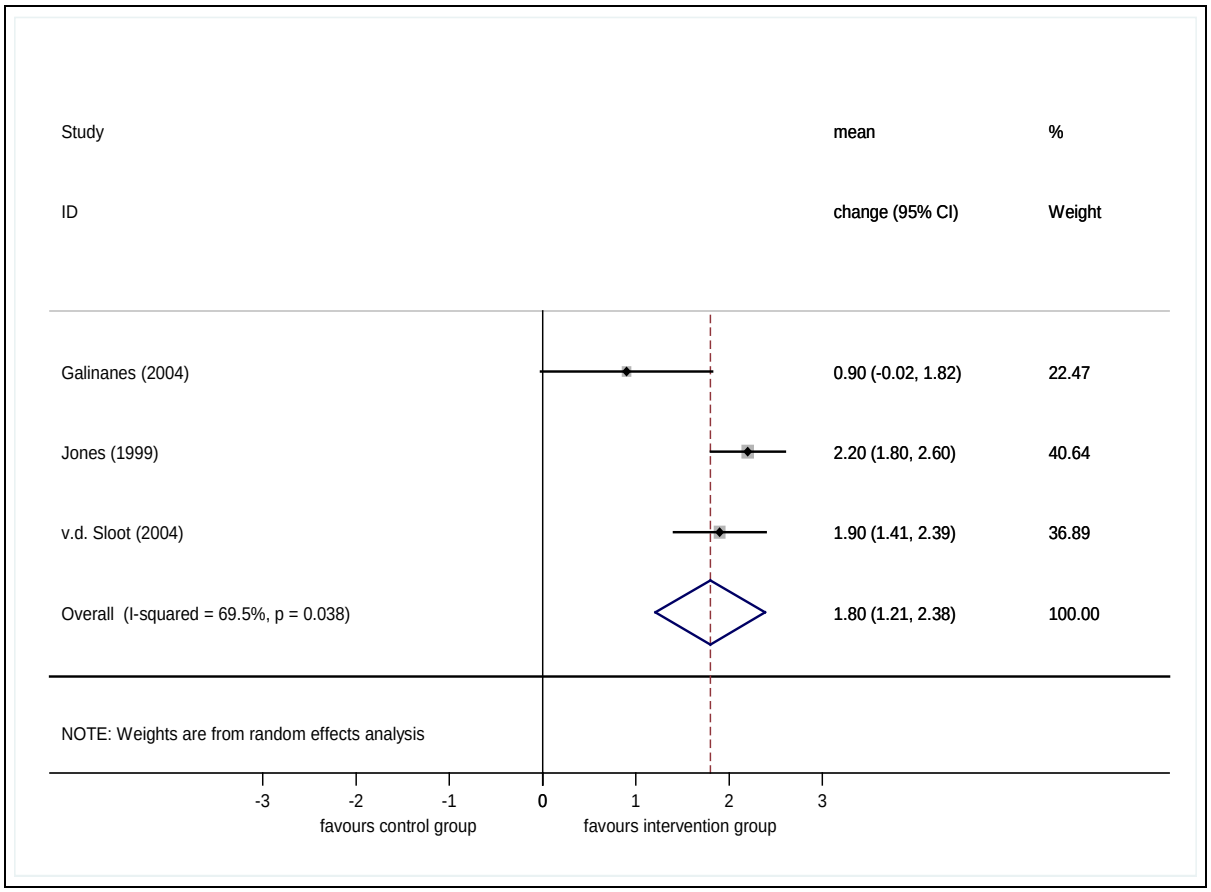
Outcome	measure	adjusted*	level	study	diff **	95% CI	p ***
exercise tolerance	PMR1			**0 – 6 months**			
				Leon[1]	18.3	-33.3, 69.9	
				McNab	-60.6	-217.0, 95.8	
				Oesterle	76.5	51.4, 101.6	
					Pooled		
		none			40.3	-14.7, 95.3	0.041
		blinding	no		73.1	48.3, 97.8	
			yes		18.3	-44.1, 80.7	
				0 – 12 months			
				Leon[1]	14.0	-41.2, 69.1	
				McNab	-55.1	-211.7, 101.5	
				Oesterle	25.0	-4.6, 54.6	
				Salem	-9.0	-153.0, 135.0	
				Stone	17.0	1.3, 32.7	
					Pooled		
		none			17.7	4.4, 31.0	0.875
		blinding	no		18.2	4.4, 32.0	
			yes		11.0	-44.0, 66.1	

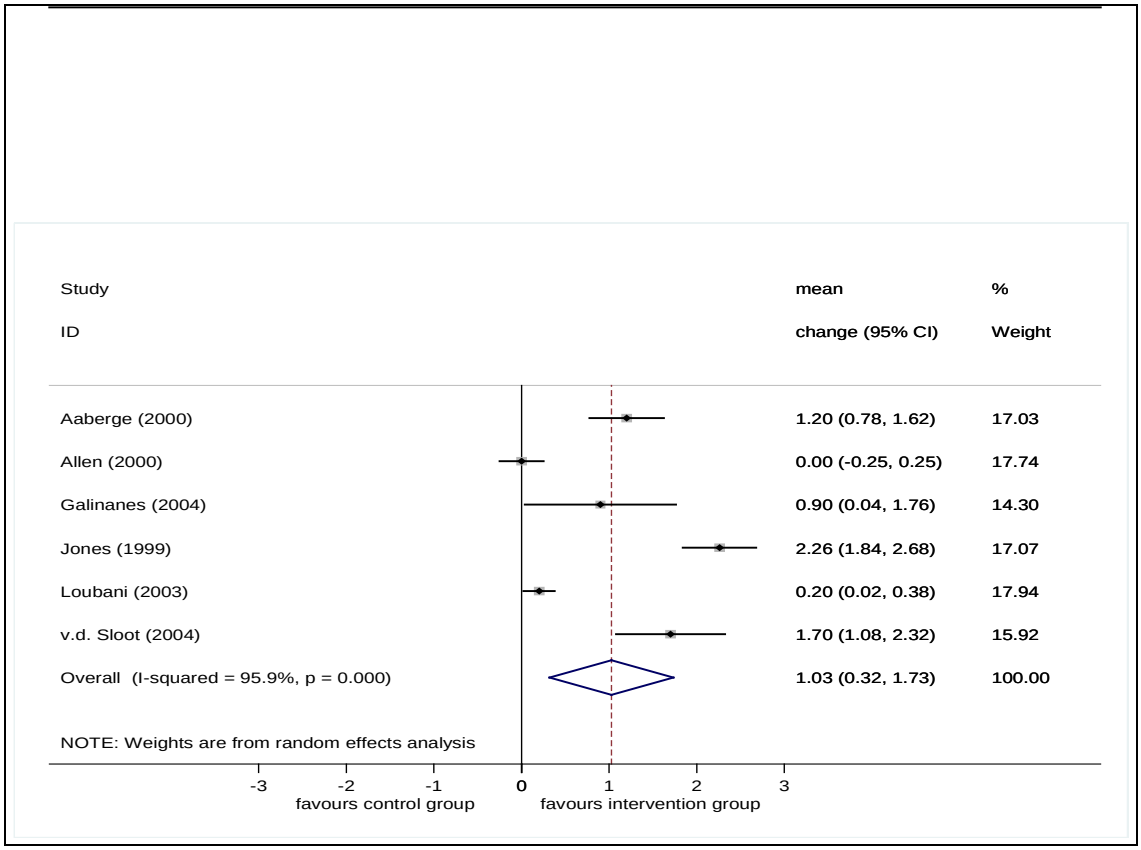
1 results for two active treatment arms were combined (sample size weighting – usual approach)





Outcome	measure	adjusted*	level	study	diff **	95% CI	p ***
angina score	TMLR			**0 – 6 months**			
				Galinanes	-0.9	-1.8, 0.0	
				Jones	-2.2	-2.6, -1.8	
				v.d. Sloot	-1.9	-2.4, -1.4	
					Pooled		
		none			-1.8	-2.4, -1.1	0.038
				0 – 12 months			
				Aaberge	-1.2	-1.6, -0.8	
				Allen	0	-0.3, 0.3	
				Galinanes	-0.9	-1.8, 0.0	
				Jones	-2.26	-2.7, -1.8	
				Loubani	-0.2	-0.4, 0.0	
				v.d. Sloot	-1.7	-2.3, -1.1	
					Pooled		
		none			-1.0	-1.7, -0.3	< 0.001
		NYHA scale	no		-1.0	-1.9, -0.1	
			yes		-1.2	-3.5, 1.1	

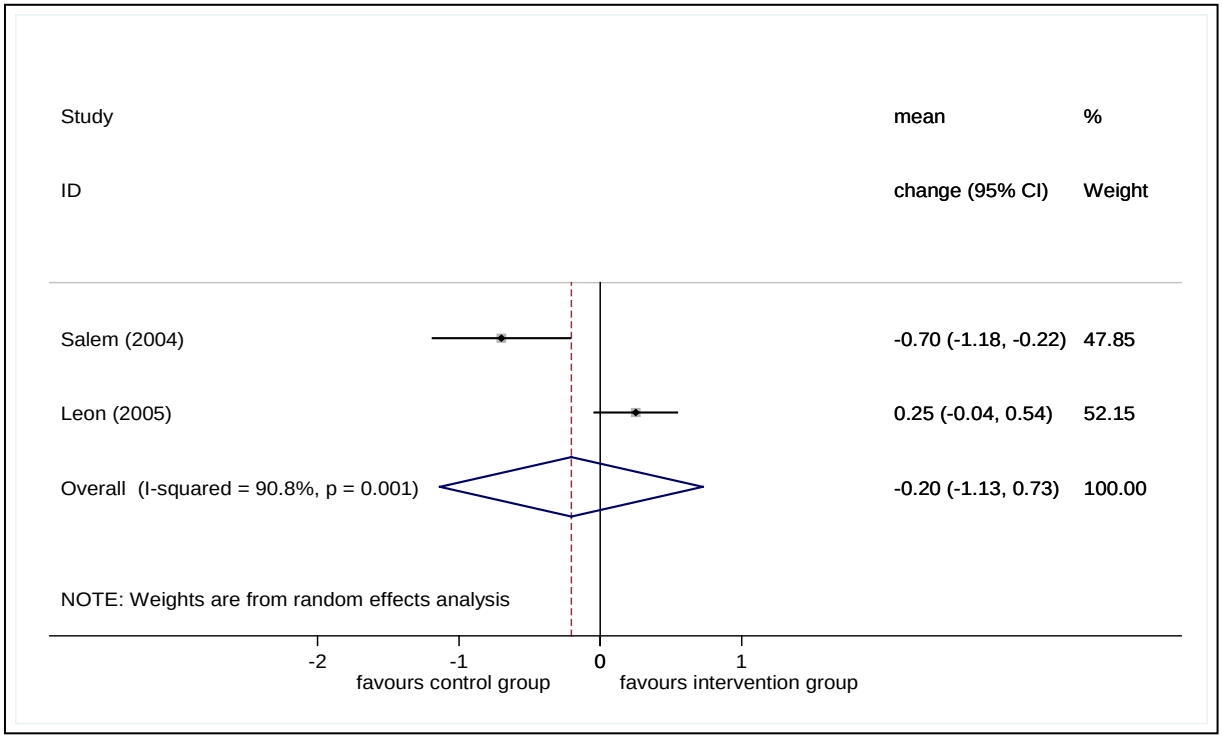

Study
ID
mean
change (95% CI)
%
Weight
Galinanes (2004)
0.90 (-0.02, 1.82)
22.47
Jones (1999)
2.20 (1.80, 2.60)
40.64
v.d. Sloot (2004)
1.90 (1.41, 2.39)
36.89
Overall (I-squared = 69.5%, p = 0.038)
1.80 (1.21, 2.38)
100.00
NOTE: Weights are from random effects analysis
-3
-2
-1
0
1
2
3
favours control group
favours intervention group



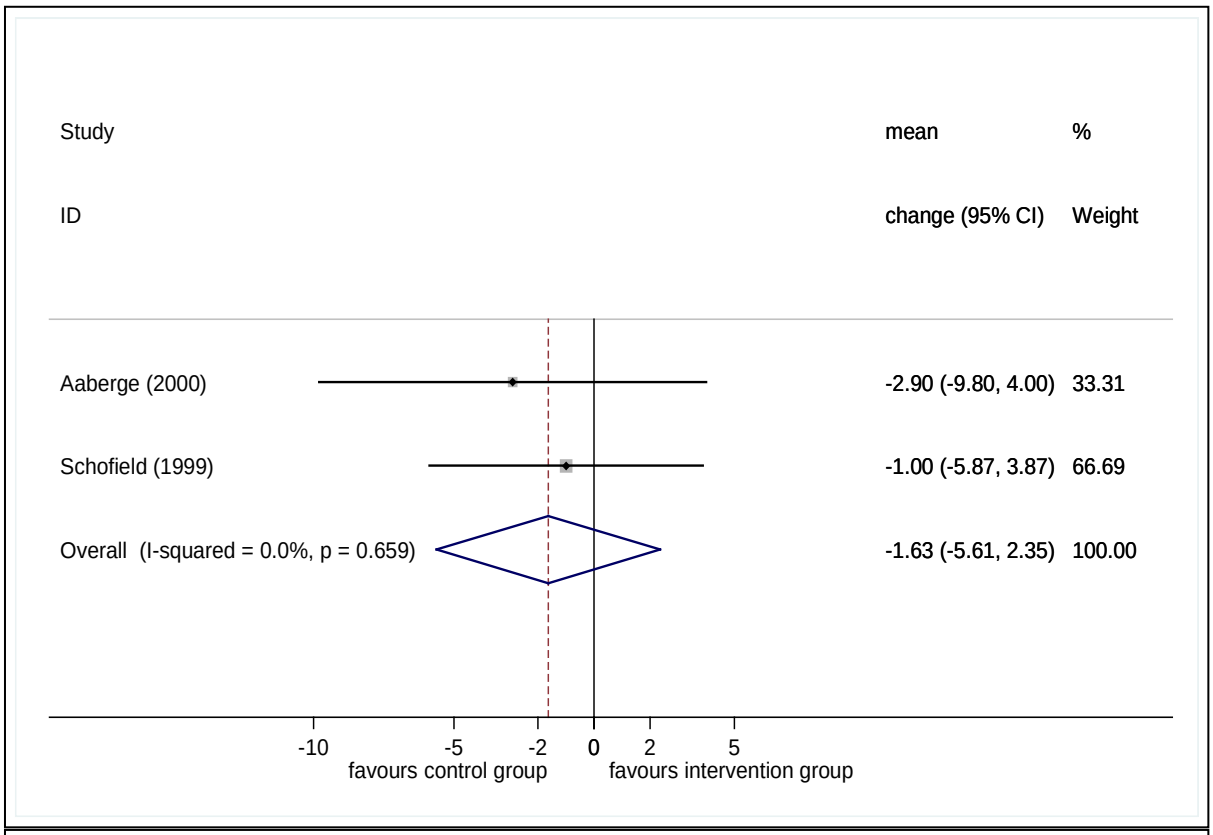
NB the following analyses are based on a high proportion of imputed values.

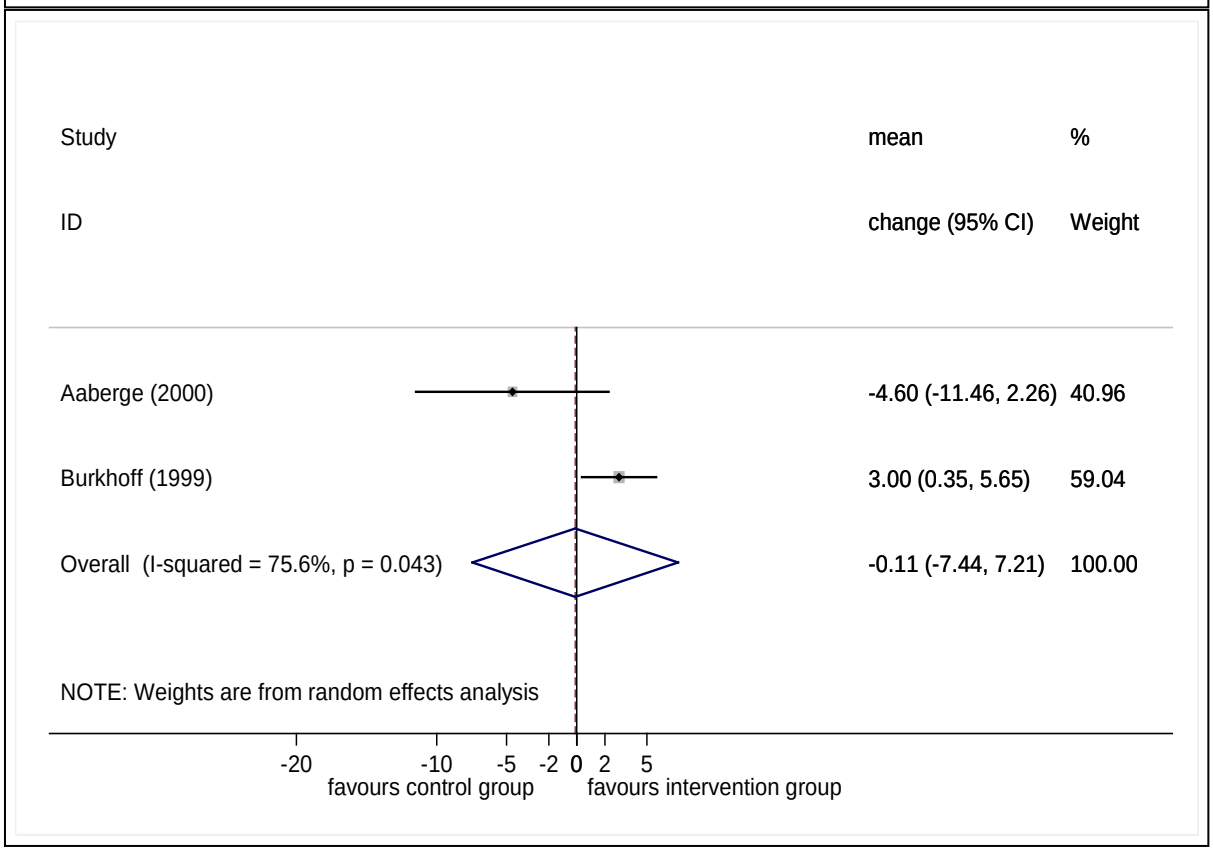
Outcome	measure	adjusted*	level	study	diff **	95% CI	p ***
angina score	PMR			**0 – 6 months**			
				Leon[1]	-0.7	-1.2, -0.2	
				Salem	0.25	0.0, 0.5	
					Pooled		
		none			-0.205	-1.1, 0.7	0.001
				0 – 12 months			
		none		Leon[1]	-0.7	-1.2, -0.2	

1 results for two active treatment arms were combined (sample size weighting – usual approach)



Outcome	measure	adjusted*	level	study	diff **	95% CI	p ***
LVEF	TMLR			**0 – 6 months**			
				Aaberge	-4.6	-11.5, 2.3	
				Burkhoff	3	0.4, 5.7	
					Pooled		
		none			-0.1	-7.4, 7.2	0.043
				0 – 12 months			
				Aaberge	-2.9	-9.8, 4.0	
				Schofield	-1	-5.9, 3.9	
					Pooled		
		none			-1.6	-5.6, 2.3	0.659


Study
ID
mean
change (95% CI)
%
Weight
Aaberge (2000)
-2.90 (-9.80, 4.00)
33.31
Schofield (1999)
-1.00 (-5.87, 3.87)
66.69
Overall (I-squared = 0.0%, p = 0.659)
-1.63 (-5.61, 2.35)
100.00
-10
-5
-2
0
2
5
favours control group
favours intervention group


Study
ID
mean
change (95% CI)
%
Weight
Aaberge (2000)
-4.60 (-11.46, 2.26)
40.96
Burkhoff (1999)
3.00 (0.35, 5.65)
59.04
Overall (I-squared = 75.6%, p = 0.043)
-0.11 (-7.44, 7.21)
100.00
NOTE: Weights are from random effects analysis
-20
-10
-5
-2
0
2
5
favours control group
favours intervention group

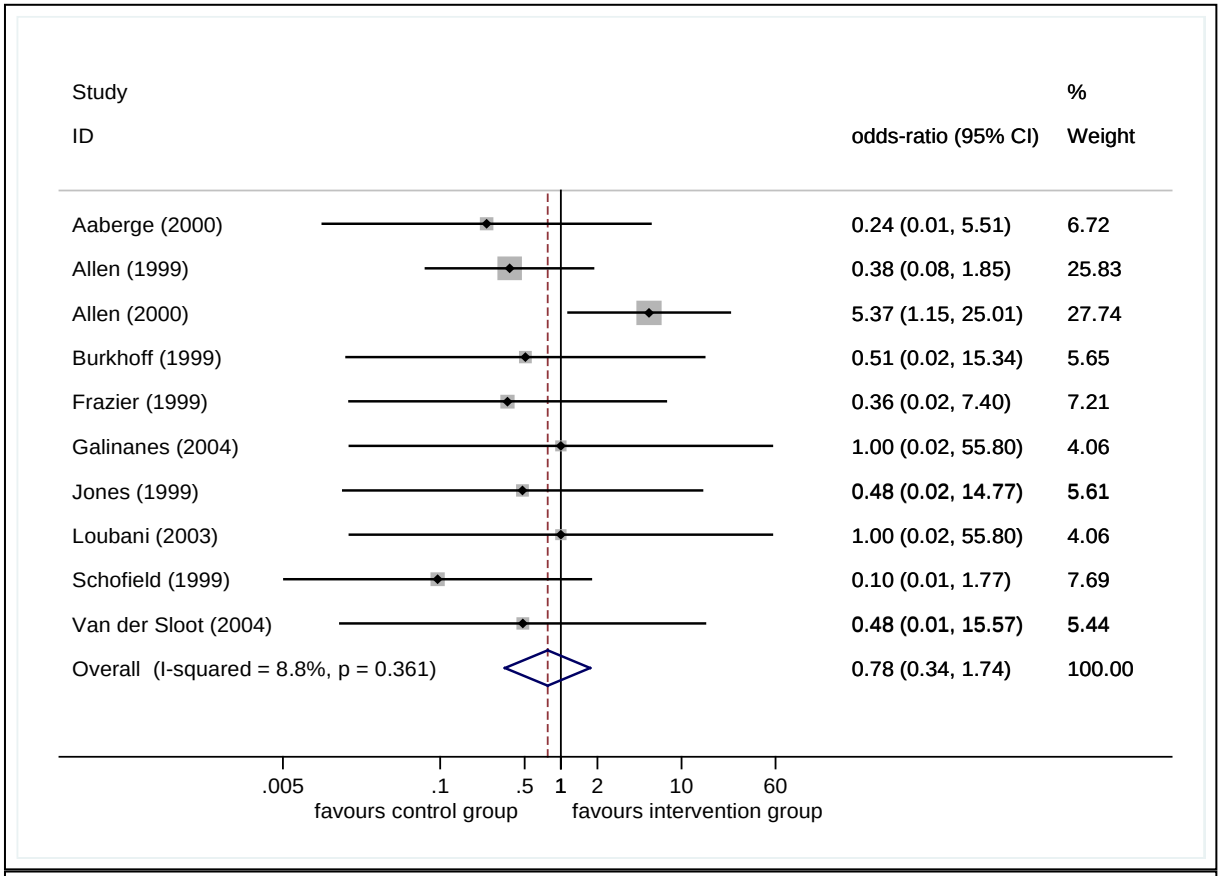
NB the following analysis is based solely on imputed standard deviations

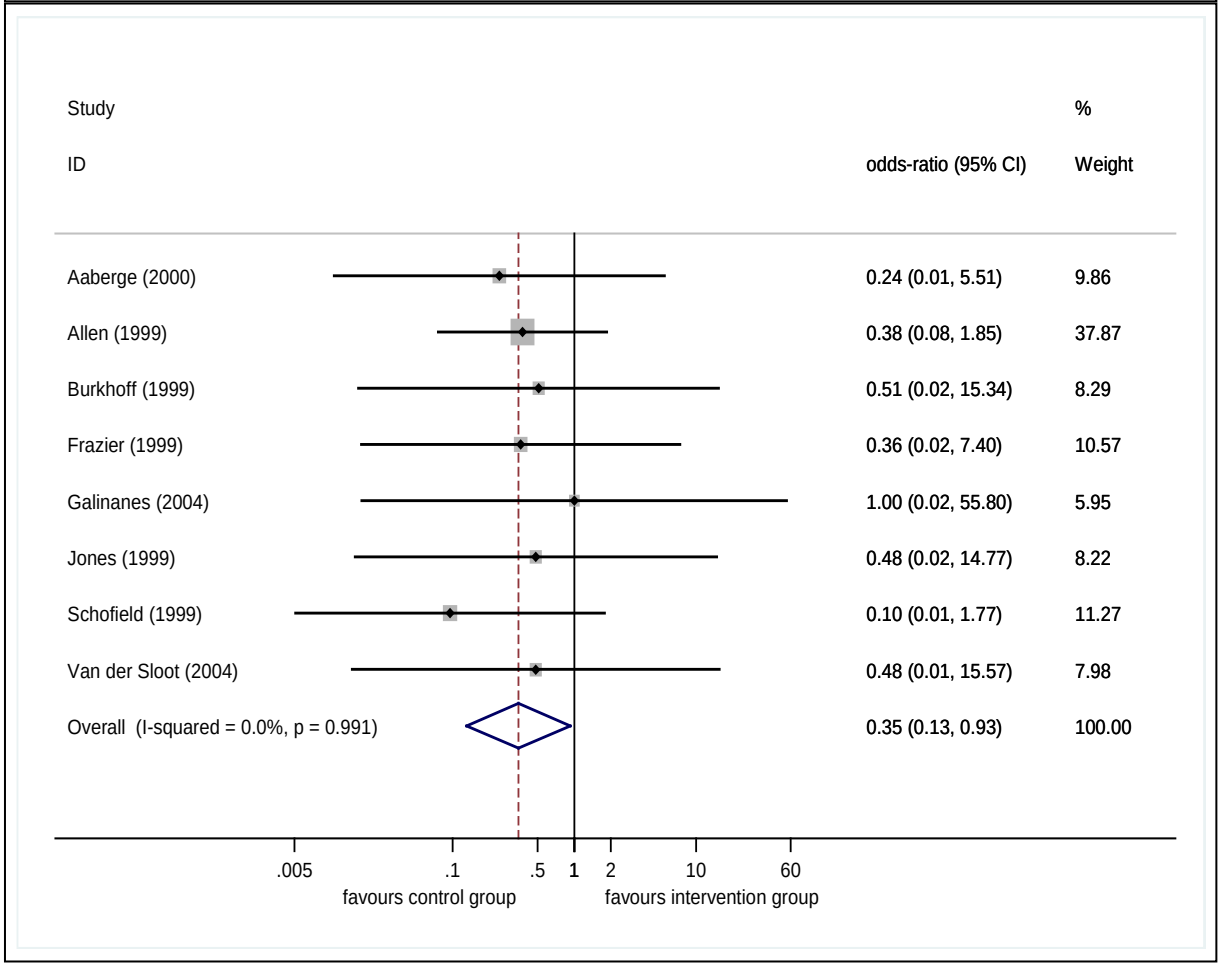
Outcome	measure	adjusted*	level	study	diff **	95% CI	p ***
LVEF	PMR			**0 – 6 months**			
				Oesterle	1.0	-6.2, 8.2	
				Salem	0.0	-13.4, 13.4	
					Pooled		
		none			0.8	-5.6, 7.1	0.897
				0 – 12 months	no data		

Due to the wide variety of instruments used, no valid analysis of QoL measures is considered possible.

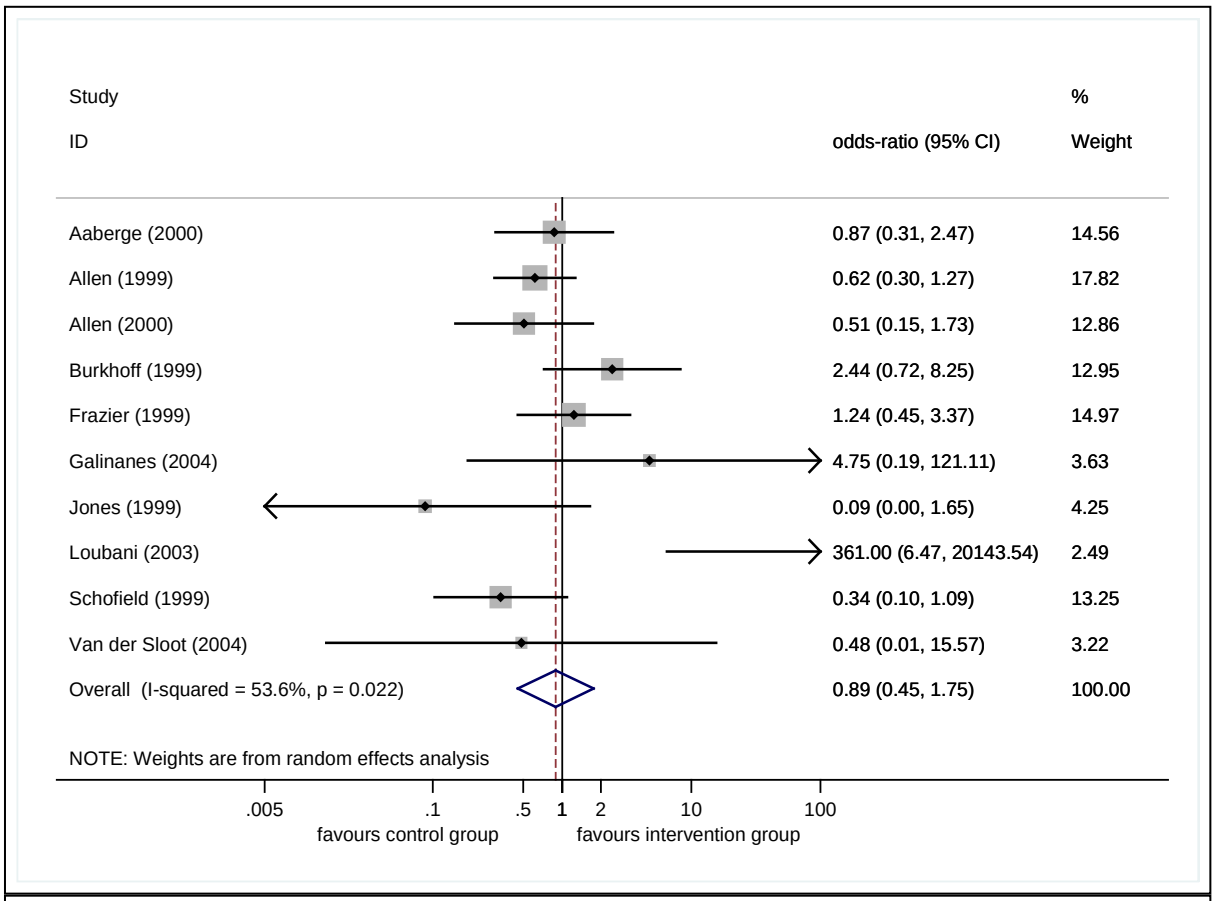
2. Dichotomous outcomes

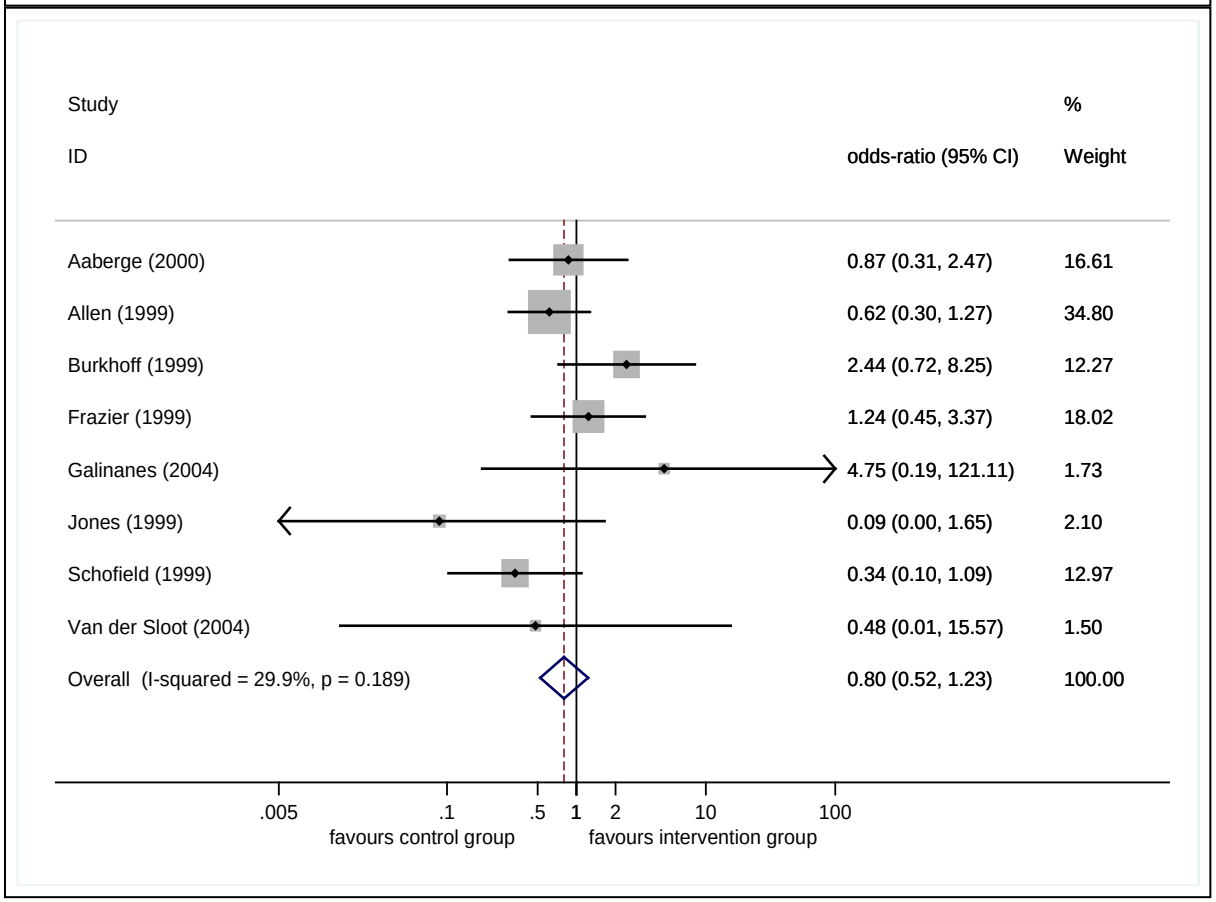
Outcome	measure	adjusted*	level	study	diff **	95% CI	p ***
perioper. mortality	TMLR						
				Aaberge (2000)	0.242	0.011, 5.514	
				Allen (1999)	0.376	0.076, 1.851	
				Allen (2000)	5.372	1.154, 25.014	
				Burkhoff (1999)	0.508	0.017, 15.344	
				Frazier (1999)	0.362	0.018, 7.398	
				Galinanes (2004)	1	0.018, 55.799	
				Jones (1999)	0.482	0.016, 14.771	
				Loubani (2003)	1	0.018, 55.799	
				Schofield (1999)	0.095	0.005, 1.768	
				v.d Sloot (2004)	0.483	0.015, 15.565	
					Pooled		
		none			0.775	0.345, 1.743	0.361
				no CABG			
				Aaberge (2000)	0.242	0.011, 5.514	
				Allen (1999)	0.376	0.076, 1.851	
				Burkhoff (1999)	0.508	0.017, 15.344	
				Frazier (1999)	0.362	0.018, 7.398	
				Galinanes (2004)	1	0.018, 55.799	
				Jones (1999)	0.482	0.016, 14.771	
				Schofield (1999)	0.095	0.005, 1.768	
				v.d Sloot (2004)	0.483	0.015, 15.565	
					Pooled		
		none			0.348	0.130, 0.927	0.991
		comparator	tmlr+med		0.325	0.118, 0.894	
			tmlr+cabg		4.335	0.571, 32.919	
			sympatht.		1.000	0.132, 7.594	
		blinding	no		0.369	0.142, 0.957	
			yes		5.372	2.071, 13.932	
		industry	no		0.723	0.263, 1.988	
			yes		0.495	0.180, 1.362	


Study
ID
%
odds-ratio (95% CI)
Weight
Aaberge (2000)
0.24 (0.01, 5.51)
6.72
Allen (1999)
0.38 (0.08, 1.85)
25.83
Allen (2000)
5.37 (1.15, 25.01)
27.74
Burkhoff (1999)
0.51 (0.02, 15.34)
5.65
Frazier (1999)
0.36 (0.02, 7.40)
7.21
Galinanes (2004)
1.00 (0.02, 55.80)
4.06
Jones (1999)
0.48 (0.02, 14.77)
5.61
Loubani (2003)
1.00 (0.02, 55.80)
4.06
Schofield (1999)
0.10 (0.01, 1.77)
7.69
Van der Sloot (2004)
0.48 (0.01, 15.57)
5.44
Overall (I-squared = 8.8%, p = 0.361)
0.78 (0.34, 1.74)
100.00
.005
.1
.5
1
2
10
60
favours control group
favours intervention group

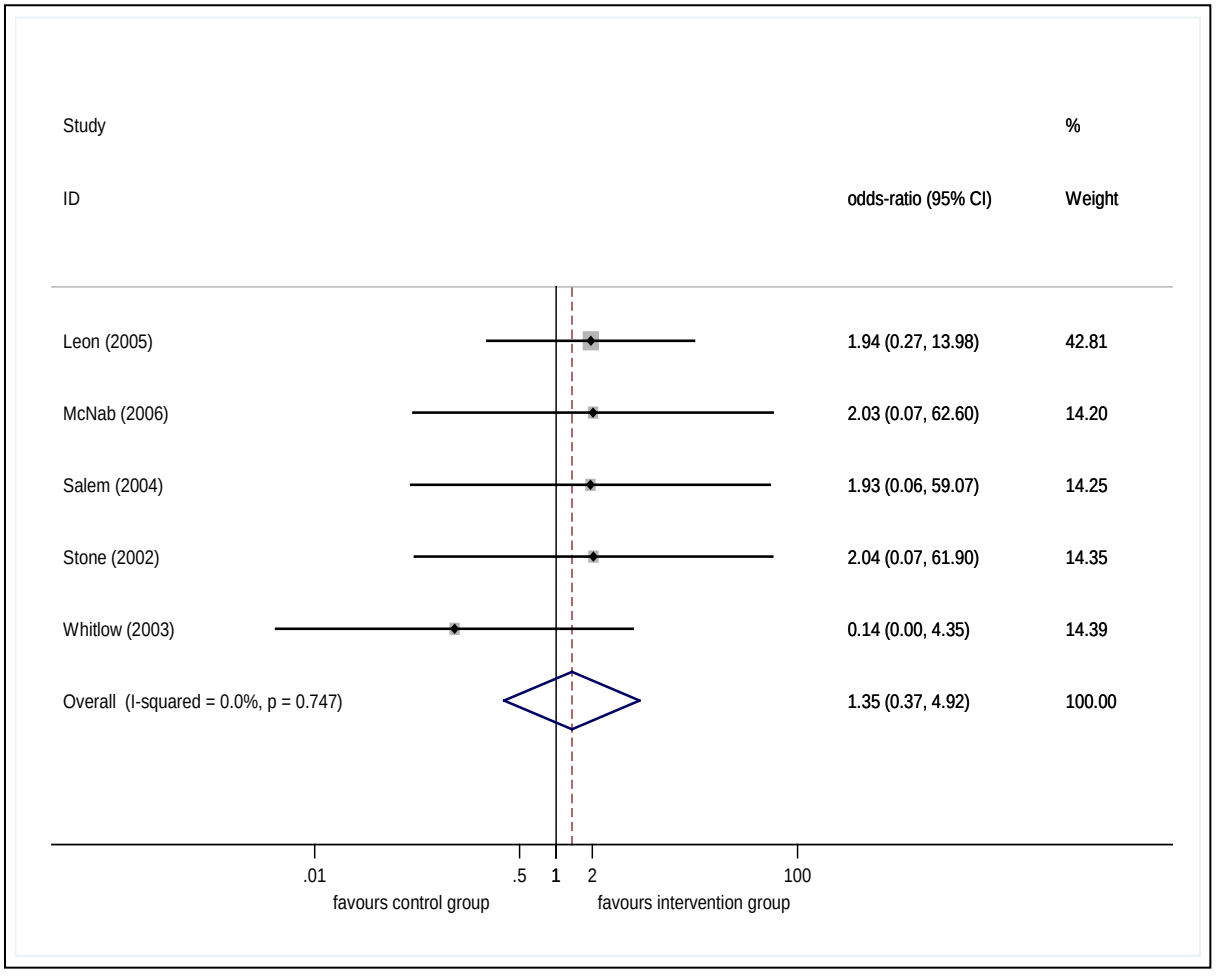

Study
ID
%
odds-ratio (95% CI)
Weight
Aaberge (2000)
0.24 (0.01, 5.51)
9.86
Allen (1999)
0.38 (0.08, 1.85)
37.87
Burkhoff (1999)
0.51 (0.02, 15.34)
8.29
Frazier (1999)
0.36 (0.02, 7.40)
10.57
Galinanes (2004)
1.00 (0.02, 55.80)
5.95
Jones (1999)
0.48 (0.02, 14.77)
8.22
Schofield (1999)
0.10 (0.01, 1.77)
11.27
Van der Sloot (2004)
0.48 (0.01, 15.57)
7.98
Overall (I-squared = 0.0%, p = 0.991)
0.35 (0.13, 0.93)
100.00
.005
.1
.5
1
2
10
60
favours control group
favours intervention group

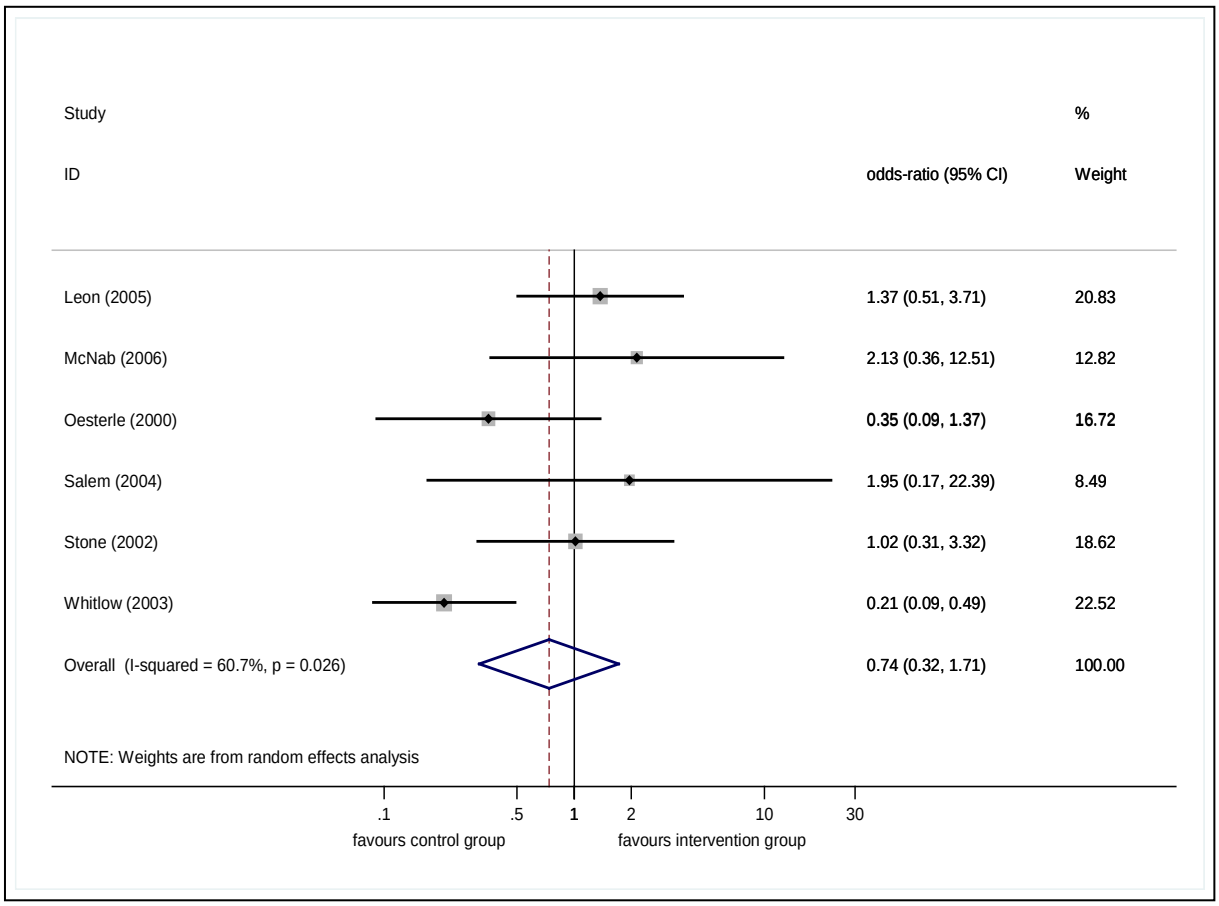
Outcome	measure	adjusted*	level	study	diff **	95% CI	p ***
total mortality	TMLR						
				Aaberge (2000)	0.868	0.305, 2.467	
				Allen (1999)	0.617	0.300, 1.269	
				Allen (2000)	0.508	0.149, 1.732	
				Burkhoff (1999)	2.444	0.725, 8.245	
				Frazier (1999)	1.235	0.453, 3.369	
				Galinanes (2004)	4.75	0.186, 121.1	
				Jones (1999)	0.087	0.005, 1.647	
				Loubani (2003)	361.0	6.470, 20000	
				Schofield (1999)	0.335	0.103, 1.094	
				v.d Sloot (2004)	0.483	0.015, 15.565	
					Pooled		
		none			0.811	0.544, 1.211	0.022
				no CABG			
				Aaberge (2000)	0.868	0.305, 2.467	
				Allen (1999)	0.617	0.300, 1.269	
				Burkhoff (1999)	2.444	0.725, 8.245	
				Frazier (1999)	1.235	0.453, 3.369	
				Galinanes (2004)	4.75	0.186, 121.1	
				Jones (1999)	0.087	0.005, 1.647	
				Schofield (1999)	0.335	0.103, 1.094	
				v.d Sloot (2004)	0.483	0.015, 15.565	
					Pooled		
		none			0.802	0.524, 1.227	0.189
		comparator	tmlr+med		0.741	0.330, 1.665	
			tmlr+cabg		1.644	0.190, 14.244	
			sympatht.		4.750	0.548, 41.155	
		blinding	no		0.981	0.457, 2.105	
			yes		0.508	0.237, 1.090	
		industry	no		0.869	0.404, 1.869	
			yes		1.044	0.485, 2.244	


Study
ID
odds-ratio (95% CI)
%
Weight
Aaberge (2000)
0.87 (0.31, 2.47)
14.56
Allen (1999)
0.62 (0.30, 1.27)
17.82
Allen (2000)
0.51 (0.15, 1.73)
12.86
Burkhoff (1999)
2.44 (0.72, 8.25)
12.95
Frazier (1999)
1.24 (0.45, 3.37)
14.97
Galinanes (2004)
4.75 (0.19, 121.11)
3.63
Jones (1999)
0.09 (0.00, 1.65)
4.25
Loubani (2003)
361.00 (6.47, 20143.54)
2.49
Schofield (1999)
0.34 (0.10, 1.09)
13.25
Van der Sloot (2004)
0.48 (0.01, 15.57)
3.22
Overall (I-squared = 53.6%, p = 0.022)
0.89 (0.45, 1.75)
100.00
NOTE: Weights are from random effects analysis
.005
.1
.5
1
2
10
100
favours control group
favours intervention group

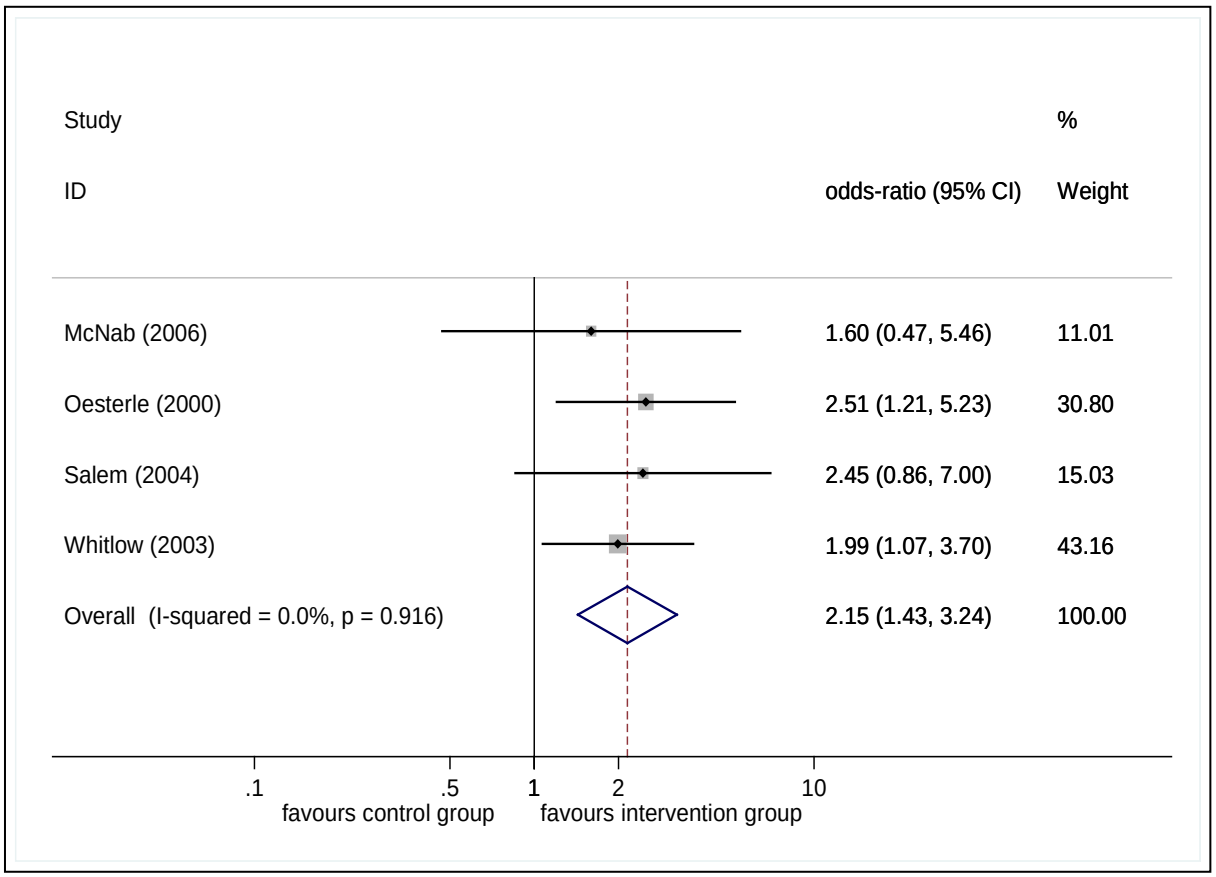

Study
ID
odds-ratio (95% CI)
%
Weight
Aaberge (2000)
0.87 (0.31, 2.47)
16.61
Allen (1999)
0.62 (0.30, 1.27)
34.80
Burkhoff (1999)
2.44 (0.72, 8.25)
12.27
Frazier (1999)
1.24 (0.45, 3.37)
18.02
Galinanes (2004)
4.75 (0.19, 121.11)
1.73
Jones (1999)
0.09 (0.00, 1.65)
2.10
Schofield (1999)
0.34 (0.10, 1.09)
12.97
Van der Sloot (2004)
0.48 (0.01, 15.57)
1.50
Overall (I-squared = 29.9%, p = 0.189)
0.80 (0.52, 1.23)
100.00
.005
.1
.5
1
2
10
100
favours control group
favours intervention group

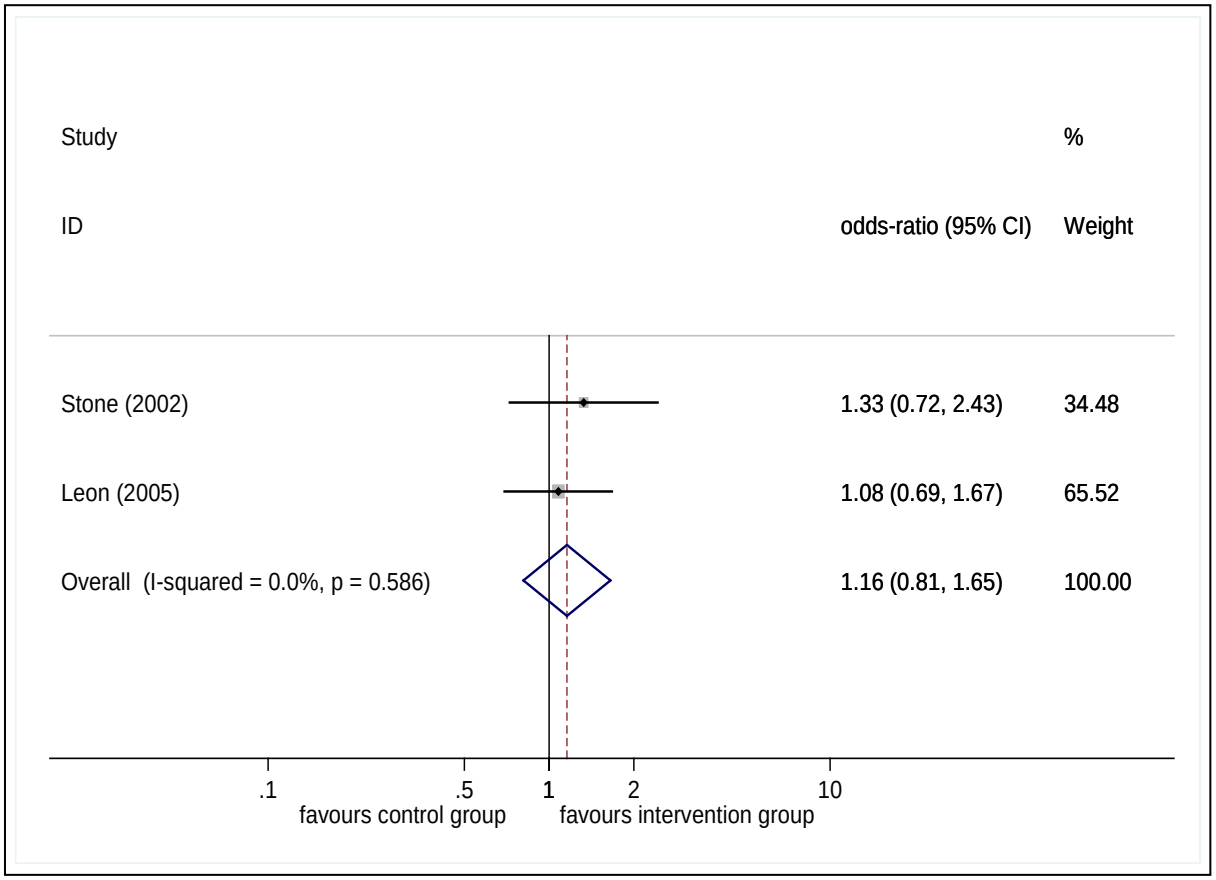
Outcome	measure	adjusted*	level	study	diff **	95% CI	p ***
perioper. mortality	PMR						
				Leon (2005)	1.94	0.269, 13.977	
				McNab (2006)	2.03	0.066, 62.603	
				Salem (2004)	1.927	0.063, 59.065	
				Stone (2002)	2.043	0.067, 61.905	
				Whitlow (2003)	0.144	0.005, 4.347	
					Pooled		
		none			1.352	0.371, 4.922	0.747
		blinding	no		0.839	0.117, 6.025	
			yes		1.937	0.270, 13.913	
total mortality	PMR						
				Leon (2005)	1.371	0.506, 3.714	
				McNab (2006)	2.133	0.364, 12.5	
				Oesterle (2000)	0.354	0.091, 1.372	
				Salem (2004)	1.95	0.170, 22.3	
				Stone (2002)	1.016	0.311, 3.315	
				Whitlow (2003)	0.207	0.088, 0.490	
					Pooled		
		none			0.737	0.317, 1.713	0.026
		blinding	no		0.532	0.213, 1.331	
			yes		1.504	0.601, 3.764	





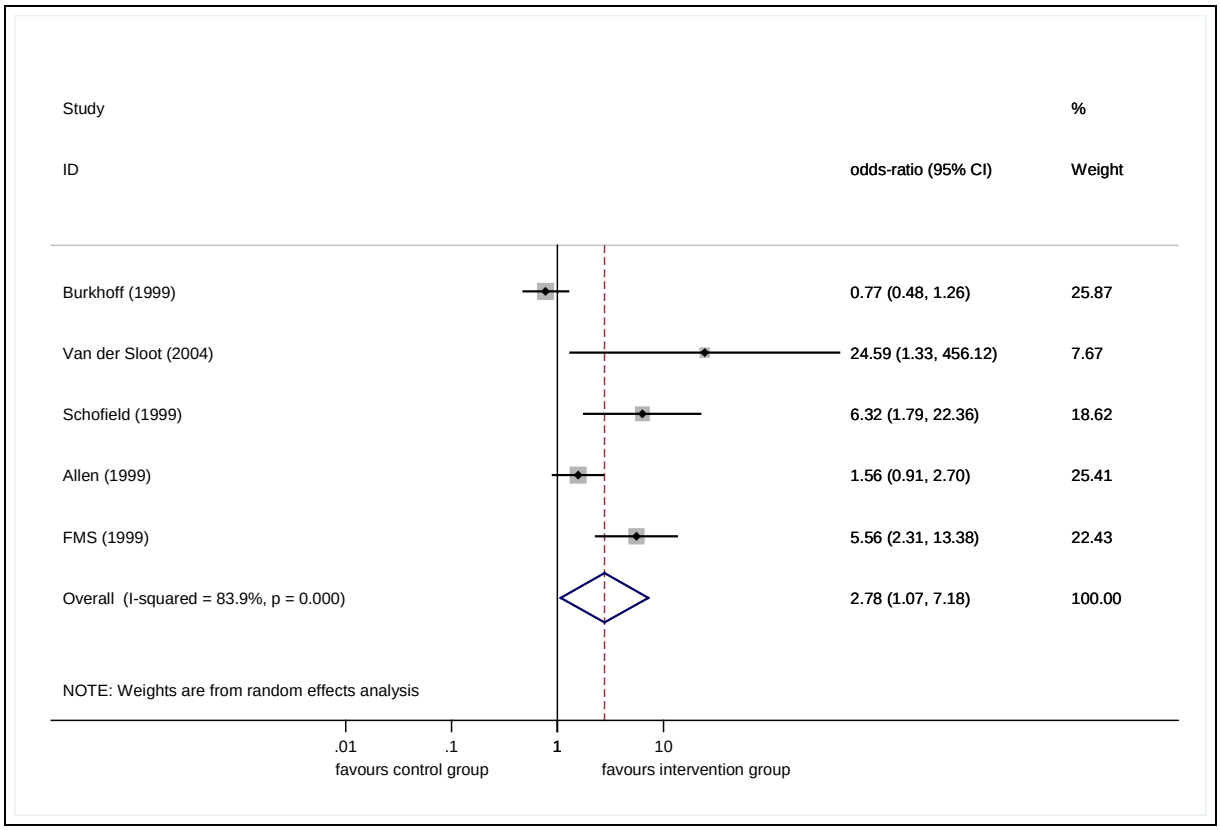
Outcome	measure	adjusted*	study	diff **	95% CI	p ***
angina score	PMR		**0-12 months**			
			McNab (2006)	1.6	0.469, 5.455	
			Oesterle (2000)	2.511	1.206, 5.228	
			Salem (2004)	2.45	0.857, 7.000	
			Whitlow (2003)	1.991	1.072, 3.700	
				Pooled		
		none		2.154	1.434, 3.236	0.916
			0-6 months			
			Stone (2002)	1.327	0.724, 2.431	
			Leon (2005)	1.078	0.695, 1.672	
				Pooled		
		none		1.158	0.812, 1.653	0.586


Study
ID
%
odds-ratio (95% CI)
Weight
McNab (2006)
1.60 (0.47, 5.46)
11.01
Oesterle (2000)
2.51 (1.21, 5.23)
30.80
Salem (2004)
2.45 (0.86, 7.00)
15.03
Whitlow (2003)
1.99 (1.07, 3.70)
43.16
Overall (I-squared = 0.0%, p = 0.916)
2.15 (1.43, 3.24)
100.00
.1
.5
1
2
10
favours control group
favours intervention group

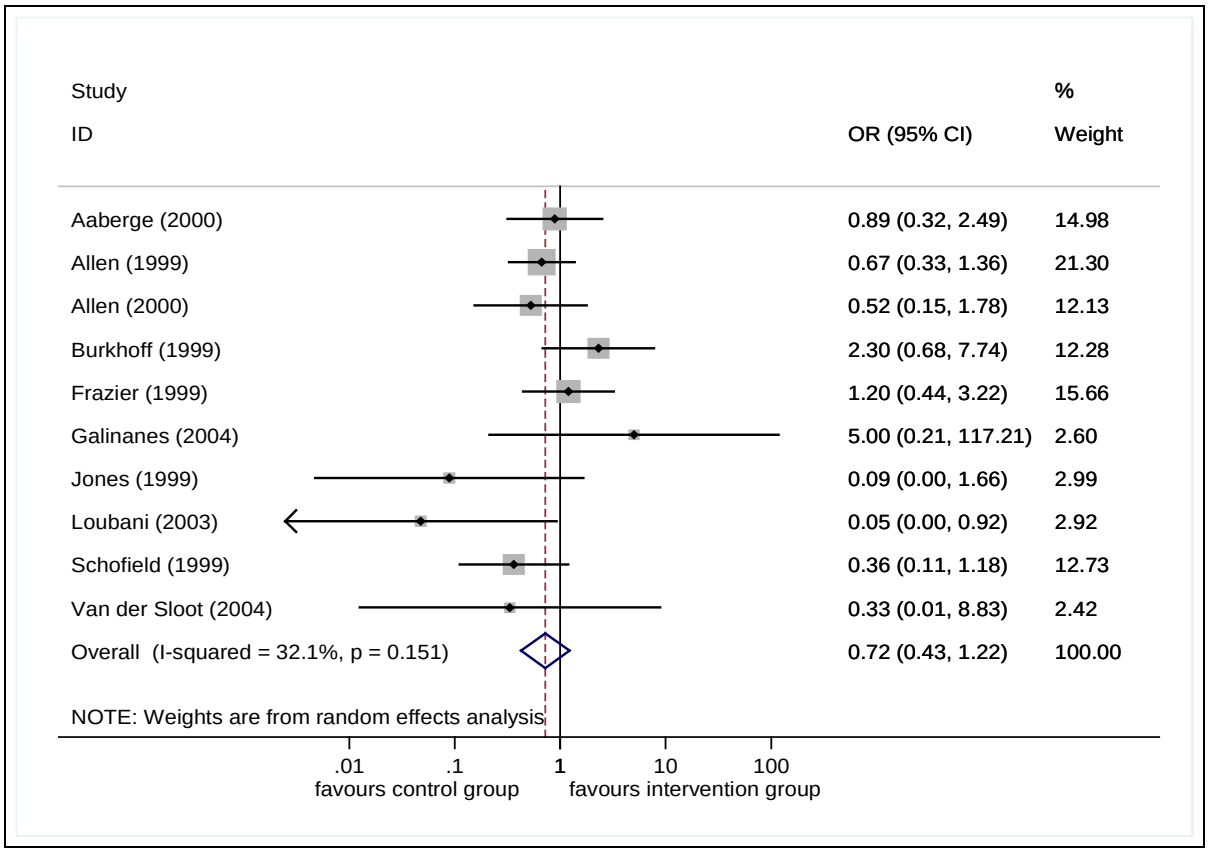

Study
ID
%
odds-ratio (95% CI)
Weight
Stone (2002)
1.33 (0.72, 2.43)
34.48
Leon (2005)
1.08 (0.69, 1.67)
65.52
Overall (I-squared = 0.0%, p = 0.586)
1.16 (0.81, 1.65)
100.00
.1
.5
1
2
10
favours control group
favours intervention group

Outcome	measure	adjusted*	level	study	diff **	95% CI	p ***
angina score	TMLR						
				Burkhoff (1999)	1.383	0.842, 2.272	
				v.d. Sloot (2004)	0.009	0.000, 0.208	
				Schofield (1999)	0.124	0.035, 0.443	
				Allen (1999)	0.012	0.001, 0.202	
				FMS[1] (1999)	0.058	0.022, 0.152	
					Pooled		
		none			0.085	0.012, 0.627	< 0.001
		NYHA scale	no		0.307	0.046, 2.039	
			yes		0.009	0.001, 0.062	
total mortality	PMR						

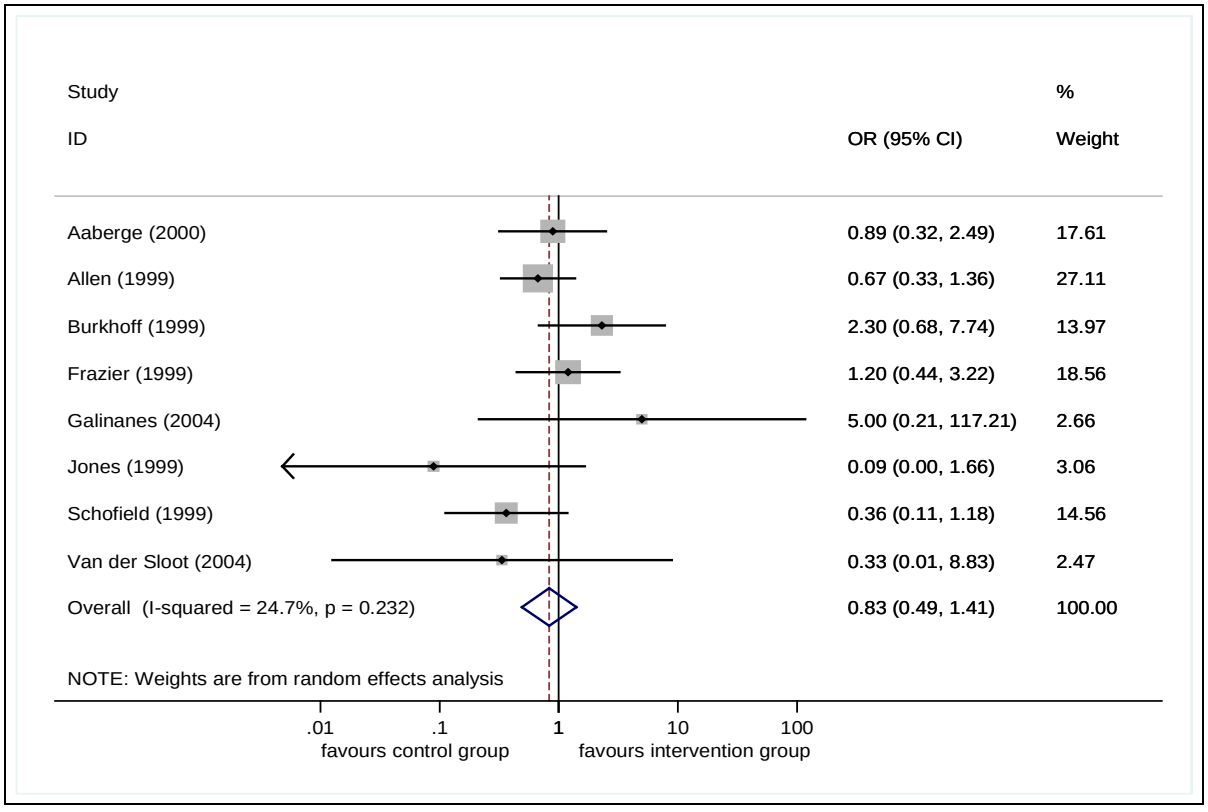
[1] Frazier/March/Spertus



All comparators:



Additional analysis of Mortality Data
Without CABG:



Percutaneous Myocardial Revascularisation

Mortality at 12 months

This first analysis includes the McNab (2006) trial with spinal cord stimulation as the control (fig 1). There is considerable heterogeneity which remains even when this trial is removed (figure 2). The one trial that when removed reduces heterogeneity is the Whitlow (2003) trial. The only obvious difference with this trial is that it has the highest proportion of patients with diabetes. We ordered the studies in percentage of patients with diabetes starting with the highest proportion at the top. McNab (2006) did not report the number with diabetes and Salem (2004) only had 15.9% participants with diabetes compared to Whitlow (2003) which had 47.8%. In figure 3 the analysis is performed according to their control.

Figure 1: PMR vs no PMR (including McNab)

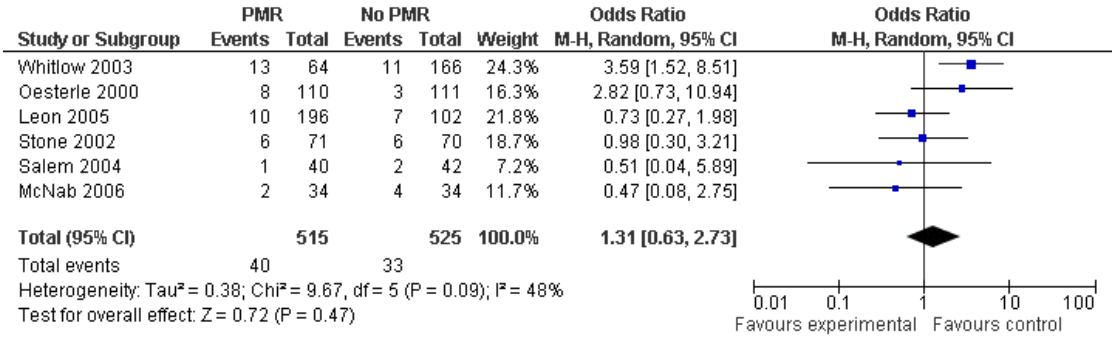


Figure 2: PMR vs placebo or usual care (without McNab)

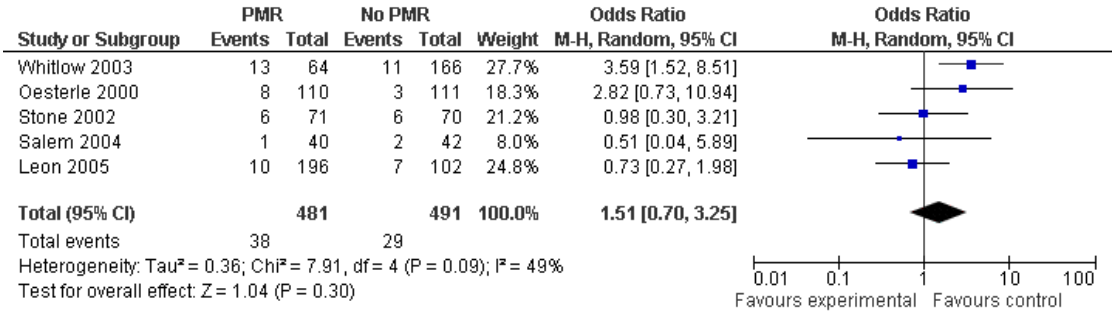


Figure 3: PMR vs controls

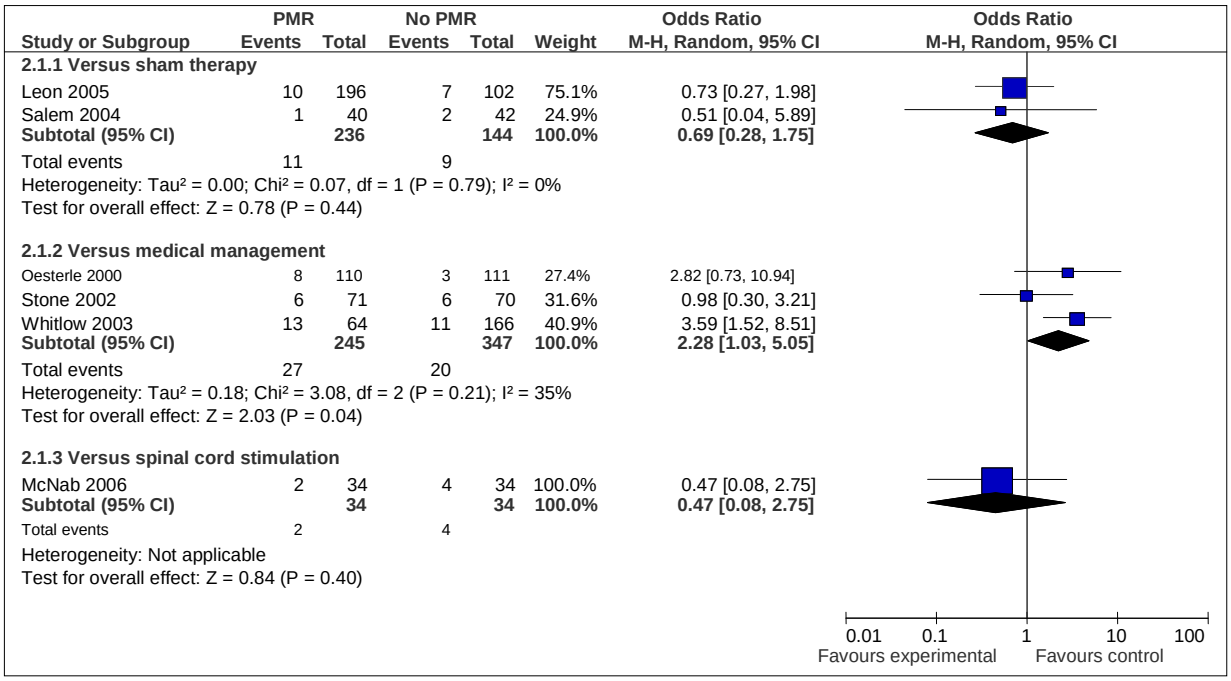


Figure 4: PMR vs usual care or placebo – Exercise Tolerance

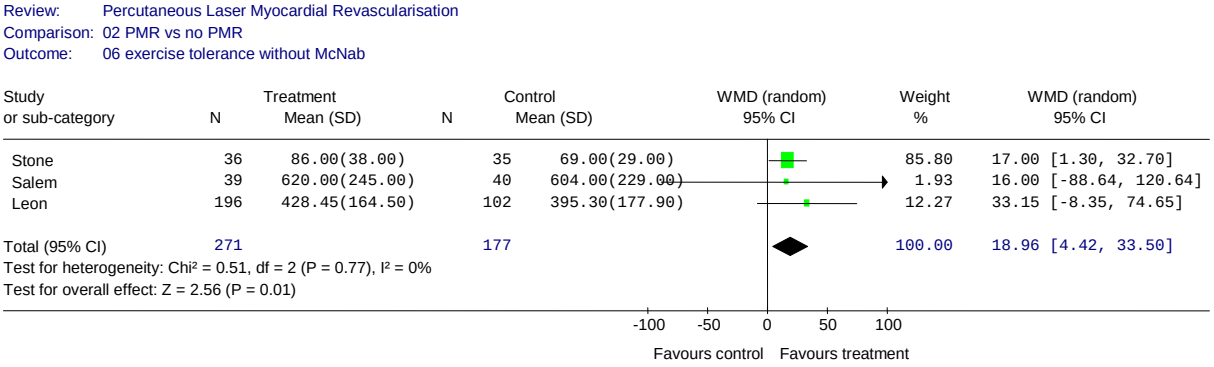


Figure 5: PMR vs usual care or placebo – improving 2 or more CCSA classes

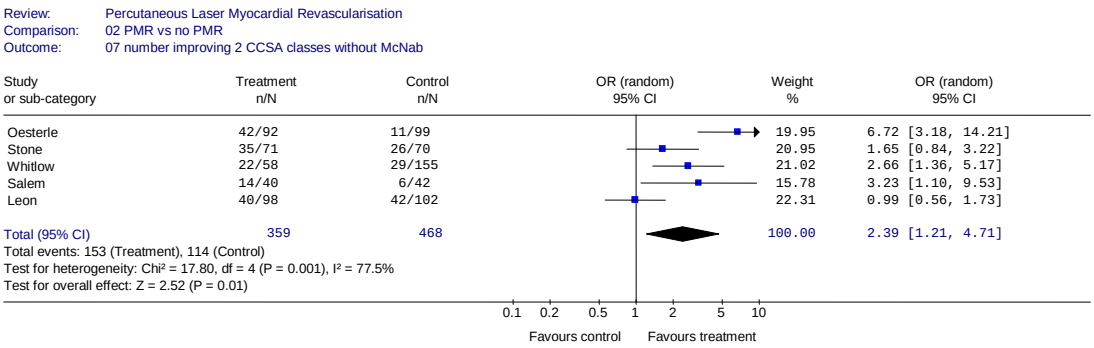


Figure 6: PMR vs usual care or placebo – sensitivity analysis – blinded studies only Angina Score