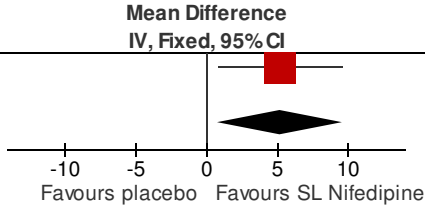
1 Sublingual nifedipine vs Placebo

1.1 Mean total work time for stepped increase in load (mins)

Study or Subgroup	Mean Difference	SE	Weight	Mean Difference IV, Fixed, 95% CI
Atterhog 1975	5.2	2.24	100.0%	5.20 [0.81, 9.59]
Total (95% CI)			**100.0%**	**5.20 [0.81, 9.59]**

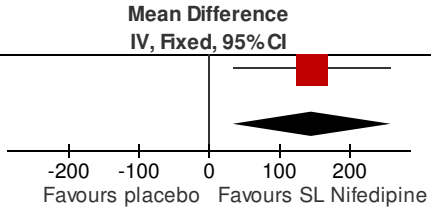
Heterogeneity: Not applicable
Test for overall effect: Z = 2.32 (P = 0.02)



1.2 Estimated workload at breakpoint for stepped increase in load (kpm/min)

Study or Subgroup	Mean Difference	SE	Weight	Mean Difference IV, Fixed, 95% CI
Atterhog 1975	146	57	100.0%	146.00 [34.28, 257.72]
Total (95% CI)			**100.0%**	**146.00 [34.28, 257.72]**

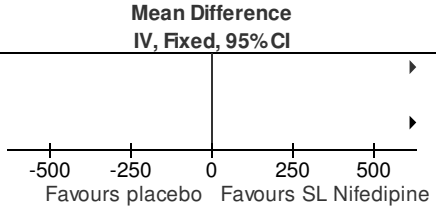
Heterogeneity: Not applicable
Test for overall effect: Z = 2.56 (P = 0.01)



1.3 Total work for stepped increase in load (kpm)

Study or Subgroup	Mean Difference	SE	Weight	Mean Difference IV, Fixed, 95% CI
Atterhog 1975	3,685	1,431	100.0%	3685.00 [880.29, 6489.71]
Total (95% CI)			**100.0%**	**3685.00 [880.29, 6489.71]**

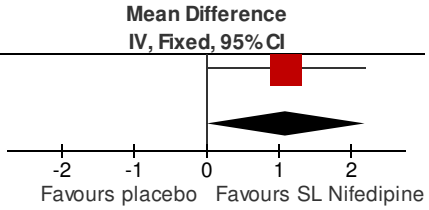
Heterogeneity: Not applicable
Test for overall effect: Z = 2.58 (P = 0.01)



1.4 Mean total work time for continuous increase in load (mins)

Study or Subgroup	Mean Difference	SE	Weight	Mean Difference IV, Fixed, 95% CI
Atterhog 1975	1.1	0.56	100.0%	1.10 [0.00, 2.20]
Total (95% CI)			**100.0%**	**1.10 [0.00, 2.20]**

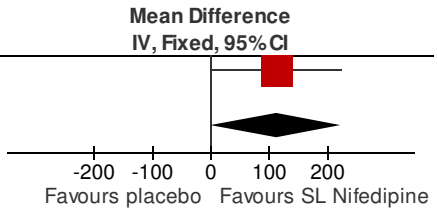
Heterogeneity: Not applicable
Test for overall effect: Z = 1.96 (P = 0.05)



1.5 Estimated workload at breakpoint for continuous increase in load (kpm/min)

Study or Subgroup	Mean Difference	SE	Weight	Mean Difference IV, Fixed, 95% CI
Atterhog 1975	112	57.1	100.0%	112.00 [0.09, 223.91]
Total (95% CI)			**100.0%**	**112.00 [0.09, 223.91]**

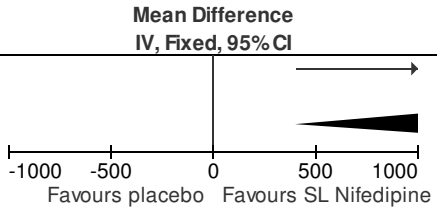
Heterogeneity: Not applicable
Test for overall effect: Z = 1.96 (P = 0.05)



1.6 Total work for continuous increase in load (kpm)

Study or Subgroup	Mean Difference	SE	Weight	Mean Difference IV, Fixed, 95% CI
Atterhog 1975	1,146	379	100.0%	1146.00 [403.17, 1888.83]
Total (95% CI)			**100.0%**	**1146.00 [403.17, 1888.83]**

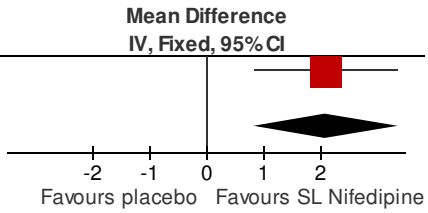
Heterogeneity: Not applicable
Test for overall effect: Z = 3.02 (P = 0.002)



1.7 Mean work capacity at angina threshold (minutes of exercise)

Study or Subgroup	Mean Difference	SE	Weight	Mean Difference IV, Fixed, 95% CI
Marra 1983	2.1	0.64	100.0%	2.10 [0.85, 3.35]
Total (95% CI)			**100.0%**	**2.10 [0.85, 3.35]**

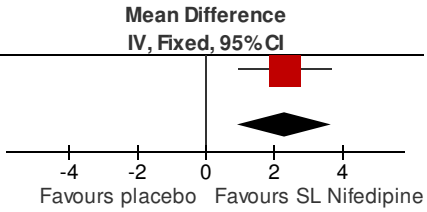
Heterogeneity: Not applicable
Test for overall effect: Z = 3.28 (P = 0.001)



1.8 Maximal work capacity at maximal exercise level (minutes of exercise)

Study or Subgroup	Mean Difference	SE	Weight	Mean Difference IV, Fixed, 95% CI
Marra 1983	2.3	0.698	100.0%	2.30 [0.93, 3.67]
Total (95% CI)			**100.0%**	**2.30 [0.93, 3.67]**

Heterogeneity: Not applicable
Test for overall effect: Z = 3.30 (P = 0.0010)

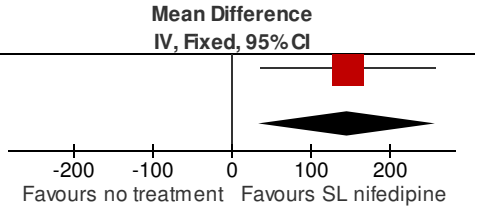


2 Sublingual nifedipine vs no treatment

2.1 Mean exercise time to 1mm ST segment depression (secs)

Study or Subgroup	Mean Difference	SE	Weight	Mean Difference IV, Fixed, 95% CI
Pupita 1993	146	56.7	100.0%	146.00 [34.87, 257.13]
Total (95% CI)			**100.0%**	**146.00 [34.87, 257.13]**

Heterogeneity: Not applicable
Test for overall effect: Z = 2.57 (P = 0.01)

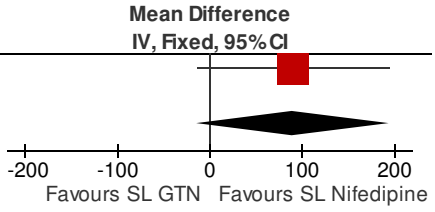


3 Sublingual GTN vs sublingual nifedipine

3.1 Mean exercise time to 1mm ST segment depression (secs)

Study or Subgroup	Mean Difference	SE	Weight	Mean Difference IV, Fixed, 95% CI
Pupita 1993	90	53.1	100.0%	90.00 [-14.07, 194.07]
Total (95% CI)			**100.0%**	**90.00 [-14.07, 194.07]**

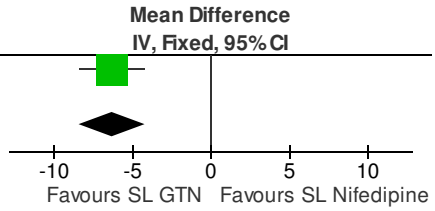
Heterogeneity: Not applicable
Test for overall effect: Z = 1.69 (P = 0.09)



3.2 Mean pain severity at 2 minutes post treatment

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Mooss 1989	1	1.7	7	7.3	2.1	6	100.0%	-6.30 [-8.40, -4.20]
Total (95% CI)			**7**			**6**	**100.0%**	**-6.30 [-8.40, -4.20]**

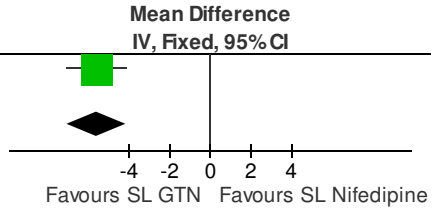
Heterogeneity: Not applicable
Test for overall effect: Z = 5.88 (P < 0.00001)



3.3 Mean pain severity at 4 minutes post treatment

Study or Subgroup	SL GTN Mean	SD	Total	SL nifedipine Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Mooss 1989	0.4	0.8	7	6	1.7	6	100.0%	-5.60 [-7.08, -4.12]
Total (95% CI)			**7**			**6**	**100.0%**	**-5.60 [-7.08, -4.12]**

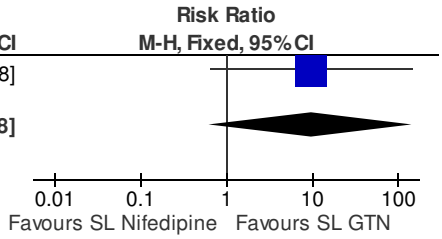
Heterogeneity: Not applicable
Test for overall effect: Z = 7.40 (P < 0.00001)



3.4 No participants with complete pain resolution at 2 minutes post treatment

Study or Subgroup	SL GTN Events	Total	SL Nifedipine Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Mooss 1989	5	7	0	6	100.0%	9.63 [0.64, 144.88]
Total (95% CI)		**7**		**6**	**100.0%**	**9.63 [0.64, 144.88]**
Total events	5		0			

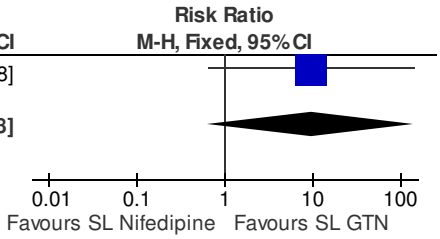
Heterogeneity: Not applicable
Test for overall effect: Z = 1.64 (P = 0.10)



3.5 No participants with complete pain resolution at 4 minutes post treatment

Study or Subgroup	SL GTN Events	Total	SL nifedipine Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Mooss 1989	5	7	0	6	100.0%	9.63 [0.64, 144.88]
Total (95% CI)		**7**		**6**	**100.0%**	**9.63 [0.64, 144.88]**
Total events	5		0			

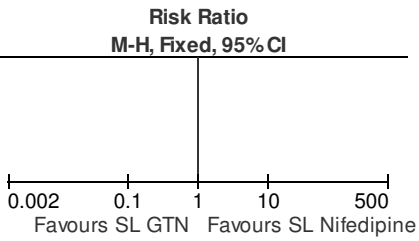
Heterogeneity: Not applicable
Test for overall effect: Z = 1.64 (P = 0.10)



3.6 No participants with complete pain resolution at 2 mins after cross over therapy

Study or Subgroup	SL GTN Events	Total	SL Nifedipine Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Mooss 1989	0	0	0	0		Not estimable
Total (95% CI)		**0**		**0**		**Not estimable**
Total events	0		0			

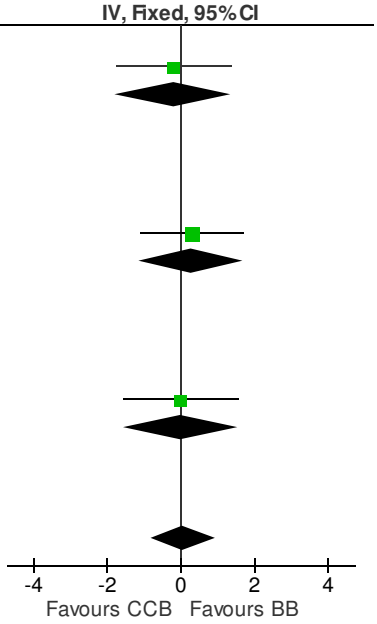
Heterogeneity: Not applicable
Test for overall effect: Not applicable



1 BB vs. CCB

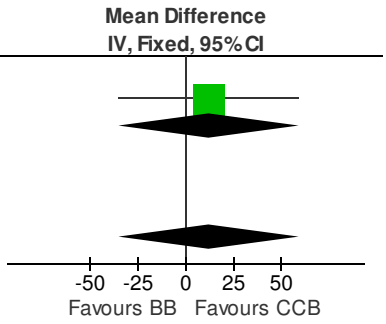
1.1 Exercise duration (min)

Study or Subgroup	BB Mean	BB SD	BB Total	CCB Mean	CCB SD	CCB Total	Weight	Mean Difference IV, Fixed, 95% CI
1.1.1 Metoprolol vs. Diltiazem								
Van Dijk 1988	9.8	3.1	33	10	3.4	33	30.8%	-0.20 [-1.77, 1.37]
Subtotal (95% CI)			**33**			**33**	**30.8%**	**-0.20 [-1.77, 1.37]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.25 (P = 0.80)								
1.1.2 Propranolol vs. Diltiazem								
O'Hara 1987	6.8	3.5	34	6.5	2.3	34	38.3%	0.30 [-1.11, 1.71]
Subtotal (95% CI)			**34**			**34**	**38.3%**	**0.30 [-1.11, 1.71]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.42 (P = 0.68)								
1.1.3 Propranolol vs. Nifedipine								
Kawanishi 1992	7.2	2.65	21	7.2	2.2	16	31.0%	0.00 [-1.56, 1.56]
Subtotal (95% CI)			**21**			**16**	**31.0%**	**0.00 [-1.56, 1.56]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.00 (P = 1.00)								
Total (95% CI)			**88**			**83**	**100.0%**	**0.05 [-0.82, 0.92]**
Heterogeneity: Chi² = 0.22, df = 2 (P = 0.89); I² = 0%								
Test for overall effect: Z = 0.12 (P = 0.90)								
Test for subgroup differences: Chi² = 0.22, df = 2 (P = 0.89), I² = 0%								



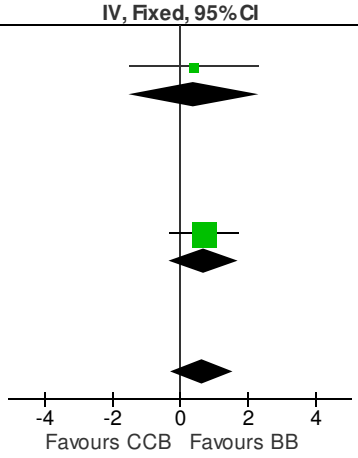
1.2 Time to 1mm ST depression (sec)

Study or Subgroup	BB Mean	BB SD	BB Total	CCB Mean	CCB SD	CCB Total	Weight	Mean Difference IV, Fixed, 95% CI
1.2.1 Metoprolol vs. Nifedipine								
Savonitto 1996 (IMAGE)	49	128.6	65	37	141.3	62	100.0%	12.00 [-35.06, 59.06]
Subtotal (95% CI)			**65**			**62**	**100.0%**	**12.00 [-35.06, 59.06]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.50 (P = 0.62)								
Total (95% CI)			**65**			**62**	**100.0%**	**12.00 [-35.06, 59.06]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.50 (P = 0.62)								
Test for subgroup differences: Not applicable								



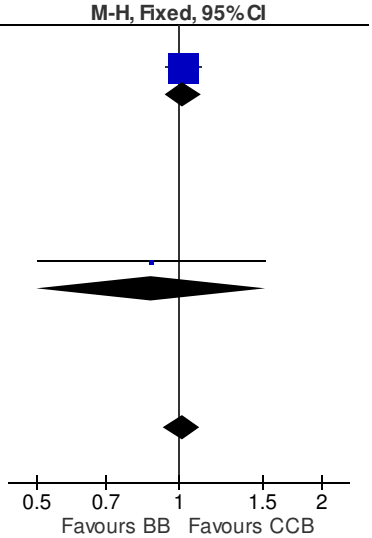
1.3 Time to onset of angina (min)

Study or Subgroup	BB Mean	BB SD	BB Total	CCB Mean	CCB SD	CCB Total	Weight	Mean Difference IV, Fixed, 95% CI
1.3.1 Metoprolol vs. Diltiazem								
Van Dijk 1988	7.4	4.4	33	7	3.5	33	22.1%	0.40 [-1.52, 2.32]
Subtotal (95% CI)			**33**			**33**	**22.1%**	**0.40 [-1.52, 2.32]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.41 (P = 0.68)								
1.3.2 Propranolol vs. Nifedipine								
Kawanishi 1992	5.7	1.2	21	5	1.8	16	77.9%	0.70 [-0.32, 1.72]
Subtotal (95% CI)			**21**			**16**	**77.9%**	**0.70 [-0.32, 1.72]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.34 (P = 0.18)								
Total (95% CI)			**54**			**49**	**100.0%**	**0.63 [-0.27, 1.53]**
Heterogeneity: Chi² = 0.07, df = 1 (P = 0.79); I² = 0%								
Test for overall effect: Z = 1.38 (P = 0.17)								
Test for subgroup differences: Chi² = 0.07, df = 1 (P = 0.79), I² = 0%								



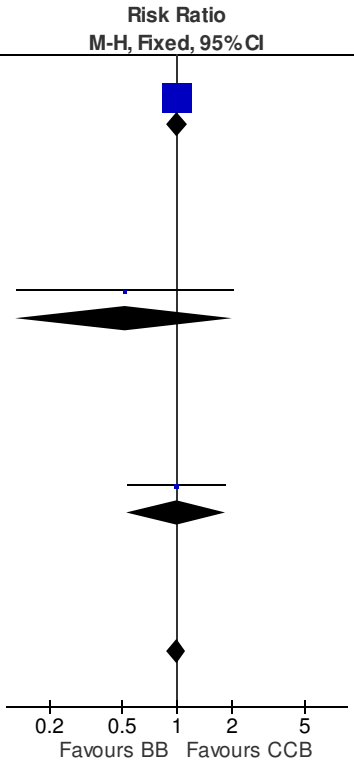
1.4 Total mortality

Study or Subgroup	BB Events	BB Total	CCB Events	CCB Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.4.1 Atenolol vs. Verapamil						
Pepine 2003 (INVEST)	893	11309	873	11267	97.2%	1.02 [0.93, 1.11]
Subtotal (95% CI)		**11309**		**11267**	**97.2%**	**1.02 [0.93, 1.11]**
Total events	893		873			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.41 (P = 0.68)						
1.4.2 Metoprolol vs. Verapamil						
Rehnqvist 1996 (APSIS)	22	406	25	403	2.8%	0.87 [0.50, 1.52]
Subtotal (95% CI)		**406**		**403**	**2.8%**	**0.87 [0.50, 1.52]**
Total events	22		25			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.48 (P = 0.63)						
Total (95% CI)		**11715**		**11670**	**100.0%**	**1.02 [0.93, 1.11]**
Total events	915		898			
Heterogeneity: Chi² = 0.29, df = 1 (P = 0.59); I² = 0%						
Test for overall effect: Z = 0.33 (P = 0.74)						
Test for subgroup differences: Chi² = 0.29, df = 1 (P = 0.59), I² = 0%						



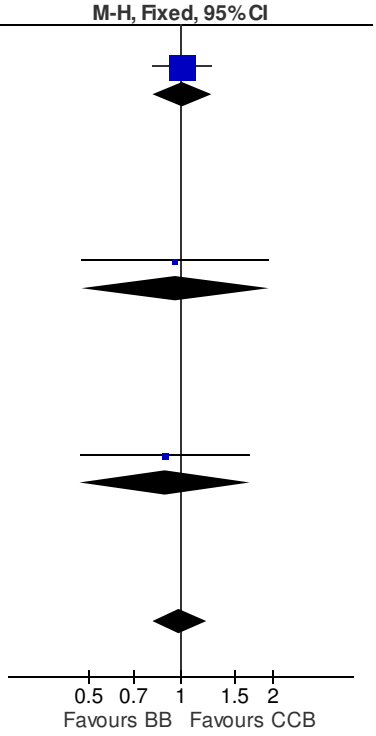
1.5 Cardiovascular death

Study or Subgroup	BB Events	BB Total	CCB Events	CCB Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.5.1 Atenolol vs. Verapamil						
Pepine 2003 (INVEST)	431	11309	431	11267	94.5%	1.00 [0.87, 1.14]
Subtotal (95% CI)		**11309**		**11267**	**94.5%**	**1.00 [0.87, 1.14]**
Total events	431		431			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.06 (P = 0.96)						
1.5.2 Atenolol vs. Nifedipine						
Dargie1996 (TIBET)	3	226	6	232	1.3%	0.51 [0.13, 2.03]
Subtotal (95% CI)		**226**		**232**	**1.3%**	**0.51 [0.13, 2.03]**
Total events	3		6			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.95 (P = 0.34)						
1.5.3 Metoprolol vs. Verapamil						
Rehnqvist 1996 (APSIS)	19	406	19	403	4.2%	0.99 [0.53, 1.85]
Subtotal (95% CI)		**406**		**403**	**4.2%**	**0.99 [0.53, 1.85]**
Total events	19		19			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.02 (P = 0.98)						
Total (95% CI)		**11941**		**11902**	**100.0%**	**0.99 [0.87, 1.12]**
Total events	453		456			
Heterogeneity: Chi² = 0.89, df = 2 (P = 0.64); I² = 0%						
Test for overall effect: Z = 0.16 (P = 0.88)						
Test for subgroup differences: Chi² = 0.89, df = 2 (P = 0.64), I² = 0%						



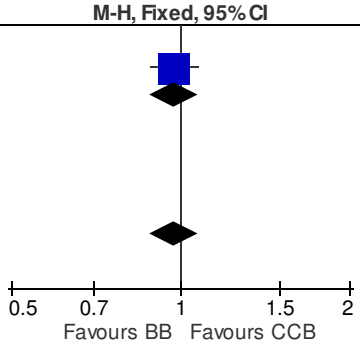
1.6 Non fatal MI

Study or Subgroup	BB Events	BB Total	CCB Events	CCB Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.6.1 Atenolol vs. Verapamil						
Pepine 2003 (INVEST)	153	11309	151	11267	81.7%	1.01 [0.81, 1.26]
Subtotal (95% CI)		**11309**		**11267**	**81.7%**	**1.01 [0.81, 1.26]**
Total events	153		151			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.08 (P = 0.93)						
1.6.2 Atenolol vs. Nifedipine						
Dargie1996 (TIBET)	14	226	15	232	8.0%	0.96 [0.47, 1.94]
Subtotal (95% CI)		**226**		**232**	**8.0%**	**0.96 [0.47, 1.94]**
Total events	14		15			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.12 (P = 0.91)						
1.6.3 Metoprolol vs. Verapamil						
Hjemdahl 2006 (APSIS)	17	406	19	403	10.3%	0.89 [0.47, 1.68]
Subtotal (95% CI)		**406**		**403**	**10.3%**	**0.89 [0.47, 1.68]**
Total events	17		19			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.36 (P = 0.72)						
Total (95% CI)		**11941**		**11902**	**100.0%**	**0.99 [0.81, 1.22]**
Total events	184		185			
Heterogeneity: Chi² = 0.15, df = 2 (P = 0.93); I² = 0%						
Test for overall effect: Z = 0.07 (P = 0.94)						
Test for subgroup differences: Chi² = 0.15, df = 2 (P = 0.93), I² = 0%						



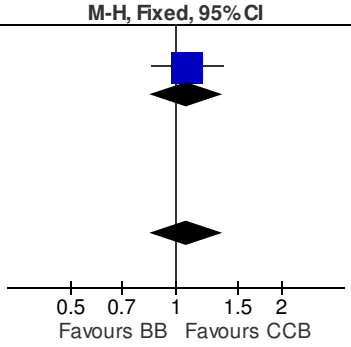
1.7 CV related hospitalisation

Study or Subgroup	BB Events	BB Total	CCB Events	CCB Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.7.1 Atenolol vs. Verapamil						
Pepine 2003 (INVEST)	709	11309	726	11267	100.0%	0.97 [0.88, 1.08]
Subtotal (95% CI)		**11309**		**11267**	**100.0%**	**0.97 [0.88, 1.08]**
Total events	709		726			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.54 (P = 0.59)						
Total (95% CI)		**11309**		**11267**	**100.0%**	**0.97 [0.88, 1.08]**
Total events	709		726			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.54 (P = 0.59)						
Test for subgroup differences: Not applicable						



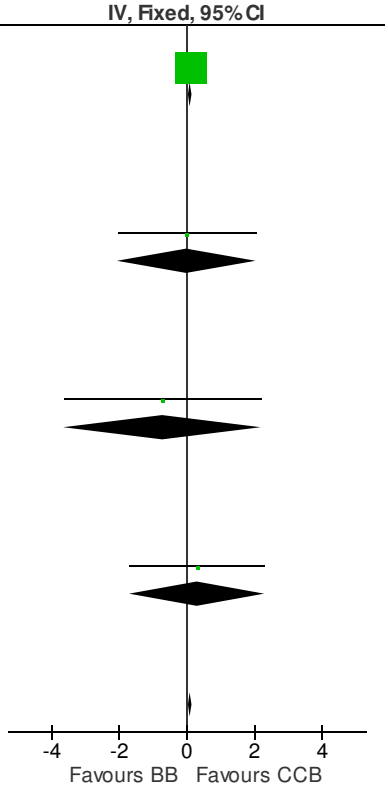
1.8 Non fatal CV events (combined)

Study or Subgroup	BB Events	BB Total	CCB Events	CCB Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.8.1 Metoprolol vs. Verapamil						
Rehnqvist 1996 (APSIS)	106	406	98	403	100.0%	1.07 [0.85, 1.36]
Subtotal (95% CI)		**406**		**403**	**100.0%**	**1.07 [0.85, 1.36]**
Total events	106		98			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.59 (P = 0.56)						
Total (95% CI)		**406**		**403**	**100.0%**	**1.07 [0.85, 1.36]**
Total events	106		98			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.59 (P = 0.56)						
Test for subgroup differences: Not applicable						



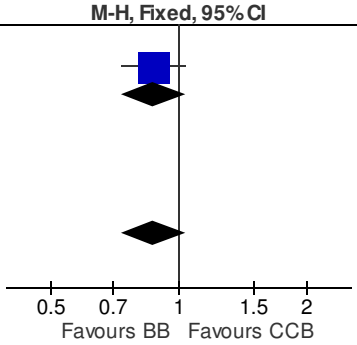
1.9 Angina episodes/week

Study or Subgroup	BB Mean	BB SD	BB Total	CCB Mean	CCB SD	CCB Total	Weight	Mean Difference IV, Fixed, 95% CI
1.9.1 Atenolol vs. Verapamil								
Pepine 2003 (INVEST)	0.88	1.62	11309	0.77	1.31	11267	99.9%	0.11 [0.07, 0.15]
Subtotal (95% CI)			**11309**			**11267**	**99.9%**	**0.11 [0.07, 0.15]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 5.61 (P < 0.00001)								
1.9.2 Metoprolol vs. Diltiazem								
Van Dijk 1988	2.5	3	33	2.5	5.2	33	0.0%	0.00 [-2.05, 2.05]
Subtotal (95% CI)			**33**			**33**	**0.0%**	**0.00 [-2.05, 2.05]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.00 (P = 1.00)								
1.9.3 Propranolol vs. Nifedipine								
Kawanishi 1992	2	2.3	21	2.7	5.6	16	0.0%	-0.70 [-3.61, 2.21]
Subtotal (95% CI)			**21**			**16**	**0.0%**	**-0.70 [-3.61, 2.21]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.47 (P = 0.64)								
1.9.4 Metoprolol vs. Nifedipine								
Savonitto 1996 (IMAGE)	-2.01	4.72	61	-2.32	6.43	61	0.0%	0.31 [-1.69, 2.31]
Subtotal (95% CI)			**61**			**61**	**0.0%**	**0.31 [-1.69, 2.31]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.30 (P = 0.76)								
Total (95% CI)			**11424**			**11377**	**100.0%**	**0.11 [0.07, 0.15]**
Heterogeneity: Chi² = 0.35, df = 3 (P = 0.95); I² = 0%								
Test for overall effect: Z = 5.61 (P < 0.00001)								
Test for subgroup differences: Chi² = 0.35, df = 3 (P = 0.95), I² = 0%								



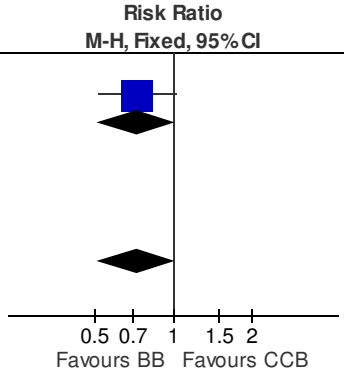
1.10 Prevalance of angina

Study or Subgroup	BB Events	BB Total	CCB Events	CCB Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.10.1 Atenolol vs. Verapamil						
Pepine 2003 (INVEST)	228	11309	261	11267	100.0%	0.87 [0.73, 1.04]
Subtotal (95% CI)		**11309**		**11267**	**100.0%**	**0.87 [0.73, 1.04]**
Total events	228		261			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.55 (P = 0.12)						
Total (95% CI)		**11309**		**11267**	**100.0%**	**0.87 [0.73, 1.04]**
Total events	228		261			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.55 (P = 0.12)						
Test for subgroup differences: Not applicable						



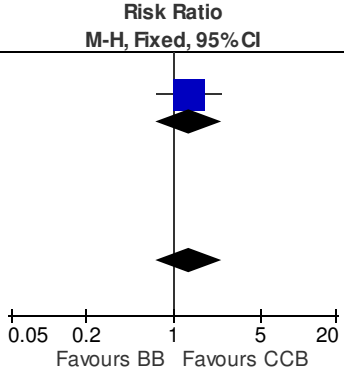
1.11 Severity of angina assessed by investigator (moderate/markedly improved)

Study or Subgroup	BB Events	BB Total	CCB Events	CCB Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.11.1 Nadolol vs. Amlodipine						
Singh 1993	21	39	29	39	100.0%	0.72 [0.51, 1.02]
Subtotal (95% CI)		**39**		**39**	**100.0%**	**0.72 [0.51, 1.02]**
Total events	21		29			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.84 (P = 0.07)						
Total (95% CI)		**39**		**39**	**100.0%**	**0.72 [0.51, 1.02]**
Total events	21		29			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.84 (P = 0.07)						
Test for subgroup differences: Not applicable						



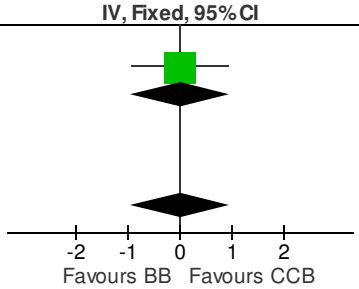
1.12 Severity of angina assessed by patients (moderate/severe)

Study or Subgroup	BB Events	BB Total	CCB Events	CCB Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.12.1 Nadolol vs. Amlodipine						
Singh 1993	16	40	12	40	100.0%	1.33 [0.73, 2.45]
Subtotal (95% CI)		**40**		**40**	**100.0%**	**1.33 [0.73, 2.45]**
Total events	16		12			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.93 (P = 0.35)						
Total (95% CI)		**40**		**40**	**100.0%**	**1.33 [0.73, 2.45]**
Total events	16		12			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.93 (P = 0.35)						
Test for subgroup differences: Not applicable						



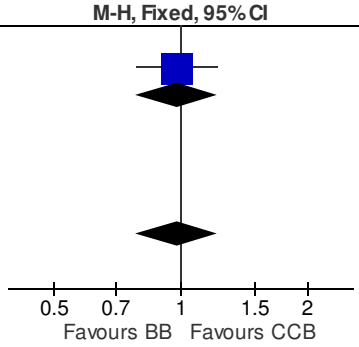
1.13 Nitroglycerin use

Study or Subgroup	BB Mean	BB SD	BB Total	CCB Mean	CCB SD	CCB Total	Weight	Mean Difference IV, Fixed, 95% CI
1.13.1 Propranolol vs. Nifedipine								
Kawanishi 1992	0.7	1.2	21	0.7	1.6	16	100.0%	0.00 [-0.94, 0.94]
Subtotal (95% CI)			**21**			**16**	**100.0%**	**0.00 [-0.94, 0.94]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.00 (P = 1.00)								
Total (95% CI)			**21**			**16**	**100.0%**	**0.00 [-0.94, 0.94]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.00 (P = 1.00)								
Test for subgroup differences: Not applicable								



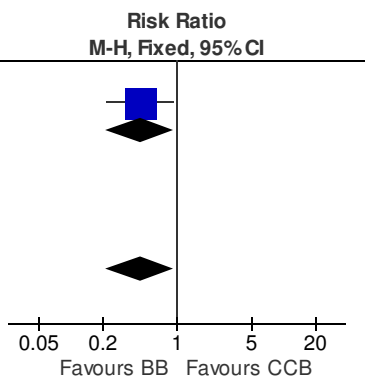
1.14 Adverse effects (dizziness)

Study or Subgroup	BB Events	BB Total	CCB Events	CCB Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.14.1 Atenolol vs. verapamil						
Pepine 2003 (INVEST)	151	11309	154	11267	100.0%	0.98 [0.78, 1.22]
Subtotal (95% CI)		**11309**		**11267**	**100.0%**	**0.98 [0.78, 1.22]**
Total events	151		154			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.21 (P = 0.84)						
Total (95% CI)		**11309**		**11267**	**100.0%**	**0.98 [0.78, 1.22]**
Total events	151		154			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.21 (P = 0.84)						
Test for subgroup differences: Not applicable						



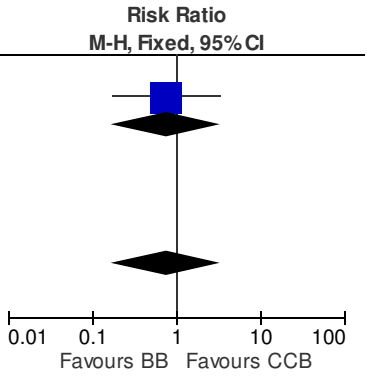
1.15 Adverse effects (GI events)

Study or Subgroup	BB Events	BB Total	CCB Events	CCB Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.15.1 Metoprolol vs. Verapamil						
Rehnqvist 1996 (APSIS)	10	406	22	403	100.0%	0.45 [0.22, 0.94]
Subtotal (95% CI)		**406**		**403**	**100.0%**	**0.45 [0.22, 0.94]**
Total events	10		22			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.12 (P = 0.03)						
Total (95% CI)		**406**		**403**	**100.0%**	**0.45 [0.22, 0.94]**
Total events	10		22			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.12 (P = 0.03)						
Test for subgroup differences: Not applicable						



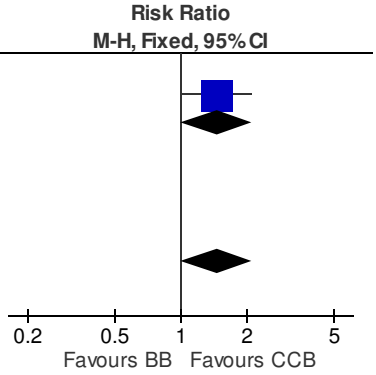
1.16 Adverse effects (head ache)

Study or Subgroup	BB Events	BB Total	CCB Events	CCB Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.16.1 Metoprolol vs. Verapamil						
Rehnqvist 1996 (APSIS)	3	406	4	403	100.0%	0.74 [0.17, 3.31]
Subtotal (95% CI)		**406**		**403**	**100.0%**	**0.74 [0.17, 3.31]**
Total events	3		4			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.39 (P = 0.70)						
Total (95% CI)		**406**		**403**	**100.0%**	**0.74 [0.17, 3.31]**
Total events	3		4			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.39 (P = 0.70)						
Test for subgroup differences: Not applicable						



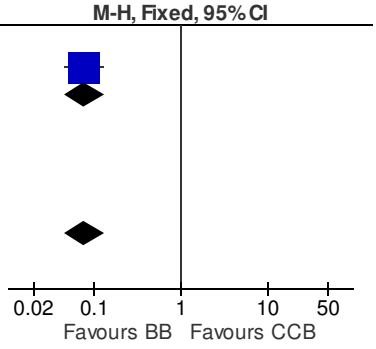
1.17 Adverse effects (light headedness)

Study or Subgroup	BB Events	BB Total	CCB Events	CCB Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.17.1 Atenolol vs. Verapamil						
Pepine 2003 (INVEST)	70	11309	48	11267	100.0%	1.45 [1.01, 2.10]
Subtotal (95% CI)		**11309**		**11267**	**100.0%**	**1.45 [1.01, 2.10]**
Total events	70		48			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.00 (P = 0.05)						
Total (95% CI)		**11309**		**11267**	**100.0%**	**1.45 [1.01, 2.10]**
Total events	70		48			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.00 (P = 0.05)						
Test for subgroup differences: Not applicable						



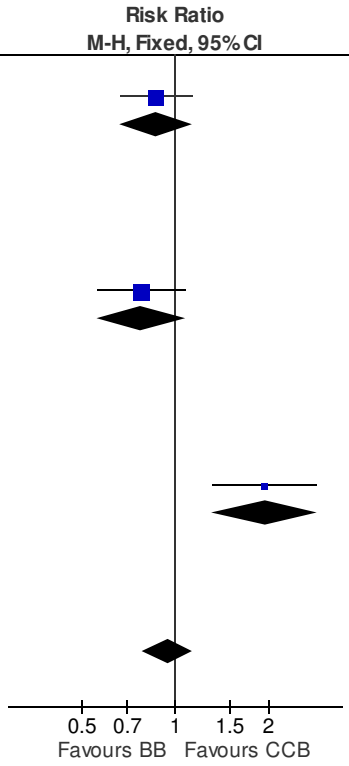
1.18 Adverse effects (constipation)

Study or Subgroup	BB Events	BB Total	CCB Events	CCB Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.18.1 Atenolol vs. Verapamil						
Pepine 2003 (INVEST)	15	11309	195	11267	100.0%	0.08 [0.05, 0.13]
Subtotal (95% CI)		**11309**		**11267**	**100.0%**	**0.08 [0.05, 0.13]**
Total events	15		195			
Heterogeneity: Not applicable						
Test for overall effect: Z = 9.60 (P < 0.00001)						
Total (95% CI)		**11309**		**11267**	**100.0%**	**0.08 [0.05, 0.13]**
Total events	15		195			
Heterogeneity: Not applicable						
Test for overall effect: Z = 9.60 (P < 0.00001)						
Test for subgroup differences: Not applicable						



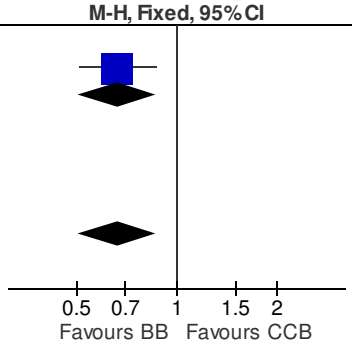
1.19 Adverse effects (overall)

Study or Subgroup	BB Events	BB Total	CCB Events	CCB Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.19.1 Atenolol vs. Amlodipine						
Pehrsson 2000	52	116	60	116	41.0%	0.87 [0.66, 1.13]
Subtotal (95% CI)		**116**		**116**	**41.0%**	**0.87 [0.66, 1.13]**
Total events	52		60			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.05 (P = 0.29)						
1.19.2 Metoprolol vs. Verapamil						
Rehnqvist 1996 (APSIS)	54	406	69	403	47.4%	0.78 [0.56, 1.08]
Subtotal (95% CI)		**406**		**403**	**47.4%**	**0.78 [0.56, 1.08]**
Total events	54		69			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.51 (P = 0.13)						
1.19.3 Nadolol vs. Amlodipine						
Singh 1993	33	40	17	40	11.6%	1.94 [1.32, 2.86]
Subtotal (95% CI)		**40**		**40**	**11.6%**	**1.94 [1.32, 2.86]**
Total events	33		17			
Heterogeneity: Not applicable						
Test for overall effect: Z = 3.35 (P = 0.0008)						
Total (95% CI)		**562**		**559**	**100.0%**	**0.95 [0.79, 1.14]**
Total events	139		146			
Heterogeneity: Chi² = 14.96, df = 2 (P = 0.0006); I² = 87%						
Test for overall effect: Z = 0.55 (P = 0.58)						
Test for subgroup differences: Chi² = 14.61, df = 2 (P = 0.0007), I² = 86.3%						



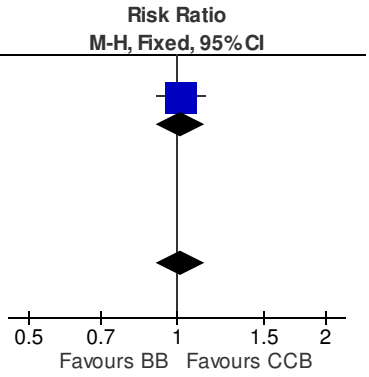
1.20 Withdrawals due to adverse effects

Study or Subgroup	BB Events	BB Total	CCB Events	CCB Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.20.1 Atenolol vs. Nifedipine						
Dargie1996 (TIBET)	60	226	93	232	100.0%	0.66 [0.51, 0.87]
Subtotal (95% CI)		**226**		**232**	**100.0%**	**0.66 [0.51, 0.87]**
Total events	60		93			
Heterogeneity: Not applicable						
Test for overall effect: Z = 3.01 (P = 0.003)						
Total (95% CI)		**226**		**232**	**100.0%**	**0.66 [0.51, 0.87]**
Total events	60		93			
Heterogeneity: Not applicable						
Test for overall effect: Z = 3.01 (P = 0.003)						
Test for subgroup differences: Not applicable						



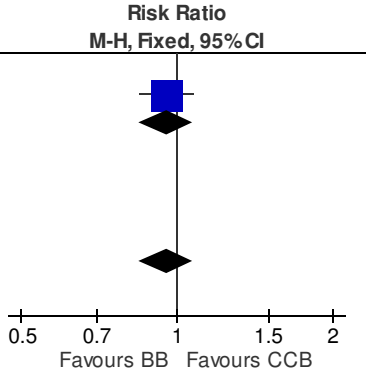
1.21 Combined outcomes (death, non fatal MI, non fatal stroke) (sub group females)

Study or Subgroup	BB Events	BB Total	CCB Events	CCB Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.21.1 Atenolol vs. Verapamil						
Pepine 2003 (INVEST)	540	5920	524	5850	100.0%	1.02 [0.91, 1.14]
Subtotal (95% CI)		**5920**		**5850**	**100.0%**	**1.02 [0.91, 1.14]**
Total events	540		524			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.31 (P = 0.76)						
Total (95% CI)		**5920**		**5850**	**100.0%**	**1.02 [0.91, 1.14]**
Total events	540		524			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.31 (P = 0.76)						
Test for subgroup differences: Not applicable						



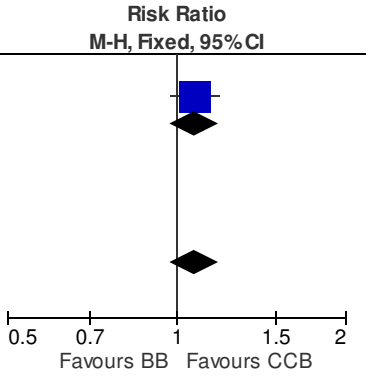
1.22 Combined outcome (death, non fatal MI, non fatal stroke) (sub group diabetes)

Study or Subgroup	BB Events	BB Total	CCB Events	CCB Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.22.1 Atenolol vs. Verapamil						
Pepine 2003 (INVEST)	450	3231	463	3169	100.0%	0.95 [0.85, 1.07]
Subtotal (95% CI)		**3231**		**3169**	**100.0%**	**0.95 [0.85, 1.07]**
Total events	450		463			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.78 (P = 0.43)						
Total (95% CI)		**3231**		**3169**	**100.0%**	**0.95 [0.85, 1.07]**
Total events	450		463			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.78 (P = 0.43)						
Test for subgroup differences: Not applicable						



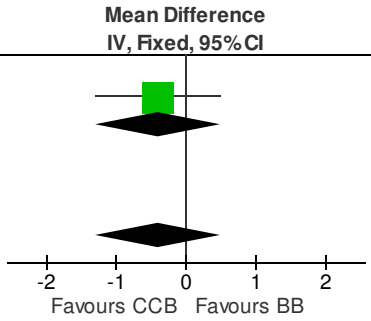
1.23 Combined (death, non fatal MI, Non fatal stroke)- Subgroup Age>70

Study or Subgroup	BB Events	BB Total	CCB Events	CCB Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.23.1 Atenolol vs. Verapamil						
Pepine 2003 (INVEST)	664	3829	596	3694	100.0%	1.07 [0.97, 1.19]
Subtotal (95% CI)		**3829**		**3694**	**100.0%**	**1.07 [0.97, 1.19]**
Total events	664		596			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.40 (P = 0.16)						
Total (95% CI)		**3829**		**3694**	**100.0%**	**1.07 [0.97, 1.19]**
Total events	664		596			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.40 (P = 0.16)						
Test for subgroup differences: Not applicable						



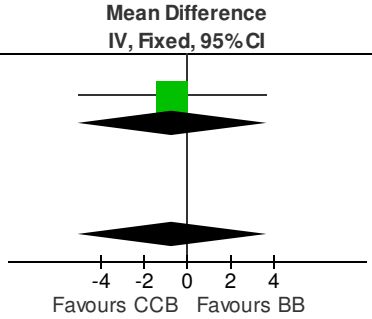
1.24 Quality of life (sleep disturbance)

Study or Subgroup	BB Mean	BB SD	BB Total	CCB Mean	CCB SD	CCB Total	Weight	Mean Difference IV, Fixed, 95% CI
1.24.1 Metoprolol vs. Verapamil								
Rehnqvist 1996 (APSIS)	16.2	5.2	270	16.6	5.5	275	100.0%	-0.40 [-1.30, 0.50]
Subtotal (95% CI)			**270**			**275**	**100.0%**	**-0.40 [-1.30, 0.50]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.87 (P = 0.38)								
Total (95% CI)			**270**			**275**	**100.0%**	**-0.40 [-1.30, 0.50]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.87 (P = 0.38)								
Test for subgroup differences: Not applicable								



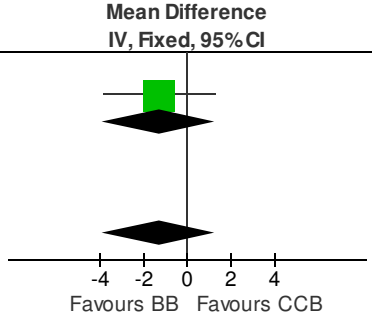
1.25 Quality of life (overall life satisfaction)

Study or Subgroup	BB Mean	BB SD	BB Total	CCB Mean	CCB SD	CCB Total	Weight	Mean Difference IV, Fixed, 95% CI
1.25.1 Metoprolol vs. Verapamil								
Rehnqvist 1996 (APSIS)	75.2	25.6	268	75.9	26.3	275	100.0%	-0.70 [-5.07, 3.67]
Subtotal (95% CI)			**268**			**275**	**100.0%**	**-0.70 [-5.07, 3.67]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.31 (P = 0.75)								
Total (95% CI)			**268**			**275**	**100.0%**	**-0.70 [-5.07, 3.67]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.31 (P = 0.75)								
Test for subgroup differences: Not applicable								



1.26 Quality of life (psychosomatic symptoms)

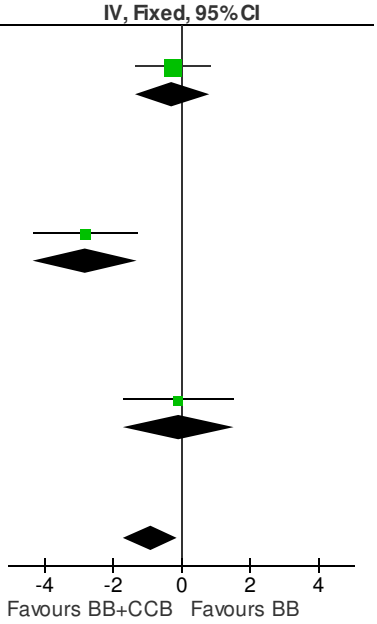
Study or Subgroup	BB Mean	BB SD	BB Total	CCB Mean	CCB SD	CCB Total	Weight	Mean Difference IV, Fixed, 95% CI
1.26.1 Metoprolol vs. Verapamil								
Rehnqvist 1996 (APSIS)	60.5	15.6	275	61.8	15.6	282	100.0%	-1.30 [-3.89, 1.29]
Subtotal (95% CI)			**275**			**282**	**100.0%**	**-1.30 [-3.89, 1.29]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.98 (P = 0.33)								
Total (95% CI)			**275**			**282**	**100.0%**	**-1.30 [-3.89, 1.29]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.98 (P = 0.33)								
Test for subgroup differences: Not applicable								



1 BB vs. BB +CCB

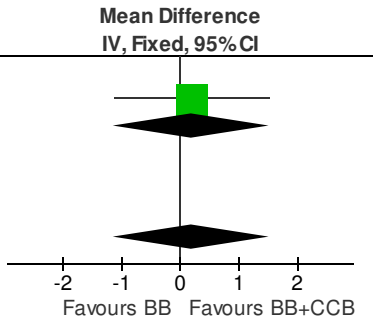
1.1 Exercise time (min)

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
1.1.1 Propranolol vs. Propranolol +Nifedipine								
Tweddel 1981	4.8	1.68	18	5.06	1.68	18	50.5%	-0.26 [-1.36, 0.84]
Subtotal (95% CI)			**18**			**18**	**50.5%**	**-0.26 [-1.36, 0.84]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.46 (P = 0.64)								
1.1.2 Propranolol vs. Propranolol +Dilitazem								
O' hara 1987	6.8	3.5	34	9.6	1.3	7	26.3%	-2.80 [-4.32, -1.28]
Subtotal (95% CI)			**34**			**7**	**26.3%**	**-2.80 [-4.32, -1.28]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 3.61 (P = 0.0003)								
1.1.3 Propranolol vs. Propranolol +Nifedipine								
Kawanishi 1992	7.2	2.6	21	7.3	2.4	16	23.2%	-0.10 [-1.72, 1.52]
Subtotal (95% CI)			**21**			**16**	**23.2%**	**-0.10 [-1.72, 1.52]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.12 (P = 0.90)								
Total (95% CI)			**73**			**41**	**100.0%**	**-0.89 [-1.67, -0.11]**
Heterogeneity: Chi² = 8.24, df = 2 (P = 0.02); I² = 76%								
Test for overall effect: Z = 2.24 (P = 0.03)								
Test for subgroup differences: Chi² = 8.24, df = 2 (P = 0.02), I² = 75.7%								



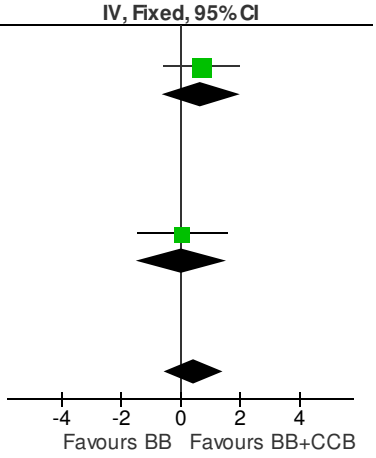
1.2 Time to onset of angina (min)

Study or Subgroup	BB Mean	SD	Total	BB+CCB Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
1.2.1 Propranolol vs. Propranolol +Nifedipine								
Kawanishi 1992	5.7	1.2	21	5.5	2.5	16	100.0%	0.20 [-1.13, 1.53]
Subtotal (95% CI)			**21**			**16**	**100.0%**	**0.20 [-1.13, 1.53]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.30 (P = 0.77)								
Total (95% CI)			**21**			**16**	**100.0%**	**0.20 [-1.13, 1.53]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.30 (P = 0.77)								
Test for subgroup differences: Not applicable								



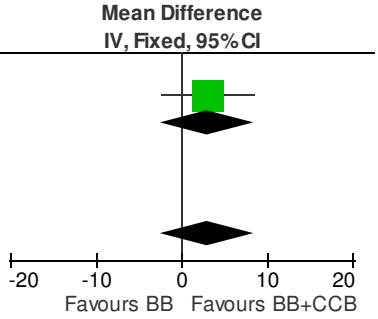
1.3 Angina attacks/week

Study or Subgroup	BB Mean	BB SD	BB Total	BB+CCB Mean	BB+CCB SD	BB+CCB Total	Weight	Mean Difference IV, Fixed, 95% CI
1.3.1 Propranolol vs. Propranolol +Nifedipine								
Kawanishi 1992	2	2.3	21	1.3	1.7	16	58.2%	0.70 [-0.59, 1.99]
Subtotal (95% CI)			**21**			**16**	**58.2%**	**0.70 [-0.59, 1.99]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.06 (P = 0.29)								
1.3.2 Metoprolol vs. Metoprolol +Nifedipine								
Savonitto 1996 (IMAGE)	-2.01	4.72	61	-2.06	3.8	61	41.8%	0.05 [-1.47, 1.57]
Subtotal (95% CI)			**61**			**61**	**41.8%**	**0.05 [-1.47, 1.57]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.06 (P = 0.95)								
Total (95% CI)			**82**			**77**	**100.0%**	**0.43 [-0.56, 1.41]**
Heterogeneity: Chi² = 0.41, df = 1 (P = 0.52); I² = 0%								
Test for overall effect: Z = 0.85 (P = 0.39)								
Test for subgroup differences: Chi² = 0.41, df = 1 (P = 0.52), I² = 0%								



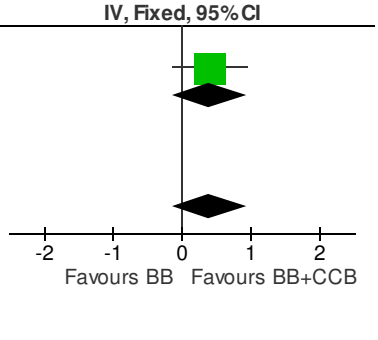
1.4 Angina attacks/day

Study or Subgroup	BB Mean	BB SD	BB Total	BB+CCB Mean	BB+CCB SD	BB+CCB Total	Weight	Mean Difference IV, Fixed, 95% CI
1.4.1 Propranolol vs. Propranolol +Nifedipine								
Tweddel 1981	7	8.4	18	4	8.4	18	100.0%	3.00 [-2.49, 8.49]
Subtotal (95% CI)			**18**			**18**	**100.0%**	**3.00 [-2.49, 8.49]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.07 (P = 0.28)								
Total (95% CI)			**18**			**18**	**100.0%**	**3.00 [-2.49, 8.49]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.07 (P = 0.28)								
Test for subgroup differences: Not applicable								



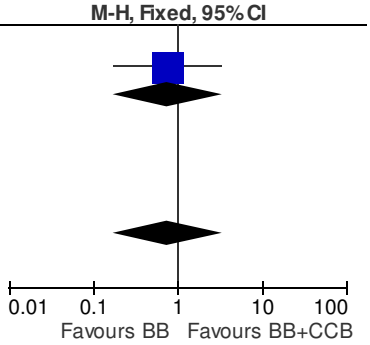
1.5 Nitroglycerin tablets/week

Study or Subgroup	BB Mean	BB SD	BB Total	BB+CCB Mean	BB+CCB SD	BB+CCB Total	Weight	Mean Difference IV, Fixed, 95% CI
1.5.1 Propranolol vs. Propranolol +Nifedipine								
Kawanishi 1992	0.7	1.2	21	0.3	0.4	16	100.0%	0.40 [-0.15, 0.95]
Subtotal (95% CI)			**21**			**16**	**100.0%**	**0.40 [-0.15, 0.95]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.43 (P = 0.15)								
Total (95% CI)			**21**			**16**	**100.0%**	**0.40 [-0.15, 0.95]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.43 (P = 0.15)								
Test for subgroup differences: Not applicable								



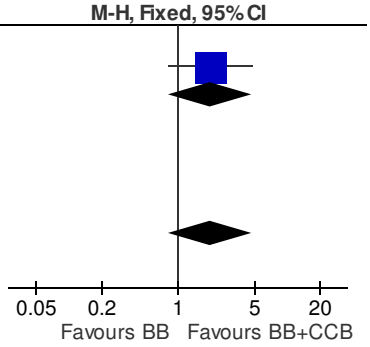
1.6 Cardiac death

Study or Subgroup	BB Events	BB Total	BB+CCB Events	BB+CCB Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.6.1 Atenolol vs. Atenolol+Nifedipine						
Dargie 1996 (TIBET)	3	226	4	224	100.0%	0.74 [0.17, 3.28]
Subtotal (95% CI)		**226**		**224**	**100.0%**	**0.74 [0.17, 3.28]**
Total events	3		4			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.39 (P = 0.70)						
Total (95% CI)		**226**		**224**	**100.0%**	**0.74 [0.17, 3.28]**
Total events	3		4			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.39 (P = 0.70)						
Test for subgroup differences: Not applicable						



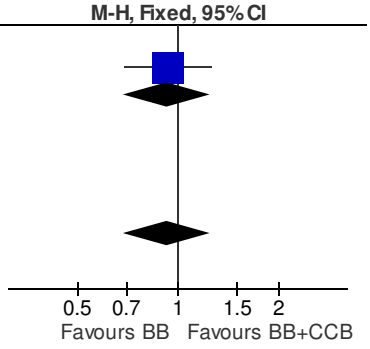
1.7 Non fatal MI

Study or Subgroup	BB Events	BB Total	BB+CCB Events	BB+CCB Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.7.1 Atenolol +Atenolol +Nifedipine						
Dargie 1996 (TIBET)	14	226	7	224	100.0%	1.98 [0.82, 4.82]
Subtotal (95% CI)		**226**		**224**	**100.0%**	**1.98 [0.82, 4.82]**
Total events	14		7			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.51 (P = 0.13)						
Total (95% CI)		**226**		**224**	**100.0%**	**1.98 [0.82, 4.82]**
Total events	14		7			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.51 (P = 0.13)						
Test for subgroup differences: Not applicable						



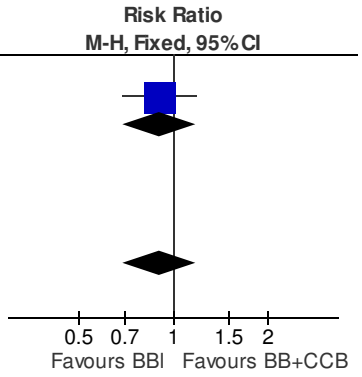
1.8 Withdrawals due to side effects

Study or Subgroup	BB Events	BB Total	BB+CCB Events	BB+CCB Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.8.1 Atenolol vs. Atenolol +Nifedipine						
Dargie 1996 (TIBET)	60	226	64	224	100.0%	0.93 [0.69, 1.25]
Subtotal (95% CI)		**226**		**224**	**100.0%**	**0.93 [0.69, 1.25]**
Total events	60		64			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.48 (P = 0.63)						
Total (95% CI)		**226**		**224**	**100.0%**	**0.93 [0.69, 1.25]**
Total events	60		64			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.48 (P = 0.63)						
Test for subgroup differences: Not applicable						



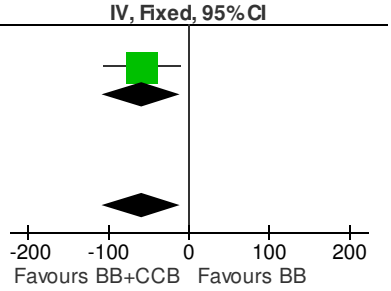
1.9 Adverse effects (overall)

Study or Subgroup	BB Events	BB Total	BB+CCB Events	BB+CCB Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.9.1 Atenolol vs. Atenolol+Amlodipine						
Pehrsson 2000	52	116	59	119	100.0%	0.90 [0.69, 1.19]
Subtotal (95% CI)		**116**		**119**	**100.0%**	**0.90 [0.69, 1.19]**
Total events	52		59			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.73 (P = 0.47)						
Total (95% CI)		**116**		**119**	**100.0%**	**0.90 [0.69, 1.19]**
Total events	52		59			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.73 (P = 0.47)						
Test for subgroup differences: Not applicable						



1.10 Time to 1mm ST depression (sec)

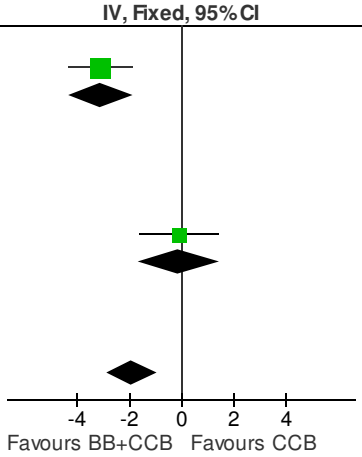
Study or Subgroup	BB Mean	BB SD	BB Total	BB+CCB Mean	BB+CCB SD	BB+CCB Total	Weight	Mean Difference IV, Fixed, 95% CI
1.10.1 Metoprolol vs. Metoprolol +Nifedipine								
Savonitto 1996 (IMAGE)	49	128.6	65	108	149.1	63	100.0%	-59.00 [-107.30, -10.70]
Subtotal (95% CI)			**65**			**63**	**100.0%**	**-59.00 [-107.30, -10.70]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 2.39 (P = 0.02)								
Total (95% CI)			**65**			**63**	**100.0%**	**-59.00 [-107.30, -10.70]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 2.39 (P = 0.02)								
Test for subgroup differences: Not applicable								



2 CCB vs. BB +CCB

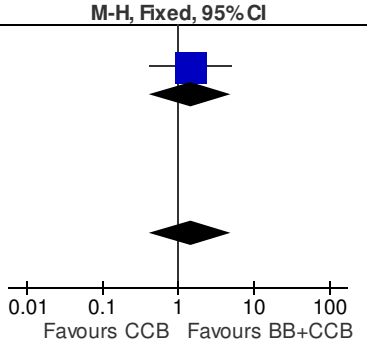
2.1 Exercise time (min)

Study or Subgroup	CCB Mean	CCB SD	CCB Total	BB+CCB Mean	BB+CCB SD	BB+CCB Total	Weight	Mean Difference IV, Fixed, 95% CI
2.1.1 Diltiazem vs. Propranolol+Diltiazem								
O' hara 1987	6.5	2.3	34	9.6	1.3	7	60.4%	-3.10 [-4.33, -1.87]
Subtotal (95% CI)			**34**			**7**	**60.4%**	**-3.10 [-4.33, -1.87]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 4.92 (P < 0.00001)								
2.1.2 Nifedipine vs. Propranolol +Nifedipine								
Kawanishi 1992	7.2	2.2	16	7.3	2.4	19	39.6%	-0.10 [-1.63, 1.43]
Subtotal (95% CI)			**16**			**19**	**39.6%**	**-0.10 [-1.63, 1.43]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.13 (P = 0.90)								
Total (95% CI)			**50**			**26**	**100.0%**	**-1.91 [-2.87, -0.95]**
Heterogeneity: Chi² = 8.98, df = 1 (P = 0.003); I² = 89%								
Test for overall effect: Z = 3.90 (P < 0.0001)								
Test for subgroup differences: Chi² = 8.98, df = 1 (P = 0.003), I² = 88.9%								



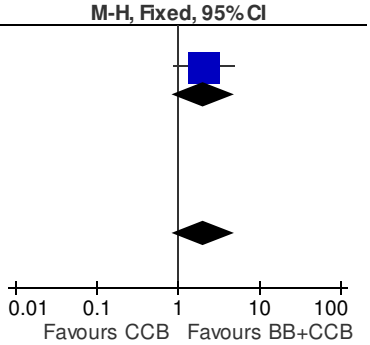
2.2 Cardiac death

Study or Subgroup	CCB Events	CCB Total	BB+CCB Events	BB+CCB Total	Weight	Risk Ratio M-H, Fixed, 95% CI
2.2.1 Nifedipine vs. Atenolol +Nifedipine						
Dargie 1996 (TIBET)	6	232	4	224	100.0%	1.45 [0.41, 5.06]
Subtotal (95% CI)		**232**		**224**	**100.0%**	**1.45 [0.41, 5.06]**
Total events	6		4			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.58 (P = 0.56)						
Total (95% CI)		**232**		**224**	**100.0%**	**1.45 [0.41, 5.06]**
Total events	6		4			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.58 (P = 0.56)						
Test for subgroup differences: Not applicable						



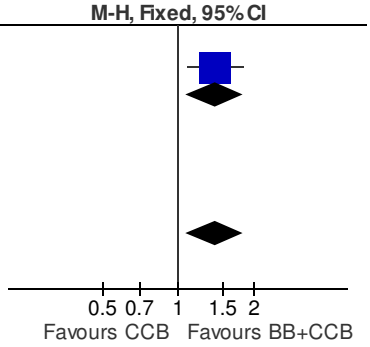
2.3 Non fatal MI

Study or Subgroup	CCB Events	CCB Total	BB+CCB Events	BB+CCB Total	Weight	Risk Ratio M-H, Fixed, 95% CI
2.3.1 Nifedipine vs. Atenolol +Nifedipine						
Dargie 1996 (TIBET)	15	232	7	224	100.0%	2.07 [0.86, 4.98]
Subtotal (95% CI)		**232**		**224**	**100.0%**	**2.07 [0.86, 4.98]**
Total events	15		7			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.62 (P = 0.10)						
Total (95% CI)		**232**		**224**	**100.0%**	**2.07 [0.86, 4.98]**
Total events	15		7			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.62 (P = 0.10)						
Test for subgroup differences: Not applicable						



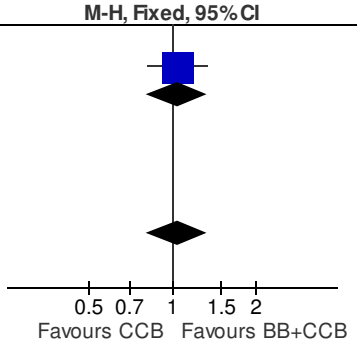
2.4 Withdrawals due to side effects

Study or Subgroup	CCB Events	CCB Total	BB+CCB Events	BB+CCB Total	Weight	Risk Ratio M-H, Fixed, 95% CI
2.4.1 Nifedipine vs. Atenolol +Nifedipine						
Dargie 1996 (TIBET)	93	232	64	224	100.0%	1.40 [1.08, 1.82]
Subtotal (95% CI)		**232**		**224**	**100.0%**	**1.40 [1.08, 1.82]**
Total events	93		64			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.55 (P = 0.01)						
Total (95% CI)		**232**		**224**	**100.0%**	**1.40 [1.08, 1.82]**
Total events	93		64			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.55 (P = 0.01)						
Test for subgroup differences: Not applicable						



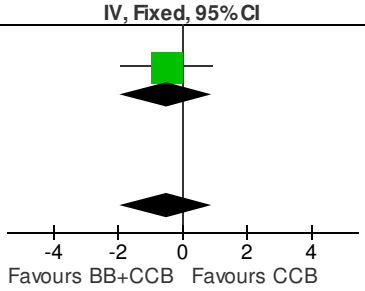
2.5 Adverse effects (overall)

Study or Subgroup	CCB Events	CCB Total	BB+CCB Events	BB+CCB Total	Weight	Risk Ratio M-H, Fixed, 95% CI
2.5.1 Amlodipine vs. Atenolol +Amlodipine						
Pehrsson 2000	60	116	59	119	100.0%	1.04 [0.81, 1.34]
Subtotal (95% CI)		**116**		**119**	**100.0%**	**1.04 [0.81, 1.34]**
Total events	60		59			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.33 (P = 0.74)						
Total (95% CI)		**116**		**119**	**100.0%**	**1.04 [0.81, 1.34]**
Total events	60		59			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.33 (P = 0.74)						
Test for subgroup differences: Not applicable						



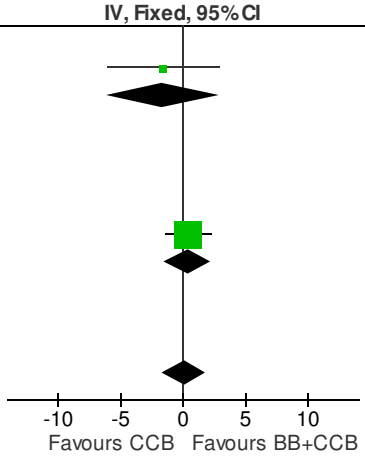
2.6 Time to onset of angina (min)

Study or Subgroup	CCB Mean	CCB SD	CCB Total	BB+CCB Mean	BB+CCB SD	BB+CCB Total	Weight	Mean Difference IV, Fixed, 95% CI
2.6.1 Nifedipine vs. Propranolol +Nifedipine								
Kawanishi 1992	5	1.8	16	5.5	2.5	19	100.0%	-0.50 [-1.93, 0.93]
Subtotal (95% CI)			**16**			**19**	**100.0%**	**-0.50 [-1.93, 0.93]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.69 (P = 0.49)								
Total (95% CI)			**16**			**19**	**100.0%**	**-0.50 [-1.93, 0.93]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.69 (P = 0.49)								
Test for subgroup differences: Not applicable								



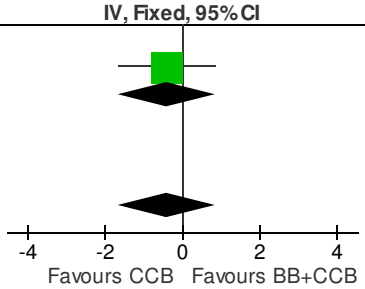
2.7 Angina episodes/week

Study or Subgroup	CCB Mean	CCB SD	CCB Total	BB+CCB Mean	BB+CCB SD	BB+CCB Total	Weight	Mean Difference IV, Fixed, 95% CI
2.7.1 Nifedipine vs. Propranolol+Nifedipine								
Kawanishi 1992	2.7	5.6	16	4.3	7.9	19	14.7%	-1.60 [-6.09, 2.89]
Subtotal (95% CI)			**16**			**19**	**14.7%**	**-1.60 [-6.09, 2.89]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.70 (P = 0.48)								
2.7.2 Nifedipine vs. Metoprolol +Nifedipine								
Savonitto 1996 (IMAGE)	-2.32	6.43	61	-2.71	3.58	57	85.3%	0.39 [-1.47, 2.25]
Subtotal (95% CI)			**61**			**57**	**85.3%**	**0.39 [-1.47, 2.25]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.41 (P = 0.68)								
Total (95% CI)			**77**			**76**	**100.0%**	**0.10 [-1.62, 1.82]**
Heterogeneity: Chi² = 0.64, df = 1 (P = 0.42); I² = 0%								
Test for overall effect: Z = 0.11 (P = 0.91)								
Test for subgroup differences: Chi² = 0.64, df = 1 (P = 0.42), I² = 0%								



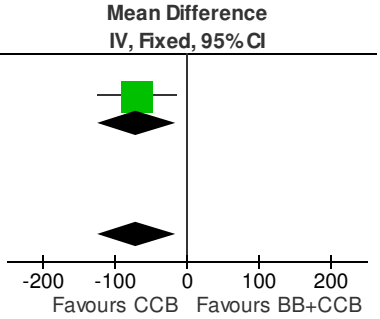
2.8 Nitroglycerin tablets/week

Study or Subgroup	CCB Mean	CCB SD	CCB Total	BB+CCB Mean	BB+CCB SD	BB+CCB Total	Weight	Mean Difference IV, Fixed, 95% CI
2.8.1 Nifedipine vs. Propranolol+Nifedipine								
Kawanishi 1992	0.7	1.6	16	1.1	2.2	19	100.0%	-0.40 [-1.66, 0.86]
Subtotal (95% CI)			**16**			**19**	**100.0%**	**-0.40 [-1.66, 0.86]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.62 (P = 0.53)								
Total (95% CI)			**16**			**19**	**100.0%**	**-0.40 [-1.66, 0.86]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.62 (P = 0.53)								
Test for subgroup differences: Not applicable								



2.9 Time to 1 mm ST segment depression

Study or Subgroup	CCB Mean	CCB SD	CCB Total	BB+CCB Mean	BB+CCB SD	BB+CCB Total	Weight	Mean Difference IV, Fixed, 95% CI
2.9.1 Nifedipine vs. Metoprolol+Nifedipine								
Savonitto 1996 (IMAGE)	37	141.28	62	107	166.4	59	100.0%	-70.00 [-125.13, -14.87]
Subtotal (95% CI)			**62**			**59**	**100.0%**	**-70.00 [-125.13, -14.87]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 2.49 (P = 0.01)								
Total (95% CI)			**62**			**59**	**100.0%**	**-70.00 [-125.13, -14.87]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 2.49 (P = 0.01)								
Test for subgroup differences: Not applicable								

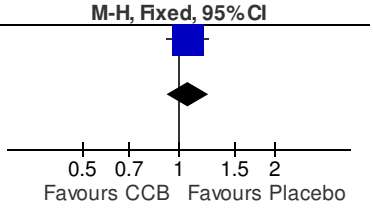


1 CCB +basic regimen vs. Placebo +basic regimen

1.1 All cause mortality

Study or Subgroup	CCB Events	CCB Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Poole-Wilson 2004(ACTION)	310	3825	291	3840	100.0%	1.07 [0.92, 1.25]
Total (95% CI)		**3825**		**3840**	**100.0%**	**1.07 [0.92, 1.25]**
Total events	310		291			

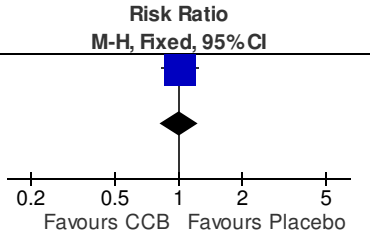
Heterogeneity: Not applicable
Test for overall effect: Z = 0.86 (P = 0.39)



1.2 Cardiovascular or unknown death

Study or Subgroup	CCB Events	CCB Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Poole-Wilson 2004(ACTION)	178	3825	177	3840	100.0%	1.01 [0.82, 1.24]
Total (95% CI)		**3825**		**3840**	**100.0%**	**1.01 [0.82, 1.24]**
Total events	178		177			

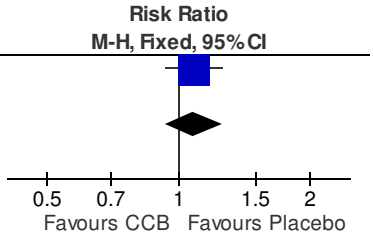
Heterogeneity: Not applicable
Test for overall effect: Z = 0.09 (P = 0.93)



1.3 MI

Study or Subgroup	CCB Events	CCB Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Poole-Wilson 2004(ACTION)	320	3825	296	3840	100.0%	1.09 [0.93, 1.26]
Total (95% CI)		**3825**		**3840**	**100.0%**	**1.09 [0.93, 1.26]**
Total events	320		296			

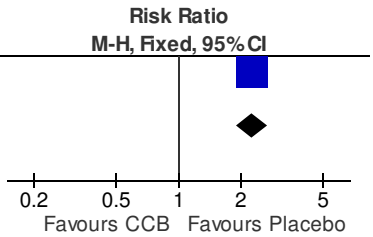
Heterogeneity: Not applicable
Test for overall effect: Z = 1.06 (P = 0.29)



1.4 Withdrawal due to adverse effects

Study or Subgroup	CCB Events	CCB Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Poole-Wilson 2004(ACTION)	389	3825	172	3840	100.0%	2.27 [1.91, 2.70]
Total (95% CI)		**3825**		**3840**	**100.0%**	**2.27 [1.91, 2.70]**
Total events	389		172			

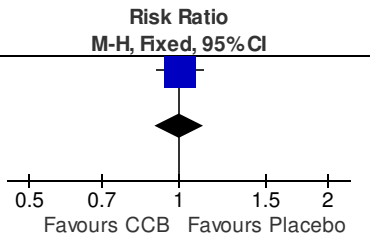
Heterogeneity: Not applicable
Test for overall effect: Z = 9.25 (P < 0.00001)



1.5 combined outcome (death, acute MI, refractory angina, new overt HF, debilitating stroke, peripheral revas) (age >65yrs)

Study or Subgroup	CCB Events	CCB Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Poole-Wilson 2004(ACTION)	467	1772	466	1776	100.0%	1.00 [0.90, 1.12]
Total (95% CI)		**1772**		**1776**	**100.0%**	**1.00 [0.90, 1.12]**
Total events	467		466			

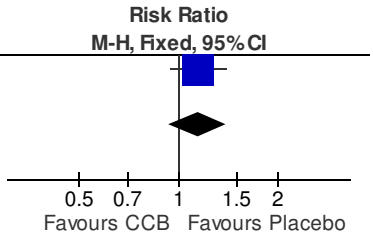
Heterogeneity: Not applicable
Test for overall effect: Z = 0.08 (P = 0.94)



1.6 combined outcome (death, acute MI, refractory angina, new overt HF, debilitating stroke, peripheral revas) (females)

Study or Subgroup	CCB Events	CCB Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Poole-Wilson 2004(ACTION)	166	784	147	797	100.0%	1.15 [0.94, 1.40]
Total (95% CI)		**784**		**797**	**100.0%**	**1.15 [0.94, 1.40]**
Total events	166		147			

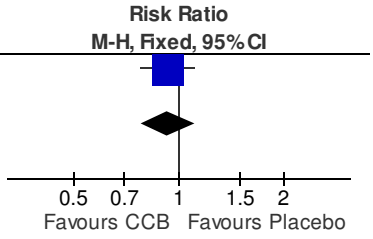
Heterogeneity: Not applicable
Test for overall effect: Z = 1.36 (P = 0.17)



1.7 combined outcome (death, acute MI, refractory angina, new overt HF, debilitating stroke, peripheral revas) (diabetes)

Study or Subgroup	CCB Events	CCB Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Poole-Wilson 2004(ACTION)	164	565	170	545	100.0%	0.93 [0.78, 1.11]
Total (95% CI)		**565**		**545**	**100.0%**	**0.93 [0.78, 1.11]**
Total events	164		170			

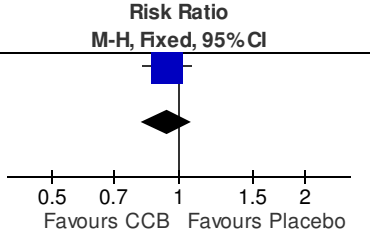
Heterogeneity: Not applicable
Test for overall effect: Z = 0.79 (P = 0.43)



1.8 Combined outcome (death from any cause, acute MI, refractory angina, new overt HF, debilitating stroke , peripheral revas)(age <65 years)

Study or Subgroup	CCB Events	CCB Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Poole-Wilson 2004(ACTION)	337	2053	362	2064	100.0%	0.94 [0.82, 1.07]
Total (95% CI)		**2053**		**2064**	**100.0%**	**0.94 [0.82, 1.07]**
Total events	337		362			

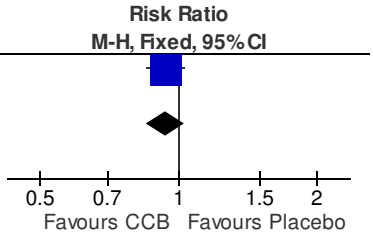
Heterogeneity: Not applicable
Test for overall effect: Z = 0.96 (P = 0.34)



1.9 combined outcome (death from any cause, acute MI, refractory angina, new overt HF, debilitating stroke ,peripheral revas)(males)

Study or Subgroup	CCB Events	CCB Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Poole-Wilson 2004(ACTION)	638	3041	681	3043	100.0%	0.94 [0.85, 1.03]
Total (95% CI)		**3041**		**3043**	**100.0%**	**0.94 [0.85, 1.03]**
Total events	638		681			

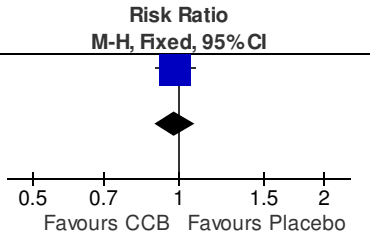
Heterogeneity: Not applicable
Test for overall effect: Z = 1.32 (P = 0.19)



1.10 combined outcome (death from any cause, acute MI, refractory angina, new overt HF, debilitating stroke ,peripheral revas)(no diabetes)

Study or Subgroup	CCB Events	CCB Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Poole-Wilson 2004(ACTION)	640	3260	658	3295	100.0%	0.98 [0.89, 1.08]
Total (95% CI)		**3260**		**3295**	**100.0%**	**0.98 [0.89, 1.08]**
Total events	640		658			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.34 (P = 0.73)

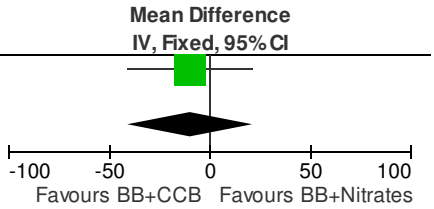


1 BB+Nitrates vs. BB+CCB

1.1 Exercise time (Sec)

Study or Subgroup	BB +Nitrates Mean	SD	Total	BB +CCB Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
De Vries 1994	12	77.2	46	22	75.2	46	100.0%	-10.00 [-41.14, 21.14]
Total (95% CI)			**46**			**46**	**100.0%**	**-10.00 [-41.14, 21.14]**

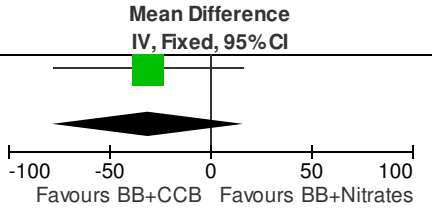
Heterogeneity: Not applicable
Test for overall effect: Z = 0.63 (P = 0.53)



1.2 Time to onset of angina (Sec)

Study or Subgroup	BB +Nitrates Mean	SD	Total	BB +CCB Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
De Vries 1994	21	115.9	46	52	114.5	46	100.0%	-31.00 [-78.08, 16.08]
Total (95% CI)			**46**			**46**	**100.0%**	**-31.00 [-78.08, 16.08]**

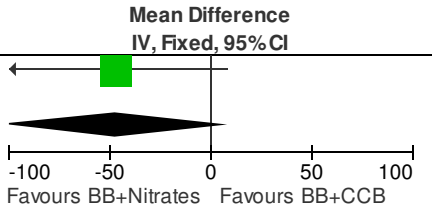
Heterogeneity: Not applicable
Test for overall effect: Z = 1.29 (P = 0.20)



1.3 Time to ST segment depression (sec)

Study or Subgroup	BB +Nitrates Mean	SD	Total	BB +CCB Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
De Vries 1994	3	136.2	46	50	134.9	46	100.0%	-47.00 [-102.40, 8.40]
Total (95% CI)			**46**			**46**	**100.0%**	**-47.00 [-102.40, 8.40]**

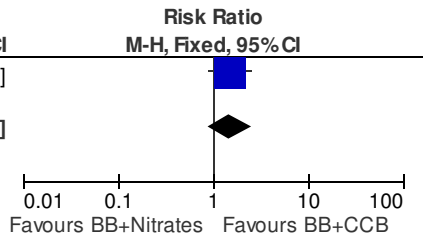
Heterogeneity: Not applicable
Test for overall effect: Z = 1.66 (P = 0.10)



1.4 Adverse effects (overall)

Study or Subgroup	BB +Nitrates Events	Total	BB +CCB Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
De Vries 1994	22	46	14	43	100.0%	1.47 [0.87, 2.48]
Total (95% CI)		**46**		**43**	**100.0%**	**1.47 [0.87, 2.48]**
Total events	22		14			

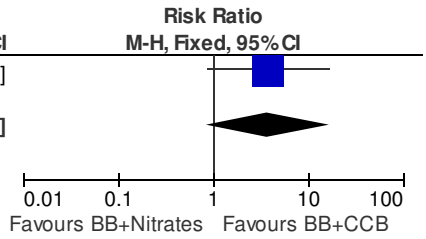
Heterogeneity: Not applicable
Test for overall effect: Z = 1.43 (P = 0.15)



1.5 Stopping due to adverse events

Study or Subgroup	BB +Nitrates Events	Total	BB +CCB Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
De Vries 1994	8	46	2	43	100.0%	3.74 [0.84, 16.64]
Total (95% CI)		**46**		**43**	**100.0%**	**3.74 [0.84, 16.64]**
Total events	8		2			

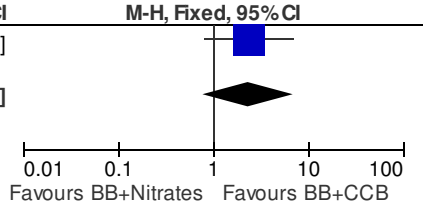
Heterogeneity: Not applicable
Test for overall effect: Z = 1.73 (P = 0.08)



1.6 Headache

Study or Subgroup	BB +Nitrates Events	Total	BB +CCB Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
De Vries 1994	10	46	4	43	100.0%	2.34 [0.79, 6.90]
Total (95% CI)		**46**		**43**	**100.0%**	**2.34 [0.79, 6.90]**
Total events	10		4			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.54 (P = 0.12)

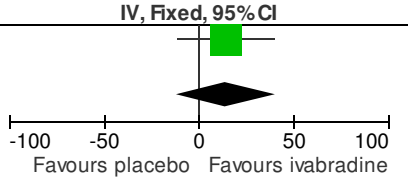


1 Ivabradine vs placebo

1.1 Time to angina onset (sec) (trough change from baseline) - 14 days

Study or Subgroup	Ivabradine Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Borer 2003	38.8	81.7	59	24.7	64.2	68	100.0%	14.10 [-11.73, 39.93]
Total (95% CI)			**59**			**68**	**100.0%**	**14.10 [-11.73, 39.93]**

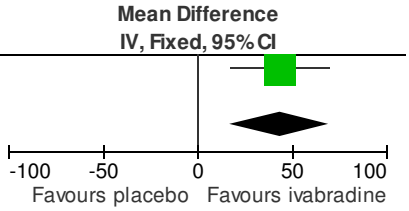
Heterogeneity: Not applicable
Test for overall effect: Z = 1.07 (P = 0.28)



1.2 Time to angina onset (sec) (peak change from baseline - 14 days

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Borer 2003	72.1	83.1	59	28.9	66.5	68	100.0%	43.20 [16.75, 69.65]
Total (95% CI)			**59**			**68**	**100.0%**	**43.20 [16.75, 69.65]**

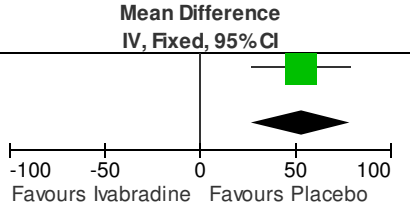
Heterogeneity: Not applicable
Test for overall effect: Z = 3.20 (P = 0.001)



1.3 Time to 1 mm S depression (sec) (at peak of drug activity) - 14 days

Study or Subgroup	Ivabradine Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Borer 2003	62.8	79.7	59	9.9	68.5	68	100.0%	52.90 [26.85, 78.95]
Total (95% CI)			**59**			**68**	**100.0%**	**52.90 [26.85, 78.95]**

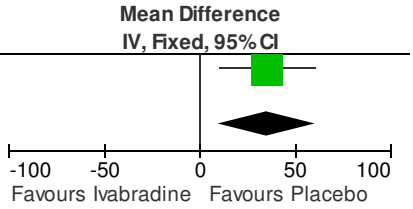
Heterogeneity: Not applicable
Test for overall effect: Z = 3.98 (P < 0.0001)



1.4 Time to 1 mm ST depression (sec) (at trough) - 14 days

Study or Subgroup	Ivabradine Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Borer 2003	44.1	80.1	59	9	63.6	68	100.0%	35.10 [9.68, 60.52]
Total (95% CI)			**59**			**68**	**100.0%**	**35.10 [9.68, 60.52]**

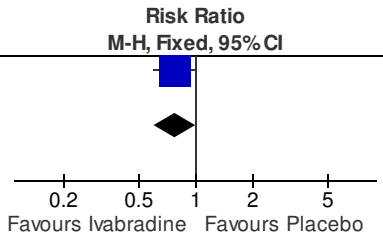
Heterogeneity: Not applicable
Test for overall effect: Z = 2.71 (P = 0.007)



1.5 With limiting angina - CV death or hospitalisation for MI or HF - median 18 months

Study or Subgroup	Ivabradine Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Fox 2009 (BEAUTIFUL)	88	734	120	773	100.0%	0.77 [0.60, 1.00]
Total (95% CI)		**734**		**773**	**100.0%**	**0.77 [0.60, 1.00]**
Total events	88		120			

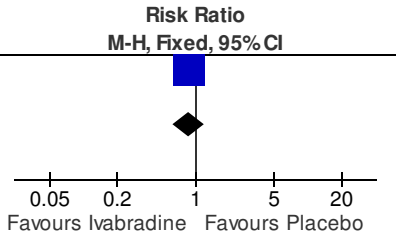
Heterogeneity: Not applicable
Test for overall effect: Z = 1.98 (P = 0.05)



1.6 With limiting angina - all cause mortality - median 18 months

Study or Subgroup	Ivabradine Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Fox 2009 (BEAUTIFUL)	64	734	77	773	100.0%	0.88 [0.64, 1.20]
Total (95% CI)		**734**		**773**	**100.0%**	**0.88 [0.64, 1.20]**
Total events	64		77			

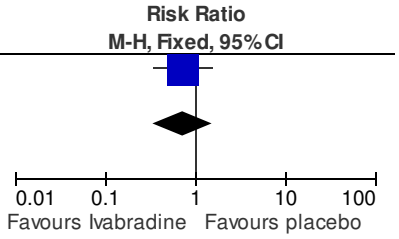
Heterogeneity: Not applicable
Test for overall effect: Z = 0.83 (P = 0.41)



1.7 With limiting angina - Cardiac death - median 18 months

Study or Subgroup	Experimental Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Fox 2009 (BEAUTIFUL)	11	734	16	773	100.0%	0.72 [0.34, 1.55]
Total (95% CI)		**734**		**773**	**100.0%**	**0.72 [0.34, 1.55]**
Total events	11		16			

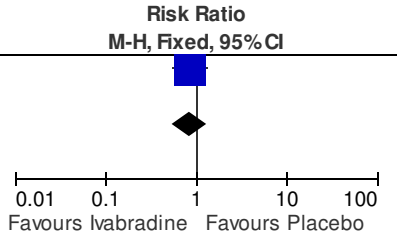
Heterogeneity: Not applicable
Test for overall effect: Z = 0.83 (P = 0.41)



1.8 With limiting angina - hospitalisation for HF - median 18 months

Study or Subgroup	Experimental Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Fox 2009 (BEAUTIFUL)	33	734	41	773	100.0%	0.85 [0.54, 1.33]
Total (95% CI)		**734**		**773**	**100.0%**	**0.85 [0.54, 1.33]**
Total events	33		41			

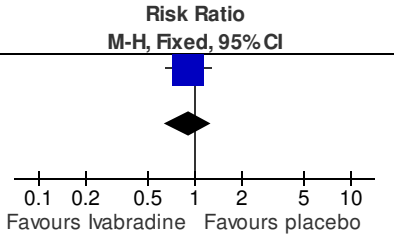
Heterogeneity: Not applicable
Test for overall effect: Z = 0.72 (P = 0.47)



1.9 With limiting angina - Hospitalisation for MI or unstable angina - median 18 months

Study or Subgroup	Ivabradine Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Fox 2009 (BEAUTIFUL)	56	734	65	773	100.0%	0.91 [0.64, 1.28]
Total (95% CI)		**734**		**773**	**100.0%**	**0.91 [0.64, 1.28]**
Total events	56		65			

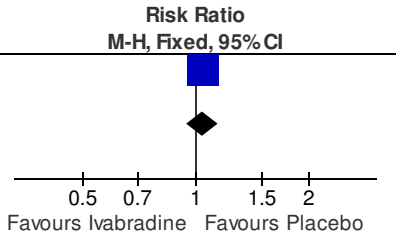
Heterogeneity: Not applicable
Test for overall effect: Z = 0.56 (P = 0.58)



1.10 Without limiting angina - CV death or hospitalisation for MI or HF - median 18 months

Study or Subgroup	Ivabradine Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Fox 2009 (BEAUTIFUL)	756	4745	712	4665	100.0%	1.04 [0.95, 1.15]
Total (95% CI)		**4745**		**4665**	**100.0%**	**1.04 [0.95, 1.15]**
Total events	756		712			

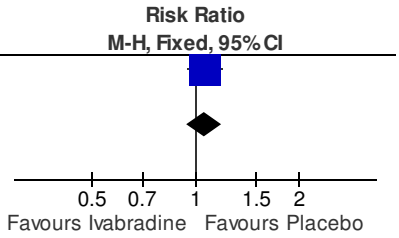
Heterogeneity: Not applicable
Test for overall effect: Z = 0.90 (P = 0.37)



1.11 Without limiting angina - all cause mortality - median 18 months

Study or Subgroup	Ivabradine Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Fox 2009 (BEAUTIFUL)	508	4745	470	4665	100.0%	1.06 [0.94, 1.20]
Total (95% CI)		**4745**		**4665**	**100.0%**	**1.06 [0.94, 1.20]**
Total events	508		470			

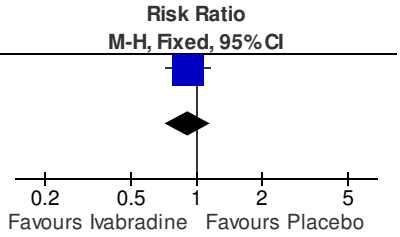
Heterogeneity: Not applicable
Test for overall effect: Z = 1.00 (P = 0.32)



1.12 Without limiting angina - Cardiac death - median 18 months

Study or Subgroup	Experimental Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Fox 2009 (BEAUTIFUL)	125	4745	135	4665	100.0%	0.91 [0.72, 1.16]
Total (95% CI)		**4745**		**4665**	**100.0%**	**0.91 [0.72, 1.16]**
Total events	125		135			

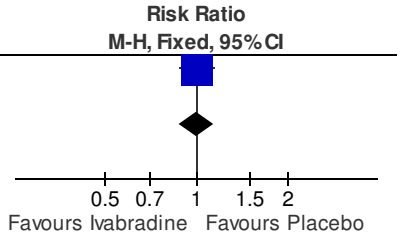
Heterogeneity: Not applicable
Test for overall effect: Z = 0.77 (P = 0.44)



1.13 Without limiting angina - hospitalisation for HF - median 18 months

Study or Subgroup	Experimental Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Fox 2009 (BEAUTIFUL)	393	4745	386	4665	100.0%	1.00 [0.87, 1.15]
Total (95% CI)		**4745**		**4665**	**100.0%**	**1.00 [0.87, 1.15]**
Total events	393		386			

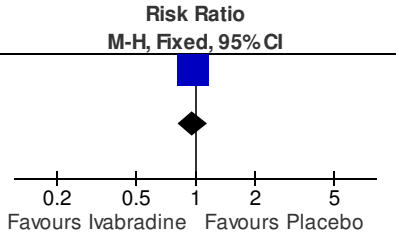
Heterogeneity: Not applicable
Test for overall effect: Z = 0.01 (P = 0.99)



1.14 Without limiting angina - Hospitalisation for MI or unstable angina - median 18 months

Study or Subgroup	Ivabradine Events	Total	Palcebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Fox 2009 (BEAUTIFUL)	247	4745	252	4665	100.0%	0.96 [0.81, 1.14]
Total (95% CI)		**4745**		**4665**	**100.0%**	**0.96 [0.81, 1.14]**
Total events	247		252			

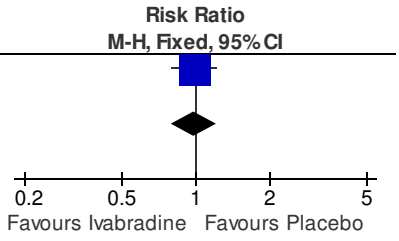
Heterogeneity: Not applicable
Test for overall effect: Z = 0.43 (P = 0.67)



1.15 All serious adverse events

Study or Subgroup	Ivabradine Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Fox 2009 (BEAUTIFUL)	135	734	144	773	100.0%	0.99 [0.80, 1.22]
Total (95% CI)		**734**		**773**	**100.0%**	**0.99 [0.80, 1.22]**
Total events	135		144			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.12 (P = 0.91)

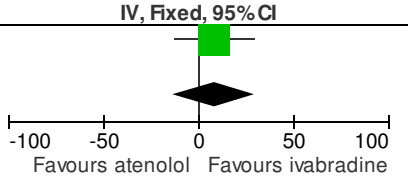


2 Ivabradine vs atenolol

2.1 Total exercise duration (sec)(trough change from baseline) - 16 weeks

Study or Subgroup	Ivabradine Mean	SD	Total	Atenolol Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Tardif 2005	86.8	129	300	78.8	133.4	286	100.0%	8.00 [-13.26, 29.26]
Total (95% CI)			**300**			**286**	**100.0%**	**8.00 [-13.26, 29.26]**

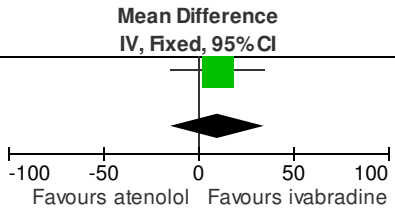
Heterogeneity: Not applicable
Test for overall effect: Z = 0.74 (P = 0.46)



2.2 Time to angina onset (sec) (trough change from baseline) - 16 weeks

Study or Subgroup	Ivabradine Mean	SD	Total	Atenolol Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Tardif 2005	145.2	153.4	300	135.2	154.7	286	100.0%	10.00 [-14.96, 34.96]
Total (95% CI)			**300**			**286**	**100.0%**	**10.00 [-14.96, 34.96]**

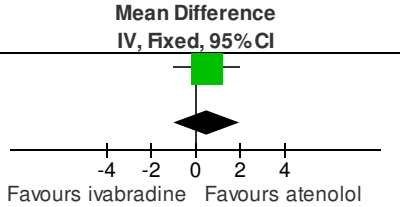
Heterogeneity: Not applicable
Test for overall effect: Z = 0.79 (P = 0.43)



2.3 Weekly number of angina attacks - 16 weeks

Study or Subgroup	Ivabradine Mean	SD	Total	Atenolol Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Tardif 2005	-2.2	4.4	307	-2.7	12.3	294	100.0%	0.50 [-0.99, 1.99]
Total (95% CI)			**307**			**294**	**100.0%**	**0.50 [-0.99, 1.99]**

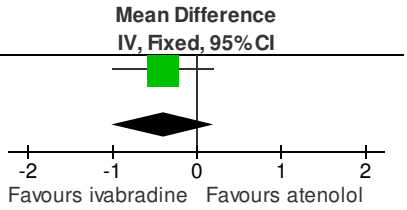
Heterogeneity: Not applicable
Test for overall effect: Z = 0.66 (P = 0.51)



2.4 Short-acting nitrate consumption units/week - 16 weeks

Study or Subgroup	Ivabradine Mean	SD	Total	Atenolol Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Tardif 2005	-1.6	4.1	307	-1.2	3.4	294	100.0%	-0.40 [-1.00, 0.20]
Total (95% CI)			**307**			**294**	**100.0%**	**-0.40 [-1.00, 0.20]**

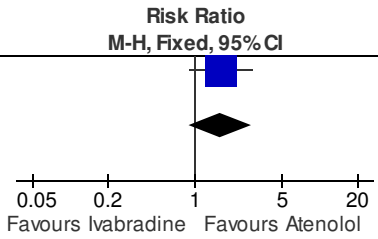
Heterogeneity: Not applicable
Test for overall effect: Z = 1.30 (P = 0.19)



2.5 Withdrawal due to AEs-16 weeks

Study or Subgroup	Ivabradine Events	Total	Atenolol Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Tardif 2005	28	315	17	307	100.0%	1.61 [0.90, 2.87]
Total (95% CI)		**315**		**307**	**100.0%**	**1.61 [0.90, 2.87]**
Total events	28		17			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.59 (P = 0.11)

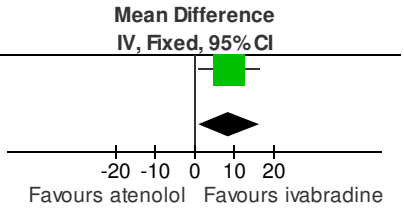


3 Ivabradine +atenolol vs atenolol+ placebo

3.1 Total exercise duration (sec) (change from baseline) - 2 months

Study or Subgroup	Ivabradine + atenolol Mean	SD	Total	atenolol Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Tardif 2009	15.5	60	441	6.8	56.5	434	100.0%	8.70 [0.98, 16.42]
Total (95% CI)			**441**			**434**	**100.0%**	**8.70 [0.98, 16.42]**

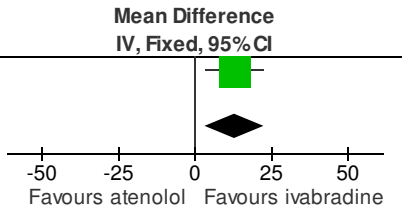
Heterogeneity: Not applicable
Test for overall effect: Z = 2.21 (P = 0.03)



3.2 Time to angina onset (sec) (change from baseline) - 2 mths

Study or Subgroup	Ivabradine + atenolol Mean	SD	Total	atenolol Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Tardif 2009	30.2	72.2	441	17.2	72.3	434	100.0%	13.00 [3.43, 22.57]
Total (95% CI)			**441**			**434**	**100.0%**	**13.00 [3.43, 22.57]**

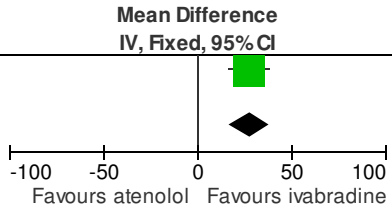
Heterogeneity: Not applicable
Test for overall effect: Z = 2.66 (P = 0.008)



3.3 Time to 1 mm S depression (sec) (change from baseline)- 2months

Study or Subgroup	Ivabradine + atenolol Mean	SD	Total	atenolol Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Tardif 2009	35	84.1	441	7.8	82.6	434	100.0%	27.20 [16.15, 38.25]
Total (95% CI)			**441**			**434**	**100.0%**	**27.20 [16.15, 38.25]**

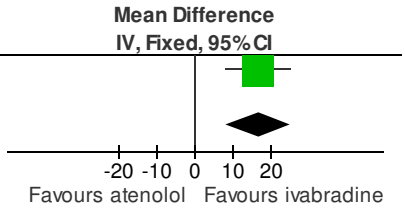
Heterogeneity: Not applicable
Test for overall effect: Z = 4.83 (P < 0.00001)



3.4 Total exercise duration (sec) (change from baseline-4 months

Study or Subgroup	Ivabradine + atenolol Mean	SD	Total	atenolol Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Tardif 2009	24.3	65.3	441	7.7	63.8	434	100.0%	16.60 [8.05, 25.15]
Total (95% CI)			**441**			**434**	**100.0%**	**16.60 [8.05, 25.15]**

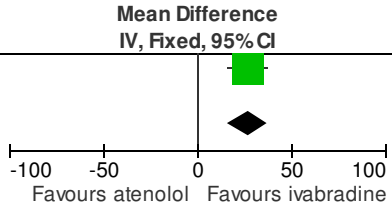
Heterogeneity: Not applicable
Test for overall effect: Z = 3.80 (P = 0.0001)



3.5 Time to onset of angina(sec) (change from baseline) - 4 months

Study or Subgroup	Ivabradine + atenolol Mean	SD	Total	atenolol Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Tardif 2009	49.1	83.3	441	22.7	79.1	434	100.0%	26.40 [15.64, 37.16]
Total (95% CI)			**441**			**434**	**100.0%**	**26.40 [15.64, 37.16]**

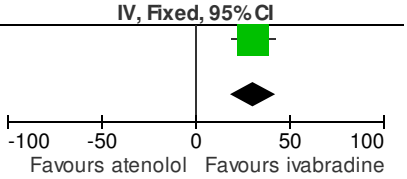
Heterogeneity: Not applicable
Test for overall effect: Z = 4.81 (P < 0.00001)



3.6 Time to 1 mm ST depression (sec) (change from baseline-4 months

Study or Subgroup	Ivabradine + atenolol Mean	SD	Total	atenolol Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Tardif 2009	45.7	93	441	15.4	86.6	434	100.0%	30.30 [18.40, 42.20]
Total (95% CI)			**441**			**434**	**100.0%**	**30.30 [18.40, 42.20]**

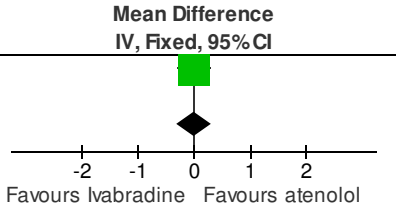
Heterogeneity: Not applicable
Test for overall effect: Z = 4.99 (P < 0.00001)



3.7 angina attacks/week

Study or Subgroup	Ivabradine + atenolol Mean	SD	Total	atenolol+placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Tardif 2009	0.9	2.4	441	0.9	2.1	434	100.0%	0.00 [-0.30, 0.30]
Total (95% CI)			**441**			**434**	**100.0%**	**0.00 [-0.30, 0.30]**

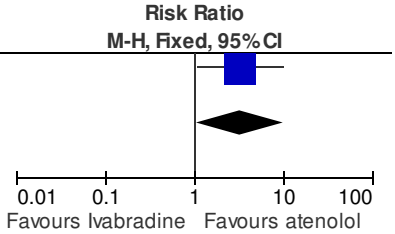
Heterogeneity: Not applicable
Test for overall effect: Z = 0.00 (P = 1.00)



3.8 Adverse events (4 months)

Study or Subgroup	Ivabradine + atenolol Events	Total	atenolol Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Tardif 2009	13	441	4	434	100.0%	3.20 [1.05, 9.73]
Total (95% CI)		**441**		**434**	**100.0%**	**3.20 [1.05, 9.73]**
Total events	13		4			

Heterogeneity: Not applicable
Test for overall effect: Z = 2.05 (P = 0.04)

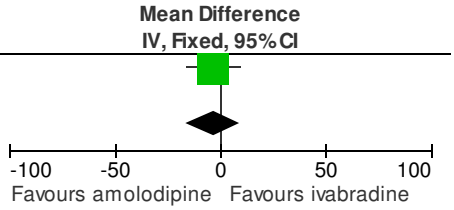


4 Ivabradine vs amolodipine

4.1 Total exercise duration (sec) - 3 months

Study or Subgroup	Ivabradine Mean	SD	Total	amolodipine Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Ruzyllo 2007	27.6	91.7	381	31.2	92	398	100.0%	-3.60 [-16.50, 9.30]
Total (95% CI)			**381**			**398**	**100.0%**	**-3.60 [-16.50, 9.30]**

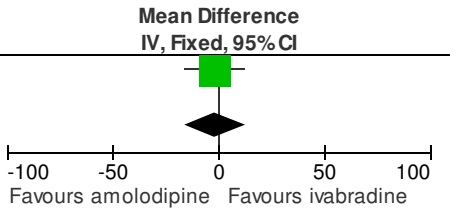
Heterogeneity: Not applicable
Test for overall effect: Z = 0.55 (P = 0.58)



4.2 Time angina onset (sec) - 3 months

Study or Subgroup	Ivabradine Mean	SD	Total	amolodipine Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Ruzyllo 2007	64.7	104.9	381	66.6	99.1	398	100.0%	-1.90 [-16.24, 12.44]
Total (95% CI)			**381**			**398**	**100.0%**	**-1.90 [-16.24, 12.44]**

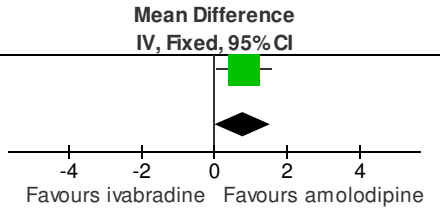
Heterogeneity: Not applicable
Test for overall effect: Z = 0.26 (P = 0.80)



4.3 Short-acting nitrate use (units/week) - 3 months

Study or Subgroup	Ivabradine Mean	SD	Total	amolodipine Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Ruzyllo 2007	-1.9	4.5	389	-2.7	6.3	398	100.0%	0.80 [0.04, 1.56]
Total (95% CI)			**389**			**398**	**100.0%**	**0.80 [0.04, 1.56]**

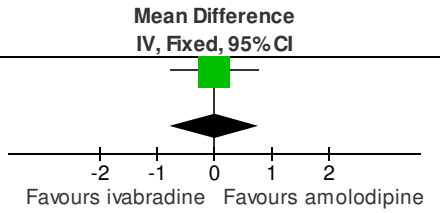
Heterogeneity: Not applicable
Test for overall effect: Z = 2.05 (P = 0.04)



4.4 Frequency of angina attacks/week - 3 months

Study or Subgroup	Ivabradine Mean	SD	Total	amolodipine Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Ruzyllo 2007	-3	5	389	-3	6	398	100.0%	0.00 [-0.77, 0.77]
Total (95% CI)			**389**			**398**	**100.0%**	**0.00 [-0.77, 0.77]**

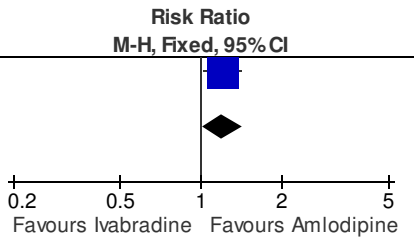
Heterogeneity: Not applicable
Test for overall effect: Z = 0.00 (P = 1.00)



4.5 Adverse events - 3 months

Study or Subgroup	Ivabradine Events	Total	amolodipine Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Ruzyllo 2007	181	400	152	404	100.0%	1.20 [1.02, 1.42]
Total (95% CI)		**400**		**404**	**100.0%**	**1.20 [1.02, 1.42]**
Total events	181		152			

Heterogeneity: Not applicable
Test for overall effect: Z = 2.19 (P = 0.03)

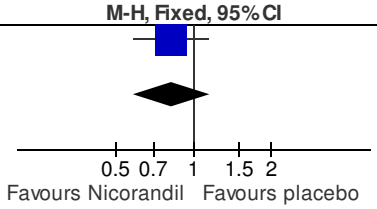


1 Nicorandil vs. Placebo (Follow-up 1.6 years)

1.1 CHD death

Study or Subgroup	Nicorandil Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
IONA (2002)	60	2565	73	2561	100.0%	0.82 [0.59, 1.15]
Total (95% CI)		**2565**		**2561**	**100.0%**	**0.82 [0.59, 1.15]**
Total events	60		73			

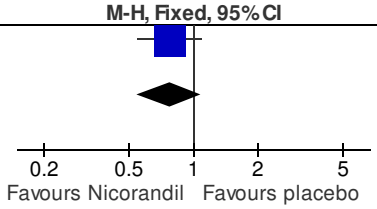
Heterogeneity: Not applicable
Test for overall effect: Z = 1.15 (P = 0.25)



1.2 Non fatal MI

Study or Subgroup	Nicorandil Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
IONA (2002)	56	2565	72	2561	100.0%	0.78 [0.55, 1.10]
Total (95% CI)		**2565**		**2561**	**100.0%**	**0.78 [0.55, 1.10]**
Total events	56		72			

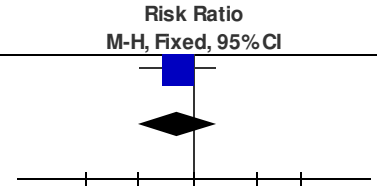
Heterogeneity: Not applicable
Test for overall effect: Z = 1.44 (P = 0.15)



1.3 Unstable Angina

Study or Subgroup	Nicorandil Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
IONA (2002)	115	2565	127	2561	100.0%	0.90 [0.71, 1.16]
Total (95% CI)		**2565**		**2561**	**100.0%**	**0.90 [0.71, 1.16]**
Total events	115		127			

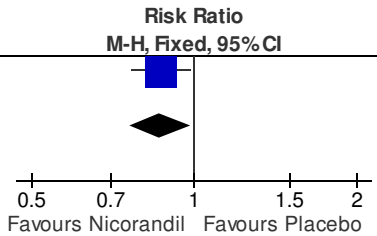
Heterogeneity: Not applicable
Test for overall effect: Z = 0.80 (P = 0.42)



1.4 All cardiovascular events

Study or Subgroup	Nicorandil Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
IONA (2002)	378	2565	436	2561	100.0%	0.87 [0.76, 0.98]
Total (95% CI)		**2565**		**2561**	**100.0%**	**0.87 [0.76, 0.98]**
Total events	378		436			

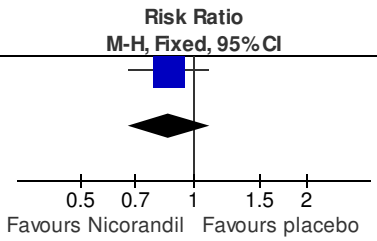
Heterogeneity: Not applicable
Test for overall effect: Z = 2.24 (P = 0.03)



1.5 All cause mortality

Study or Subgroup	Nicorandil Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
IONA (2002)	111	2565	129	2561	100.0%	0.86 [0.67, 1.10]
Total (95% CI)		**2565**		**2561**	**100.0%**	**0.86 [0.67, 1.10]**
Total events	111		129			

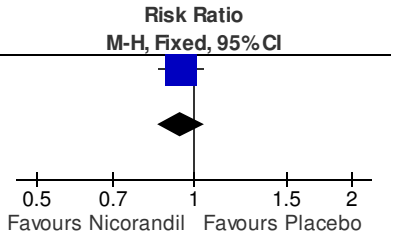
Heterogeneity: Not applicable
Test for overall effect: Z = 1.20 (P = 0.23)



1.6 Worsening of angina status

Study or Subgroup	Nicorandil Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
IONA (2002)	569	2565	602	2561	100.0%	0.94 [0.85, 1.04]
Total (95% CI)		**2565**		**2561**	**100.0%**	**0.94 [0.85, 1.04]**
Total events	569		602			

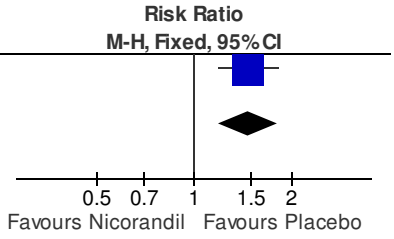
Heterogeneity: Not applicable
Test for overall effect: Z = 1.13 (P = 0.26)



1.7 GI disturbances

Study or Subgroup	Nicorandil Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
IONA (2002)	194	2565	132	2561	100.0%	1.47 [1.18, 1.82]
Total (95% CI)		**2565**		**2561**	**100.0%**	**1.47 [1.18, 1.82]**
Total events	194		132			

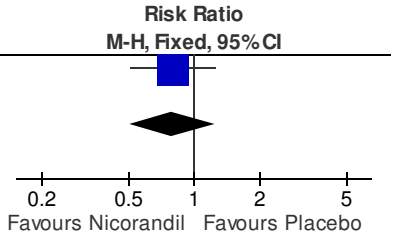
Heterogeneity: Not applicable
Test for overall effect: Z = 3.51 (P = 0.0005)



1.8 Combined outcome (diabetes subgroup)

Study or Subgroup	Nicorandil Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
IONA (2004)	27	197	40	232	100.0%	0.79 [0.51, 1.25]
Total (95% CI)		**197**		**232**	**100.0%**	**0.79 [0.51, 1.25]**
Total events	27		40			

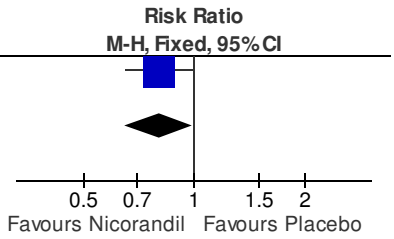
Heterogeneity: Not applicable
Test for overall effect: Z = 1.00 (P = 0.32)



1.9 Combined outcomes (age subgroup >70 yrs)

Study or Subgroup	Nicorandil Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
IONA (2004)	131	927	167	948	100.0%	0.80 [0.65, 0.99]
Total (95% CI)		**927**		**948**	**100.0%**	**0.80 [0.65, 0.99]**
Total events	131		167			

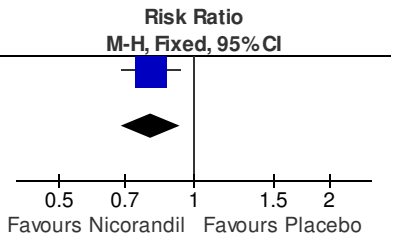
Heterogeneity: Not applicable
Test for overall effect: Z = 2.06 (P = 0.04)



1.10 combined outcomes (male subgroup)

Study or Subgroup	Nicorandil Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
IONA (2004)	251	1962	311	1948	100.0%	0.80 [0.69, 0.93]
Total (95% CI)		**1962**		**1948**	**100.0%**	**0.80 [0.69, 0.93]**
Total events	251		311			

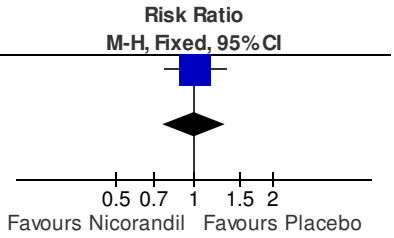
Heterogeneity: Not applicable
Test for overall effect: Z = 2.82 (P = 0.005)



1.11 Combined outcomes (female subgroup)

Study or Subgroup	Nicorandil Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
IONA (2004)	86	603	87	613	100.0%	1.00 [0.76, 1.32]
Total (95% CI)		**603**		**613**	**100.0%**	**1.00 [0.76, 1.32]**
Total events	86		87			

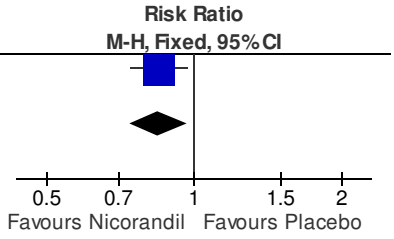
Heterogeneity: Not applicable
Test for overall effect: Z = 0.03 (P = 0.97)



1.12 Composite (CHD death,non fatal MI or hospital adm. for chest pain)

Study or Subgroup	Nicorandil Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
IONA (2002)	337	2565	398	2561	100.0%	0.85 [0.74, 0.97]
Total (95% CI)		**2565**		**2561**	**100.0%**	**0.85 [0.74, 0.97]**
Total events	337		398			

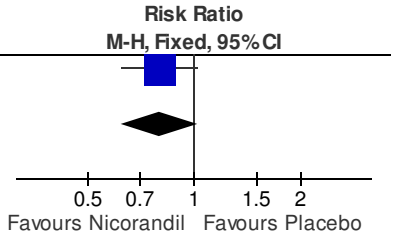
Heterogeneity: Not applicable
Test for overall effect: Z = 2.45 (P = 0.01)



1.13 composite (CHD death or non fatal MI)

Study or Subgroup	Nicorandil Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
IONA (2002)	107	2565	134	2561	100.0%	0.80 [0.62, 1.02]
Total (95% CI)		**2565**		**2561**	**100.0%**	**0.80 [0.62, 1.02]**
Total events	107		134			

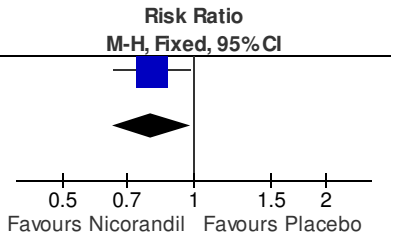
Heterogeneity: Not applicable
Test for overall effect: Z = 1.79 (P = 0.07)



1.14 Compiste (CHD death, non fatal MI, or unstable angina)

Study or Subgroup	Nicorandil Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
IONA (2002)	156	2565	195	2561	100.0%	0.80 [0.65, 0.98]
Total (95% CI)		**2565**		**2561**	**100.0%**	**0.80 [0.65, 0.98]**
Total events	156		195			

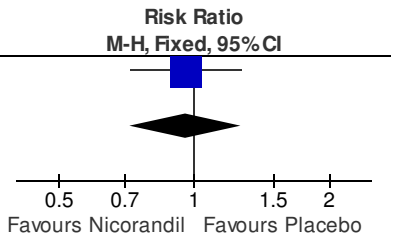
Heterogeneity: Not applicable
Test for overall effect: Z = 2.17 (P = 0.03)



1.15 Combined outcome (age subgroup 65-70 yrs)

Study or Subgroup	Nicorandil Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
IONA (2004)	82	599	81	567	100.0%	0.96 [0.72, 1.27]
Total (95% CI)		**599**		**567**	**100.0%**	**0.96 [0.72, 1.27]**
Total events	82		81			

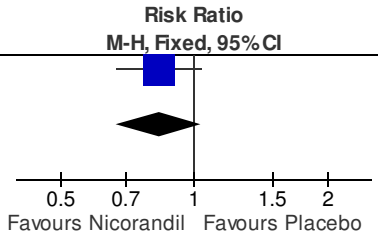
Heterogeneity: Not applicable
Test for overall effect: Z = 0.29 (P = 0.77)



1.16 Combined outcomes (age subgroup <65 yrs)

Study or Subgroup	Nicorandil Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
IONA (2004)	124	1039	150	1046	100.0%	0.83 [0.67, 1.04]
Total (95% CI)		**1039**		**1046**	**100.0%**	**0.83 [0.67, 1.04]**
Total events	124		150			

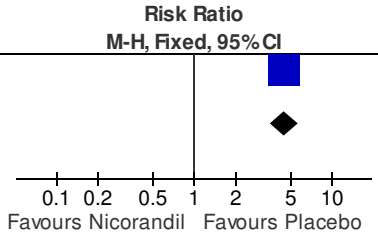
Heterogeneity: Not applicable
Test for overall effect: Z = 1.62 (P = 0.10)



1.17 Headache

Study or Subgroup	Nicorandil Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
IONA (2002)	364	2565	81	2561	100.0%	4.49 [3.55, 5.67]
Total (95% CI)		**2565**		**2561**	**100.0%**	**4.49 [3.55, 5.67]**
Total events	364		81			

Heterogeneity: Not applicable
Test for overall effect: Z = 12.55 (P < 0.00001)

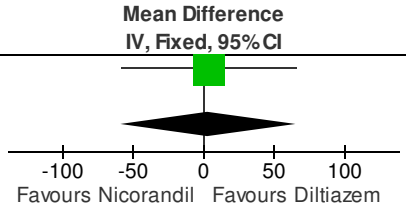


2 Nicorandil vs. Diltiazem (Follow-up 90 days)

2.1 Excercise capacity (work to angina onset)

Study or Subgroup	Nicorandil Mean	SD	Total	Diltiazem Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Guermonprez 1993	48.1	174.7	50	44.7	149.7	56	100.0%	3.40 [-58.91, 65.71]
Total (95% CI)			**50**			**56**	**100.0%**	**3.40 [-58.91, 65.71]**

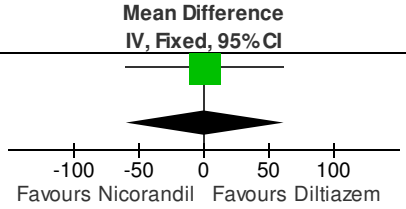
Heterogeneity: Not applicable
Test for overall effect: Z = 0.11 (P = 0.91)



2.2 Excercise capacity (work to ischemic threshold)

Study or Subgroup	Nicorandil Mean	SD	Total	Diltiazem Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Guermonprez 1993	38.7	171.1	50	37.8	145.2	56	100.0%	0.90 [-59.89, 61.69]
Total (95% CI)			**50**			**56**	**100.0%**	**0.90 [-59.89, 61.69]**

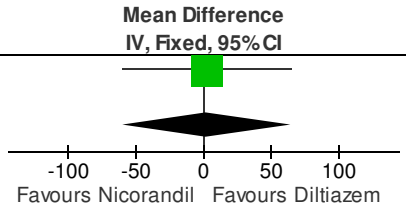
Heterogeneity: Not applicable
Test for overall effect: Z = 0.03 (P = 0.98)



2.3 Excercise capacity (work to peak excercise)

Study or Subgroup	Nicorandil Mean	SD	Total	Diltiazem Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Guermonprez 1993	49.2	172.3	50	46.8	154.2	56	100.0%	2.40 [-60.15, 64.95]
Total (95% CI)			**50**			**56**	**100.0%**	**2.40 [-60.15, 64.95]**

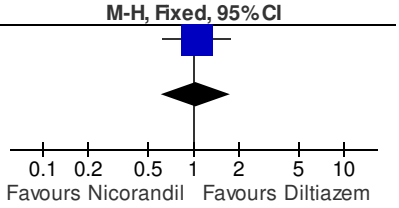
Heterogeneity: Not applicable
Test for overall effect: Z = 0.08 (P = 0.94)



2.4 Adverse events (combined)

Study or Subgroup	Nicorandil Events	Nicorandil Total	Diltiazem Events	Diltiazem Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Guermonprez 1993	19	60	19	63	100.0%	1.05 [0.62, 1.78]
Total (95% CI)		**60**		**63**	**100.0%**	**1.05 [0.62, 1.78]**
Total events	19		19			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.18 (P = 0.86)

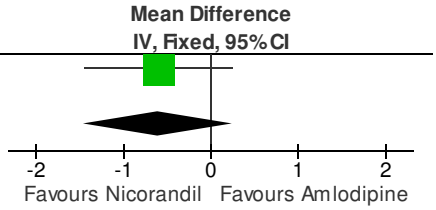


3 Nicorandil vs. Amlodipine (Follow-up 8 weeks)

3.1 ETT (Time to ST-segment depression)

Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Fixed, 95% CI
Chatterjee 1999	5.1	2.3	56	5.7	2.4	62	100.0%	-0.60 [-1.45, 0.25]
Total (95% CI)			**56**			**62**	**100.0%**	**-0.60 [-1.45, 0.25]**

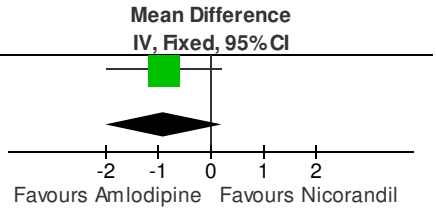
Heterogeneity: Not applicable
Test for overall effect: Z = 1.39 (P = 0.17)



3.2 ETT (Time to onset of anginal pain)

Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Fixed, 95% CI
Chatterjee 1999	6.1	3	56	7	3.1	62	100.0%	-0.90 [-2.00, 0.20]
Total (95% CI)			**56**			**62**	**100.0%**	**-0.90 [-2.00, 0.20]**

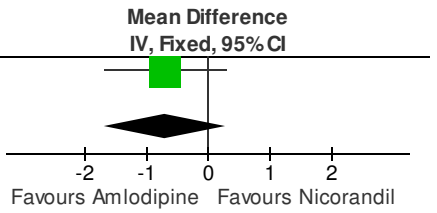
Heterogeneity: Not applicable
Test for overall effect: Z = 1.60 (P = 0.11)



3.3 ETT (Total excercise duration)

Study or Subgroup	Nicorandil Mean	Nicorandil SD	Nicorandil Total	Amlodipine Mean	Amlodipine SD	Amlodipine Total	Weight	Mean Difference IV, Fixed, 95% CI
Chatterjee 1999	7.2	3	56	7.9	2.4	62	100.0%	-0.70 [-1.69, 0.29]
Total (95% CI)			**56**			**62**	**100.0%**	**-0.70 [-1.69, 0.29]**

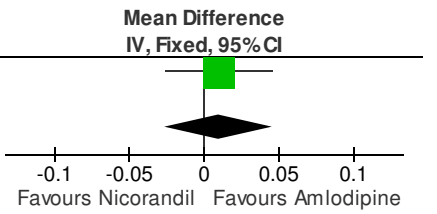
Heterogeneity: Not applicable
Test for overall effect: Z = 1.39 (P = 0.16)



3.4 ETT (Segment depression at maximal identical workload)

Study or Subgroup	Nicorandil Mean	Nicorandil SD	Nicorandil Total	Amlodipine Mean	Amlodipine SD	Amlodipine Total	Weight	Mean Difference IV, Fixed, 95% CI
Chatterjee 1999	0.13	0.1	56	0.12	0.1	62	100.0%	0.01 [-0.03, 0.05]
Total (95% CI)			**56**			**62**	**100.0%**	**0.01 [-0.03, 0.05]**

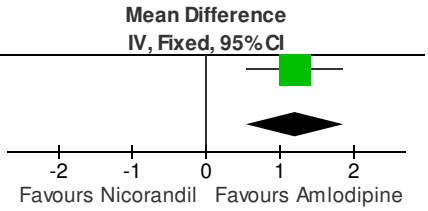
Heterogeneity: Not applicable
Test for overall effect: Z = 0.54 (P = 0.59)



3.5 Sum of weekly anginal attacks

Study or Subgroup	Nicorandil Mean	SD	Total	Amlodipine Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Chatterjee 1999	2.1	2	56	0.9	1.6	62	100.0%	1.20 [0.54, 1.86]
Total (95% CI)			**56**			**62**	**100.0%**	**1.20 [0.54, 1.86]**

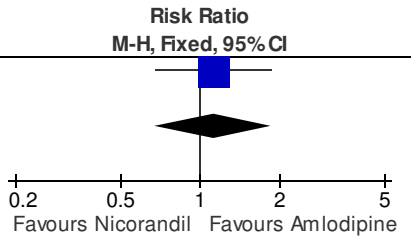
Heterogeneity: Not applicable
Test for overall effect: Z = 3.57 (P = 0.0004)



3.6 Adverse events (combined)

Study or Subgroup	Nicorandil Events	Total	Amlodipine Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Chatterjee 1999	20	57	20	64	100.0%	1.12 [0.68, 1.86]
Total (95% CI)		**57**		**64**	**100.0%**	**1.12 [0.68, 1.86]**
Total events	20		20			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.45 (P = 0.65)

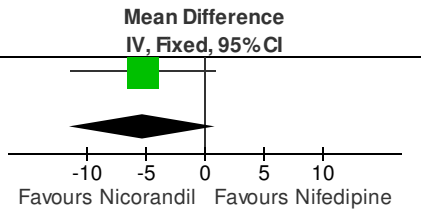


4 Nicorandil vs. Nifedipine (Follow-up immediately after 8 weeks of treatment)

4.1 Weekly anginal attack rate

Study or Subgroup	Nicorandil Mean	SD	Total	Nifedipine Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Ulvenstam1992	2.1	2.1	27	7.4	15	23	100.0%	-5.30 [-11.48, 0.88]
Total (95% CI)			**27**			**23**	**100.0%**	**-5.30 [-11.48, 0.88]**

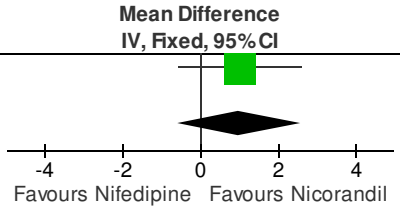
Heterogeneity: Not applicable
Test for overall effect: Z = 1.68 (P = 0.09)



4.2 Exercise duration (min)

Study or Subgroup	Nicorandil Mean	SD	Total	Nifedipine Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Ulvenstam1992	11.4	3.2	25	10.4	2.4	23	100.0%	1.00 [-0.59, 2.59]
Total (95% CI)			**25**			**23**	**100.0%**	**1.00 [-0.59, 2.59]**

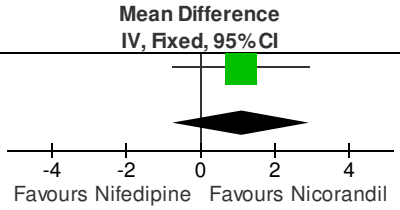
Heterogeneity: Not applicable
Test for overall effect: Z = 1.23 (P = 0.22)



4.3 Time to onset of angina pectoris (min)

Study or Subgroup	Nicorandil Mean	SD	Total	Nifedipine Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Ulvenstam1992	8.7	3.6	23	7.6	2.7	22	100.0%	1.10 [-0.75, 2.95]
Total (95% CI)			**23**			**22**	**100.0%**	**1.10 [-0.75, 2.95]**

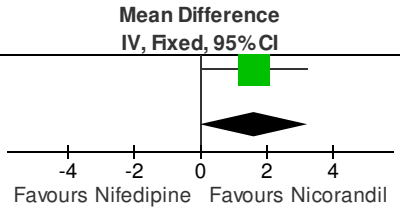
Heterogeneity: Not applicable
Test for overall effect: Z = 1.16 (P = 0.24)



4.4 Time to 1mm ST-depression (min)

Study or Subgroup	Nicorandil Mean	SD	Total	Nifedipine Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Ulvenstam1992	8	3.2	23	6.4	2.2	20	100.0%	1.60 [-0.02, 3.22]
Total (95% CI)			**23**			**20**	**100.0%**	**1.60 [-0.02, 3.22]**

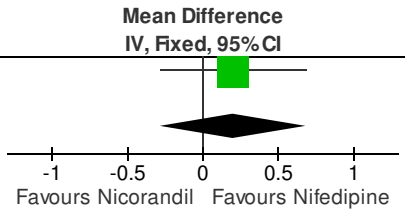
Heterogeneity: Not applicable
Test for overall effect: Z = 1.93 (P = 0.05)



4.5 ST depression on maximal identical workload (mm)

Study or Subgroup	Nicorandil Mean	SD	Total	Nifedipine Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Ulvenstam1992	1.9	0.89	24	1.7	0.75	20	100.0%	0.20 [-0.28, 0.68]
Total (95% CI)			**24**			**20**	**100.0%**	**0.20 [-0.28, 0.68]**

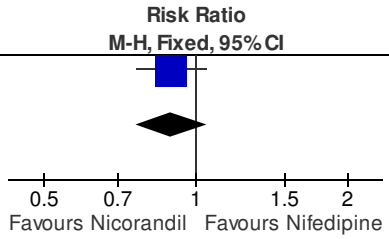
Heterogeneity: Not applicable
Test for overall effect: Z = 0.81 (P = 0.42)



4.6 Adverse events (combined)

Study or Subgroup	Nicorandil Events	Total	Nifedipine Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Ulvenstam1992	25	29	28	29	100.0%	0.89 [0.76, 1.05]
Total (95% CI)		**29**		**29**	**100.0%**	**0.89 [0.76, 1.05]**
Total events	25		28			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.38 (P = 0.17)

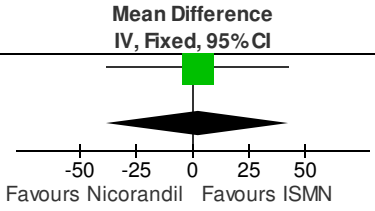


5 Nicorandil vs. ISMN (Follow-up 2 weeks)

5.1 ETT (Time to ST-depression)

Study or Subgroup	Nicorandil Mean	SD	Total	ISMN Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Zhu 2007	392.8	169.1	114	390.4	141.9	116	100.0%	2.40 [-37.98, 42.78]
Total (95% CI)			**114**			**116**	**100.0%**	**2.40 [-37.98, 42.78]**

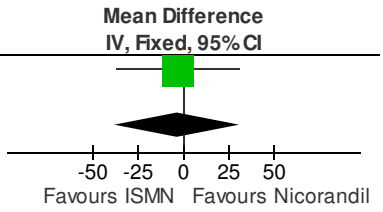
Heterogeneity: Not applicable
Test for overall effect: Z = 0.12 (P = 0.91)



5.2 ETT (Total excercise time)

Study or Subgroup	Nicorandil Mean	SD	Total	ISMN Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Zhu 2007	439.7	135.2	115	442.9	129.4	117	100.0%	-3.20 [-37.26, 30.86]
Total (95% CI)			**115**			**117**	**100.0%**	**-3.20 [-37.26, 30.86]**

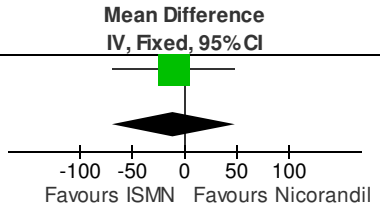
Heterogeneity: Not applicable
Test for overall effect: Z = 0.18 (P = 0.85)



5.3 ETT (Time to onset of chest pain)

Study or Subgroup	Nicorandil Mean	SD	Total	ISMN Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Zhu 2007	408.2	137.1	37	418.6	119.2	37	100.0%	-10.40 [-68.94, 48.14]
Total (95% CI)			**37**			**37**	**100.0%**	**-10.40 [-68.94, 48.14]**

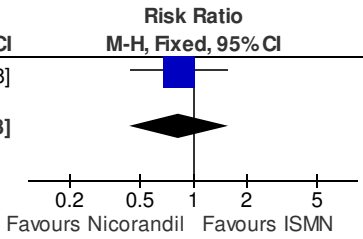
Heterogeneity: Not applicable
Test for overall effect: Z = 0.35 (P = 0.73)



5.4 Adverse event (Headache)

Study or Subgroup	Nicorandil Events	Total	ISMN Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Zhu 2007	15	123	18	123	100.0%	0.83 [0.44, 1.58]
Total (95% CI)		**123**		**123**	**100.0%**	**0.83 [0.44, 1.58]**
Total events	15		18			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.56 (P = 0.58)

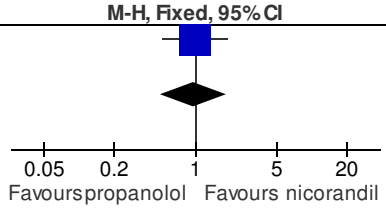


1 Nicorandil vs propanalol (Follow-up 6 weeks)

1.1 Angina free in daily life

Study or Subgroup	Nicorandil Events	Total	Propanolol Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Meeter 1992	11	32	13	37	100.0%	0.98 [0.51, 1.87]
Total (95% CI)		**32**		**37**	**100.0%**	**0.98 [0.51, 1.87]**
Total events	11		13			

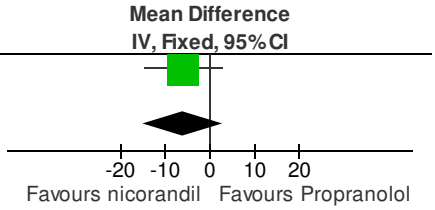
Heterogeneity: Not applicable
Test for overall effect: Z = 0.07 (P = 0.95)



1.2 12 hrs after medication - change in maximal work load (W) (baseline vs 3 weeks)

Study or Subgroup	Nicorandil Mean	SD	Total	Propanolol Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Meeter 1992	-1	19	32	5	18	37	100.0%	-6.00 [-14.77, 2.77]
Total (95% CI)			**32**			**37**	**100.0%**	**-6.00 [-14.77, 2.77]**

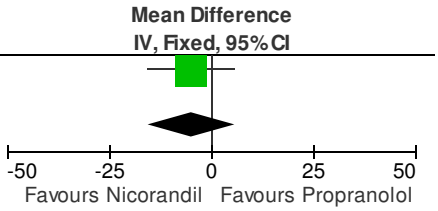
Heterogeneity: Not applicable
Test for overall effect: Z = 1.34 (P = 0.18)



1.3 12 hrs after medication - change in maximal work load (W) - baseline vs 6 wks

Study or Subgroup	Nicorandil Mean	SD	Total	Propanolol Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Meeter 1992	1	24	32	6	21	37	100.0%	-5.00 [-15.72, 5.72]
Total (95% CI)			**32**			**37**	**100.0%**	**-5.00 [-15.72, 5.72]**

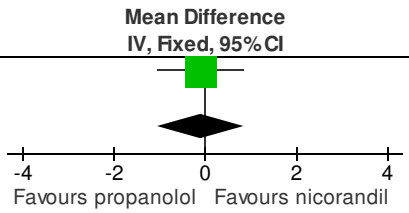
Heterogeneity: Not applicable
Test for overall effect: Z = 0.91 (P = 0.36)



1.4 12 hrs after medication - change in time to angina decimal min (baseline vs 3wks)

Study or Subgroup	Nicorandil Mean	SD	Total	Propanolol Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Meeter 1992	0.4	2	32	0.5	2	37	100.0%	-0.10 [-1.05, 0.85]
Total (95% CI)			**32**			**37**	**100.0%**	**-0.10 [-1.05, 0.85]**

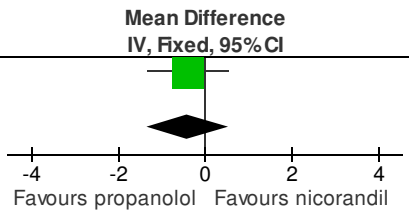
Heterogeneity: Not applicable
Test for overall effect: Z = 0.21 (P = 0.84)



1.5 12 hrs after medication - change in time to angina (baseline vs 6 wks)

Study or Subgroup	Nicorandil Mean	SD	Total	Propanolol Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Meeter 1992	0.4	2	32	0.8	2	37	100.0%	-0.40 [-1.35, 0.55]
Total (95% CI)			**32**			**37**	**100.0%**	**-0.40 [-1.35, 0.55]**

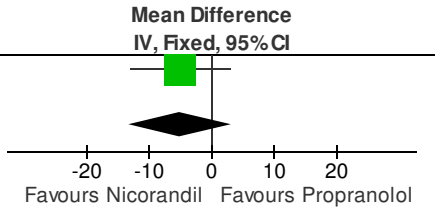
Heterogeneity: Not applicable
Test for overall effect: Z = 0.83 (P = 0.41)



1.6 2 hrs after medication - change in maximal work load (W) (baseline vs 3ks)

Study or Subgroup	Nicorandil Mean	SD	Total	Propanolol Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Meeter 1992	3	14	32	8	20	37	100.0%	-5.00 [-13.07, 3.07]
Total (95% CI)			**32**			**37**	**100.0%**	**-5.00 [-13.07, 3.07]**

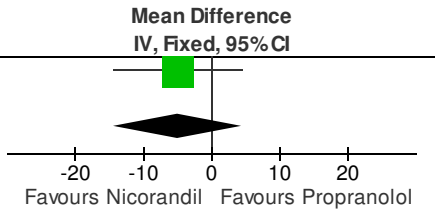
Heterogeneity: Not applicable
Test for overall effect: Z = 1.21 (P = 0.22)



1.7 2 hrs after medication - change in maximal work load (W) (baseline vs 6 wks)

Study or Subgroup	Nicorandil Mean	SD	Total	Propanolol Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Meeter 1992	4	17	32	9	23	37	100.0%	-5.00 [-14.47, 4.47]
Total (95% CI)			**32**			**37**	**100.0%**	**-5.00 [-14.47, 4.47]**

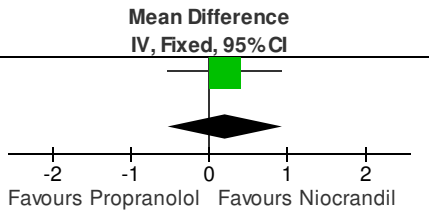
Heterogeneity: Not applicable
Test for overall effect: Z = 1.04 (P = 0.30)



1.8 2 hrs after medication time to angina

Study or Subgroup	Nicorandil Mean	SD	Total	Propanolol Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Meeter 1992	1	1	32	0.8	2	37	100.0%	0.20 [-0.53, 0.93]
Total (95% CI)			**32**			**37**	**100.0%**	**0.20 [-0.53, 0.93]**

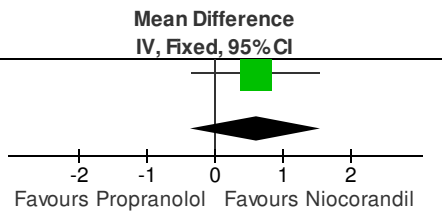
Heterogeneity: Not applicable
Test for overall effect: Z = 0.54 (P = 0.59)



1.9 2 hrs after medication time to angina

Study or Subgroup	Nicorandil Mean	SD	Total	Propanolol Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Meeter 1992	1.5	2	32	0.9	2	37	100.0%	0.60 [-0.35, 1.55]
Total (95% CI)			**32**			**37**	**100.0%**	**0.60 [-0.35, 1.55]**

Heterogeneity: Not applicable
Test for overall effect: Z = 1.24 (P = 0.21)

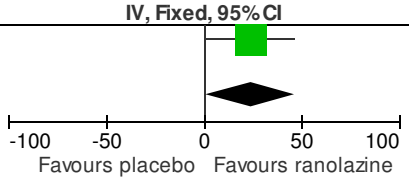


1 Ranolazine (750 mg bid) + antianginal vs Placebo + antianginal (Follow-up 12 weeks)

1.1 Exercise duration (trough - change from baseline), s - 12 wks

Study or Subgroup	Ranolazine Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Chaitman (CARISA) 2004	115.4	131.92	272	91.7	133.3	258	100.0%	23.70 [1.11, 46.29]
Total (95% CI)			**272**			**258**	**100.0%**	**23.70 [1.11, 46.29]**

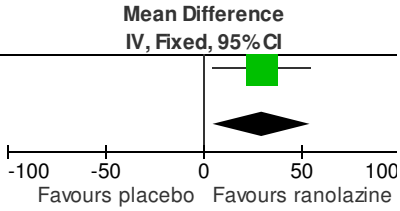
Heterogeneity: Not applicable
Test for overall effect: Z = 2.06 (P = 0.04)



1.2 Time to onset of angina (trough - change from baseline) s - 12 wks

Study or Subgroup	Ranolazine Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Chaitman (CARISA) 2004	144	146.76	272	114.3	147.75	258	100.0%	29.70 [4.62, 54.78]
Total (95% CI)			**272**			**258**	**100.0%**	**29.70 [4.62, 54.78]**

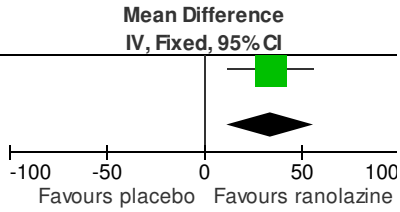
Heterogeneity: Not applicable
Test for overall effect: Z = 2.32 (P = 0.02)



1.3 Exercise duration (peak - change from baseline) s - 12 wks

Study or Subgroup	Ranolazine Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Chaitman (CARISA) 2004	99.4	128.15	270	65.4	129.6	256	100.0%	34.00 [11.96, 56.04]
Total (95% CI)			**270**			**256**	**100.0%**	**34.00 [11.96, 56.04]**

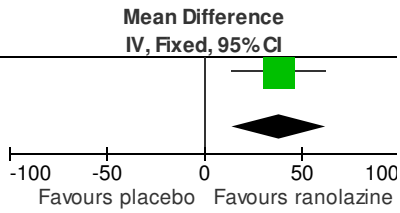
Heterogeneity: Not applicable
Test for overall effect: Z = 3.02 (P = 0.002)



1.4 Time to onset of angina (peak - change from baseline) s - 12 wks

Study or Subgroup	Ranolazine Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Chaitman (CARISA) 2004	126.9	149.51	272	88.9	132.8	256	100.0%	38.00 [13.91, 62.09]
Total (95% CI)			**272**			**256**	**100.0%**	**38.00 [13.91, 62.09]**

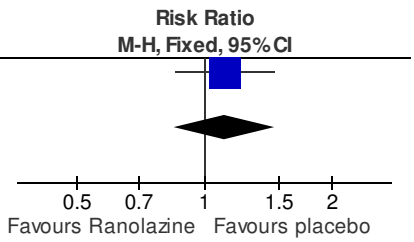
Heterogeneity: Not applicable
Test for overall effect: Z = 3.09 (P = 0.002)



1.5 Adverse events

Study or Subgroup	Ranolazine Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Chaitman (CARISA) 2004	82	279	71	269	100.0%	1.11 [0.85, 1.46]
Total (95% CI)		**279**		**269**	**100.0%**	**1.11 [0.85, 1.46]**
Total events	82		71			

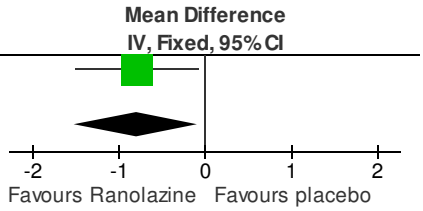
Heterogeneity: Not applicable
Test for overall effect: Z = 0.78 (P = 0.44)



1.6 Angina attacks per week

Study or Subgroup	Ranolazine Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Chaitman (CARISA) 2004	2.5	3.3	272	3.3	4.9	258	100.0%	-0.80 [-1.52, -0.08]
Total (95% CI)			**272**			**258**	**100.0%**	**-0.80 [-1.52, -0.08]**

Heterogeneity: Not applicable
Test for overall effect: Z = 2.19 (P = 0.03)

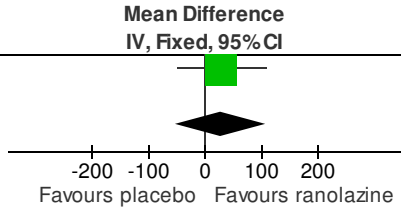


2 Ranolazine (750 mg bid) + antianginal treatment vs Placebo+antianginal treatment - diabetic patients (Follow-up 12 weeks)

2.1 Exercise duration (trough change from baseline) s - 12 wks

Study or Subgroup	Ranolazine Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Timmis (CARISA) 2006	114.1	213.13	68	85.4	236.5	57	100.0%	28.70 [-50.90, 108.30]
Total (95% CI)			**68**			**57**	**100.0%**	**28.70 [-50.90, 108.30]**

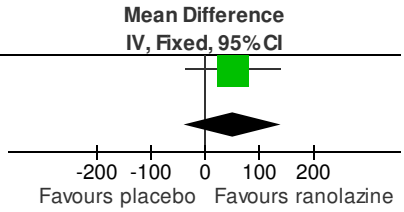
Heterogeneity: Not applicable
Test for overall effect: Z = 0.71 (P = 0.48)



2.2 Time to onset of angina (trough change from baseline) s - 12 wks

Study or Subgroup	Ranolazine Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Timmis (CARISA) 2006	145.7	236.5	68	94.9	262.63	57	100.0%	50.80 [-37.56, 139.16]
Total (95% CI)			**68**			**57**	**100.0%**	**50.80 [-37.56, 139.16]**

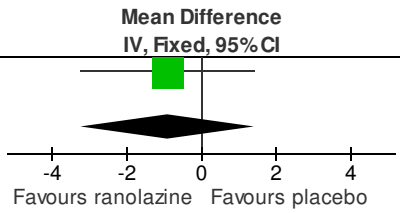
Heterogeneity: Not applicable
Test for overall effect: Z = 1.13 (P = 0.26)



2.3 Angina episodes per week - 12 wks

Study or Subgroup	Ranolazine Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Timmis (CARISA) 2006	2.08	5.09	68	2.99	7.7	57	100.0%	-0.91 [-3.25, 1.43]
Total (95% CI)			**68**			**57**	**100.0%**	**-0.91 [-3.25, 1.43]**

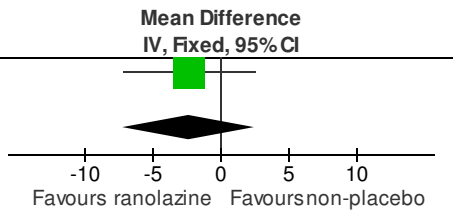
Heterogeneity: Not applicable
Test for overall effect: Z = 0.76 (P = 0.45)



2.4 Nitroglycerin consumption per week - 12 wks

Study or Subgroup	Ranolazine Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Timmis (CARISA) 2006	2.03	7.43	68	4.35	17.46	57	100.0%	-2.32 [-7.18, 2.54]
Total (95% CI)			**68**			**57**	**100.0%**	**-2.32 [-7.18, 2.54]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.93 (P = 0.35)

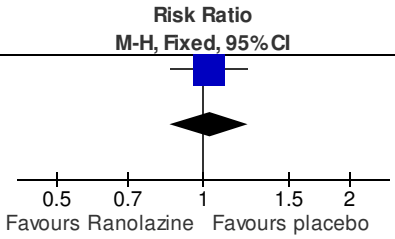


3 Ranolazine (1000 mg bid) + antianginal treatment vs Placebo +antianginal treatment- age (Follow-up 6 weeks)

3.1 Adverse events<70 years

Study or Subgroup	Ranolazine Events	Ranolazine Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Rich (CARISA) 2007	194	604	131	420	100.0%	1.03 [0.86, 1.24]
Total (95% CI)		**604**		**420**	**100.0%**	**1.03 [0.86, 1.24]**
Total events	194		131			

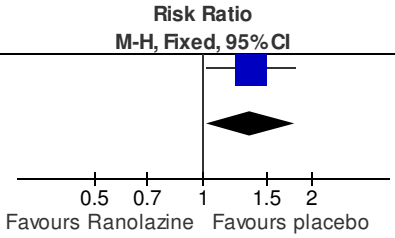
Heterogeneity: Not applicable
Test for overall effect: Z = 0.31 (P = 0.75)



3.2 Adverse events >70 years

Study or Subgroup	Ranolazine Events	Ranolazine Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Rich (CARISA) 2007	102	231	43	132	100.0%	1.36 [1.02, 1.80]
Total (95% CI)		**231**		**132**	**100.0%**	**1.36 [1.02, 1.80]**
Total events	102		43			

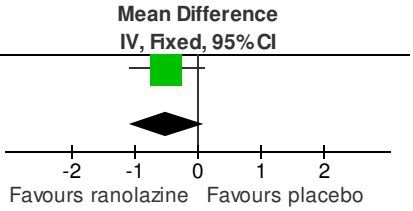
Heterogeneity: Not applicable
Test for overall effect: Z = 2.09 (P = 0.04)



3.5 Weekly angina attacks < 70 yrs

Study or Subgroup	Ranolazine Mean	Ranolazine SD	Ranolazine Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean Difference IV, Fixed, 95% CI
Rich (CARISA) 2007	3.11	4.62	403	3.61	4.04	409	100.0%	-0.50 [-1.10, 0.10]
Total (95% CI)			**403**			**409**	**100.0%**	**-0.50 [-1.10, 0.10]**

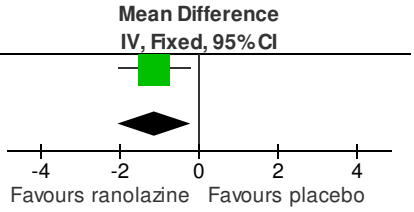
Heterogeneity: Not applicable
Test for overall effect: Z = 1.64 (P = 0.10)



3.6 Weekly angina attacks > 71 yrs

Study or Subgroup	Ranolazine Mean	Ranolazine SD	Ranolazine Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean Difference IV, Fixed, 95% CI
Rich (CARISA) 2007	2.08	2.67	135	3.21	4.67	130	100.0%	-1.13 [-2.05, -0.21]
Total (95% CI)			**135**			**130**	**100.0%**	**-1.13 [-2.05, -0.21]**

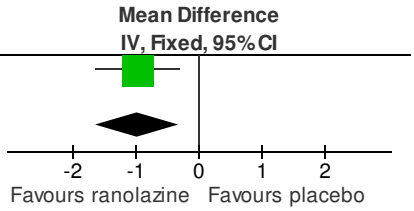
Heterogeneity: Not applicable
Test for overall effect: Z = 2.41 (P = 0.02)



3.7 Nitroglycerin consumption < 70 yrs

Study or Subgroup	Ranolazine Mean	Ranolazine SD	Ranolazine Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean Difference IV, Fixed, 95% CI
Rich (CARISA) 2007	2.18	4.42	403	3.15	5.26	409	100.0%	-0.97 [-1.64, -0.30]
Total (95% CI)			**403**			**409**	**100.0%**	**-0.97 [-1.64, -0.30]**

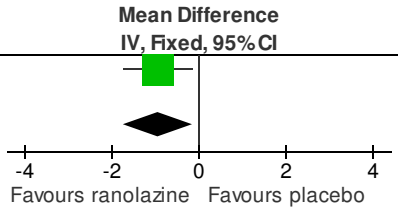
Heterogeneity: Not applicable
Test for overall effect: Z = 2.85 (P = 0.004)



3.8 Nitroglycerin consumption > 71 yrs

Study or Subgroup	Ranolazine Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Rich (CARISA) 2007	1.51	2.44	135	2.45	3.99	130	100.0%	-0.94 [-1.74, -0.14]
Total (95% CI)			**135**			**130**	**100.0%**	**-0.94 [-1.74, -0.14]**

Heterogeneity: Not applicable
Test for overall effect: Z = 2.30 (P = 0.02)

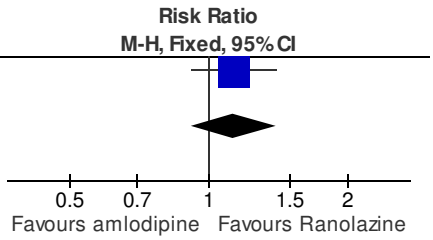


6 Ranolazine (1000 mg bid) plus amolodipine (10 mg) vs amolodipine (10mg) (Follow-up 6 weeks)

6.1 Adverse events

Study or Subgroup	Ranolazine Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Stone (ERICA) 2006	112	281	100	284	100.0%	1.13 [0.91, 1.40]
Total (95% CI)		**281**		**284**	**100.0%**	**1.13 [0.91, 1.40]**
Total events	112		100			

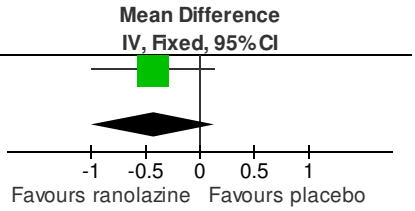
Heterogeneity: Not applicable
Test for overall effect: Z = 1.14 (P = 0.25)



6.2 Weekly angina frequency - 6 wks

Study or Subgroup	Ranolazine Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Stone (ERICA) 2006	2.88	3.16	277	3.31	3.69	281	100.0%	-0.43 [-1.00, 0.14]
Total (95% CI)			**277**			**281**	**100.0%**	**-0.43 [-1.00, 0.14]**

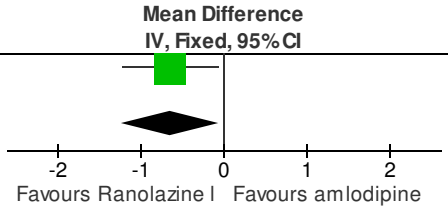
Heterogeneity: Not applicable
Test for overall effect: Z = 1.48 (P = 0.14)



6.3 Weekly nitroglycerin consumption - 6 wks

Study or Subgroup	Ranolazine Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Stone (ERICA) 2006	2.03	3.33	277	2.68	3.69	281	100.0%	-0.65 [-1.23, -0.07]
Total (95% CI)			**277**			**281**	**100.0%**	**-0.65 [-1.23, -0.07]**

Heterogeneity: Not applicable
Test for overall effect: Z = 2.19 (P = 0.03)

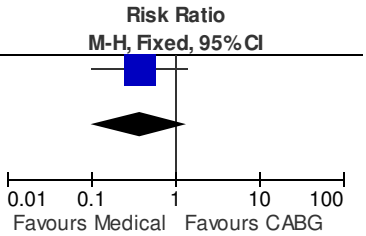


1 Multi vessel disease- Short term follow-up (1 year)

1.1 Death

Study or Subgroup	Medical Events	Medical Total	CABG Events	CABG Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Hueb 2004 (MASS-II)	3	203	8	203	100.0%	0.38 [0.10, 1.39]
Total (95% CI)		**203**		**203**	**100.0%**	**0.38 [0.10, 1.39]**
Total events	3		8			

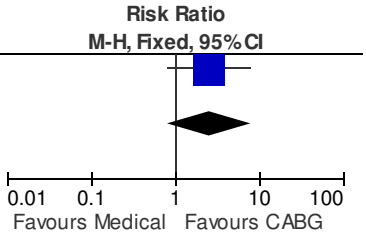
Heterogeneity: Not applicable
Test for overall effect: Z = 1.46 (P = 0.14)



1.2 Q wave MI

Study or Subgroup	Medical Events	Medical Total	CABG Events	CABG Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Hueb 2004 (MASS-II)	10	203	4	203	100.0%	2.50 [0.80, 7.84]
Total (95% CI)		**203**		**203**	**100.0%**	**2.50 [0.80, 7.84]**
Total events	10		4			

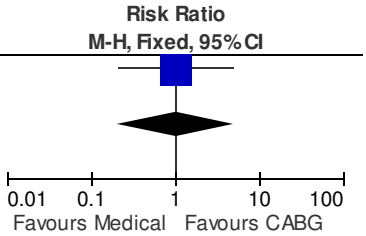
Heterogeneity: Not applicable
Test for overall effect: Z = 1.57 (P = 0.12)



1.3 Stroke

Study or Subgroup	Medical Events	Medical Total	CABG Events	CABG Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Hueb 2004 (MASS-II)	3	203	3	203	100.0%	1.00 [0.20, 4.90]
Total (95% CI)		**203**		**203**	**100.0%**	**1.00 [0.20, 4.90]**
Total events	3		3			

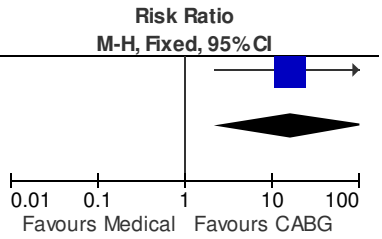
Heterogeneity: Not applicable
Test for overall effect: Z = 0.00 (P = 1.00)



1.4 Non protocol revascularisation

Study or Subgroup	Medical Events	Medical Total	CABG Events	CABG Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Hueb 2004 (MASS-II)	16	203	1	203	100.0%	16.00 [2.14, 119.52]
Total (95% CI)		**203**		**203**	**100.0%**	**16.00 [2.14, 119.52]**
Total events	16		1			

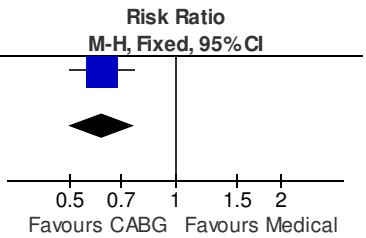
Heterogeneity: Not applicable
Test for overall effect: Z = 2.70 (P = 0.007)



1.5 Free of angina

Study or Subgroup	Medical Events	Medical Total	CABG Events	CABG Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Hueb 2004 (MASS-II)	74	203	120	203	100.0%	0.62 [0.50, 0.76]
Total (95% CI)		**203**		**203**	**100.0%**	**0.62 [0.50, 0.76]**
Total events	74		120			

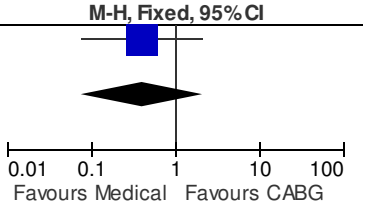
Heterogeneity: Not applicable
Test for overall effect: Z = 4.41 (P < 0.0001)



1.6 Death- subgroup diabetes

Study or Subgroup	Medical Events	Medical Total	CABG Events	CABG Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Soares 2006 (MASS -II)	2	75	4	59	100.0%	0.39 [0.07, 2.07]
Total (95% CI)		**75**		**59**	**100.0%**	**0.39 [0.07, 2.07]**
Total events	2		4			

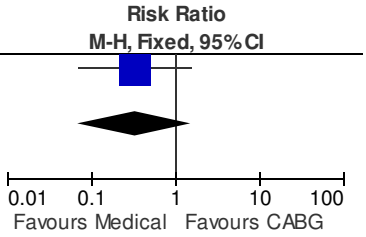
Heterogeneity: Not applicable
Test for overall effect: Z = 1.10 (P = 0.27)



1.7 Death- subgroup no diabetes

Study or Subgroup	Medical Events	Medical Total	CABG Events	CABG Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Soares 2006 (MASS -II)	2	128	7	144	100.0%	0.32 [0.07, 1.52]
Total (95% CI)		**128**		**144**	**100.0%**	**0.32 [0.07, 1.52]**
Total events	2		7			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.43 (P = 0.15)

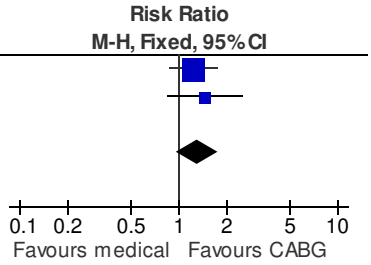


2 Multivessel disease- Medium term follow-up (2 to 4 years)

2.1 Death

Study or Subgroup	Medical Events	Medical Total	CABG Events	CABG Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Read 1977 (VA study)	60	354	46	332	69.9%	1.22 [0.86, 1.74]
Varnauskas 1979 (ECSS)	29	373	21	394	30.1%	1.46 [0.85, 2.51]
Total (95% CI)		**727**		**726**	**100.0%**	**1.29 [0.96, 1.74]**
Total events	89		67			

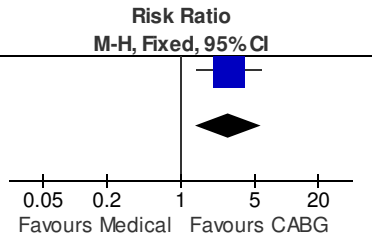
Heterogeneity: Chi² = 0.28, df = 1 (P = 0.59); I² = 0%
Test for overall effect: Z = 1.70 (P = 0.09)



2.2 cardiac death`

Study or Subgroup	Medical Events	Medical Total	CABG Events	CABG Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Varnauskas 1979 (ECSS)	27	373	10	394	100.0%	2.85 [1.40, 5.81]
Total (95% CI)		**373**		**394**	**100.0%**	**2.85 [1.40, 5.81]**
Total events	27		10			

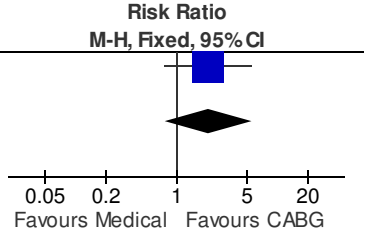
Heterogeneity: Not applicable
Test for overall effect: Z = 2.89 (P = 0.004)



2.3 MI

Study or Subgroup	Medical Events	Medical Total	CABG Events	CABG Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Guinn 1976 (VA study)	11	60	5	56	100.0%	2.05 [0.76, 5.54]
Total (95% CI)		**60**		**56**	**100.0%**	**2.05 [0.76, 5.54]**
Total events	11		5			

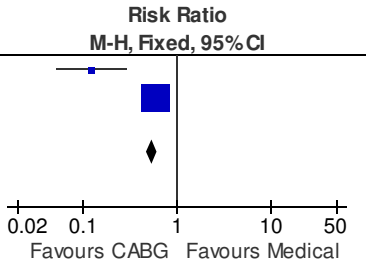
Heterogeneity: Not applicable
Test for overall effect: Z = 1.42 (P = 0.16)



2.4 Free of angina

Study or Subgroup	Medical Events	Medical Total	CABG Events	CABG Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Guinn 1976 (VA study)	5	60	38	56	11.4%	0.12 [0.05, 0.29]
Varnauskas 1979 (ECSS)	175	373	315	394	88.6%	0.59 [0.52, 0.66]
Total (95% CI)		**433**		**450**	**100.0%**	**0.53 [0.47, 0.60]**
Total events	180		353			

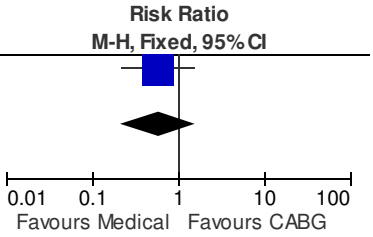
Heterogeneity: Chi² = 13.68, df = 1 (P = 0.0002); I² = 93%
Test for overall effect: Z = 10.26 (P < 0.00001)



2.5 Death- sub group 2 vessel disease

Study or Subgroup	Medical Events	Medical Total	CABG Events	CABG Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Varnauskas 1979 (ECSS)	6	154	10	147	100.0%	0.57 [0.21, 1.54]
Total (95% CI)		**154**		**147**	**100.0%**	**0.57 [0.21, 1.54]**
Total events	6		10			

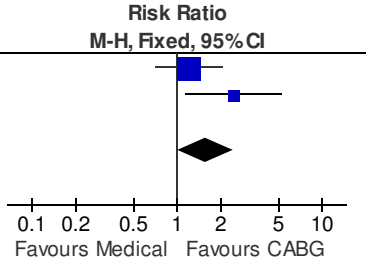
Heterogeneity: Not applicable
Test for overall effect: Z = 1.11 (P = 0.27)



2.6 Death - sub group 3 vessel disease

Study or Subgroup	Medical Events	Medical Total	CABG Events	CABG Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Detre 1977 (VA study)	27	158	19	135	71.1%	1.21 [0.71, 2.08]
Varnauskas 1979 (ECSS)	19	188	9	219	28.9%	2.46 [1.14, 5.30]
Total (95% CI)		**346**		**354**	**100.0%**	**1.57 [1.02, 2.44]**
Total events	46		28			

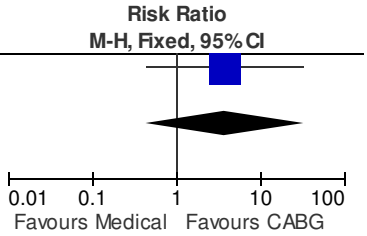
Heterogeneity: Chi² = 2.18, df = 1 (P = 0.14); I² = 54%
Test for overall effect: Z = 2.03 (P = 0.04)



2.7 Non protocol revascularisation

Study or Subgroup	Medical Events	Medical Total	CABG Events	CABG Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Guinn 1976 (VA study)	4	60	1	56	100.0%	3.73 [0.43, 32.40]
Total (95% CI)		**60**		**56**	**100.0%**	**3.73 [0.43, 32.40]**
Total events	4		1			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.19 (P = 0.23)

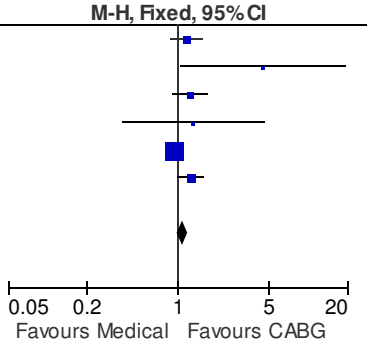


3 Multivessel disease -Long term follow-up (>4 years)

3.1 Death

Study or Subgroup	Medical Events	Medical Total	CABG Events	CABG Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Alderman 1990 (CASS)	81	390	70	390	14.3%	1.16 [0.87, 1.54]
Frick 1985	10	50	2	45	0.4%	4.50 [1.04, 19.45]
Hueb 2010 (MASS-II)	63	203	51	203	10.4%	1.24 [0.90, 1.69]
Kloster 1979	5	49	4	51	0.8%	1.30 [0.37, 4.56]
Peduzzi 1998 (VA study)	265	354	265	332	55.8%	0.94 [0.86, 1.02]
Varnauaskas 1988 (ECSS)	109	373	92	394	18.3%	1.25 [0.99, 1.59]
Total (95% CI)		**1419**		**1415**	**100.0%**	**1.08 [0.99, 1.17]**
Total events	533		484			

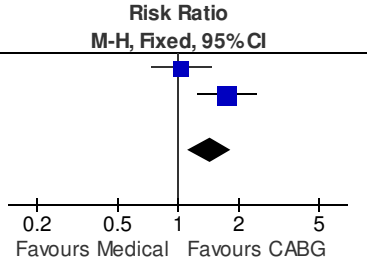
Heterogeneity: Chi² = 17.29, df = 5 (P = 0.004); I² = 71%
Test for overall effect: Z = 1.67 (P = 0.09)



3.2 cardiac death

Study or Subgroup	Medical Events	Medical Total	CABG Events	CABG Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Bhayana 1978 (VA study)	36	75	33	71	43.1%	1.03 [0.73, 1.46]
Varnauaskas 1988 (ECSS)	76	373	46	394	56.9%	1.75 [1.25, 2.45]
Total (95% CI)		**448**		**465**	**100.0%**	**1.44 [1.12, 1.84]**
Total events	112		79			

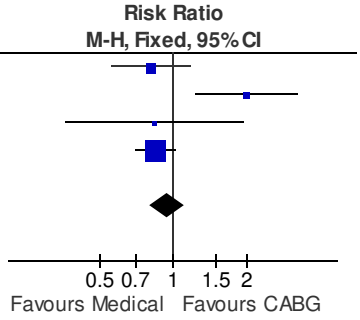
Heterogeneity: Chi² = 4.84, df = 1 (P = 0.03); I² = 79%
Test for overall effect: Z = 2.89 (P = 0.004)



3.3 MI

Study or Subgroup	Medical Events	Medical Total	CABG Events	CABG Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Fisher 1984 (CASS)	43	390	53	390	23.5%	0.81 [0.56, 1.18]
Hueb 2010 (MASS-II)	42	203	21	203	9.3%	2.00 [1.23, 3.25]
Kloster 1979	8	49	10	51	4.4%	0.83 [0.36, 1.93]
Peduzzi 1998 (VA study)	123	354	137	332	62.8%	0.84 [0.69, 1.02]
Total (95% CI)		**996**		**976**	**100.0%**	**0.94 [0.80, 1.10]**
Total events	216		221			

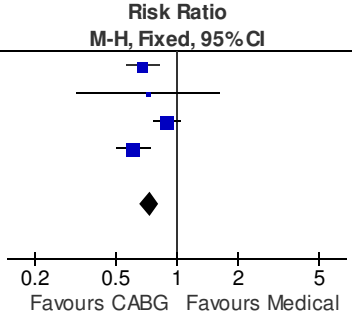
Heterogeneity: Chi² = 11.21, df = 3 (P = 0.01); I² = 73%
Test for overall effect: Z = 0.73 (P = 0.46)



3.4 Free of angina

Study or Subgroup	Medical Events	Medical Total	CABG Events	CABG Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Hueb 2010 (MASS-II)	88	203	130	203	25.9%	0.68 [0.56, 0.82]
Peduzzi 1992 (VA study)	10	354	13	332	2.7%	0.72 [0.32, 1.62]
Rogers 1990 (CASS)	163	390	183	390	36.4%	0.89 [0.76, 1.04]
Varnauskas 1982 (ECSS)	104	373	181	394	35.0%	0.61 [0.50, 0.74]
Total (95% CI)		**1320**		**1319**	**100.0%**	**0.73 [0.66, 0.81]**
Total events	365		507			

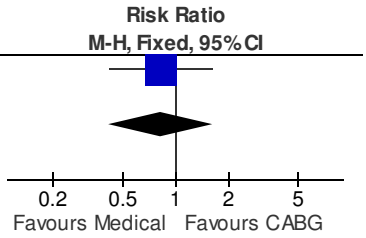
Heterogeneity: Chi² = 10.16, df = 3 (P = 0.02); I² = 70%
Test for overall effect: Z = 5.97 (P < 0.00001)



3.5 stroke

Study or Subgroup	Medical Events	Medical Total	CABG Events	CABG Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Hueb 2010 (MASS-II)	14	203	17	203	100.0%	0.82 [0.42, 1.63]
Total (95% CI)		**203**		**203**	**100.0%**	**0.82 [0.42, 1.63]**
Total events	14		17			

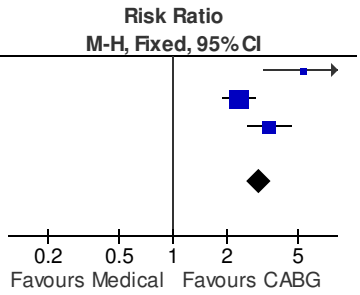
Heterogeneity: Not applicable
Test for overall effect: Z = 0.56 (P = 0.58)



3.6 Non protocol revascularisation

Study or Subgroup	Medical Events	Medical Total	CABG Events	CABG Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Hueb 2010 (MASS-II)	80	203	15	203	10.4%	5.33 [3.18, 8.94]
Peduzzi 1998 (VA study)	194	354	78	332	55.7%	2.33 [1.88, 2.89]
Rogers 1990 (CASS)	168	390	49	390	33.9%	3.43 [2.58, 4.56]
Total (95% CI)		**947**		**925**	**100.0%**	**3.02 [2.56, 3.55]**
Total events	442		142			

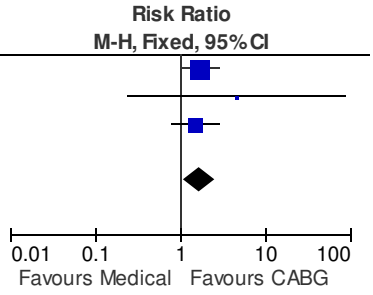
Heterogeneity: Chi² = 10.90, df = 2 (P = 0.004); I² = 82%
Test for overall effect: Z = 13.18 (P < 0.00001)



3.7 Death- sub group 2 vessel disease

Study or Subgroup	Medical Events	Medical Total	CABG Events	CABG Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Alderman 1990 (CASS)	31	148	20	160	58.2%	1.68 [1.00, 2.81]
Kloster 1979	2	19	0	17	1.6%	4.50 [0.23, 87.61]
Varnauskas 1982 (ECSS)	20	154	13	147	40.2%	1.47 [0.76, 2.84]
Total (95% CI)		**321**		**324**	**100.0%**	**1.64 [1.10, 2.45]**
Total events	53		33			

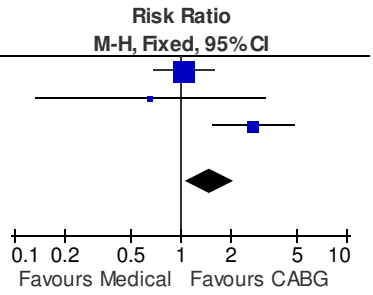
Heterogeneity: Chi² = 0.56, df = 2 (P = 0.76); I² = 0%
Test for overall effect: Z = 2.40 (P = 0.02)



3.8 Death- sub group 3 vessel disease

Study or Subgroup	Medical Events	Medical Total	CABG Events	CABG Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Alderman 1990 (CASS)	34	135	30	123	64.4%	1.03 [0.67, 1.58]
Kloster 1979	2	20	4	26	7.1%	0.65 [0.13, 3.20]
Varnauskas 1982 (ECSS)	35	188	15	219	28.4%	2.72 [1.53, 4.82]
Total (95% CI)		**343**		**368**	**100.0%**	**1.48 [1.07, 2.06]**
Total events	71		49			

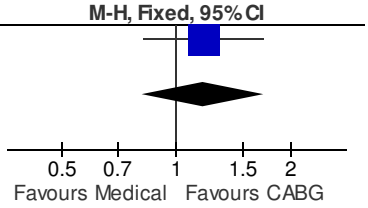
Heterogeneity: Chi² = 8.11, df = 2 (P = 0.02); I² = 75%
Test for overall effect: Z = 2.37 (P = 0.02)



3.9 Mortality- age >53 yrs

Study or Subgroup	Medical Events	Medical Total	CABG Events	CABG Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Alderman 1990 (CASS)	46	163	39	163	100.0%	1.18 [0.82, 1.70]
Total (95% CI)		**163**		**163**	**100.0%**	**1.18 [0.82, 1.70]**
Total events	46		39			

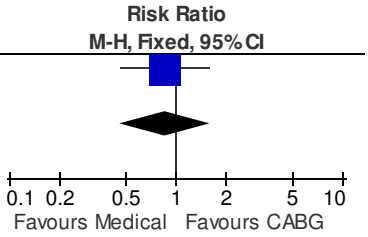
Heterogeneity: Not applicable
Test for overall effect: Z = 0.88 (P = 0.38)



3.10 Mortality- age <47 years

Study or Subgroup	Medical Events	Medical Total	CABG Events	CABG Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Alderman 1990 (CASS)	16	101	17	92	100.0%	0.86 [0.46, 1.60]
Total (95% CI)		**101**		**92**	**100.0%**	**0.86 [0.46, 1.60]**
Total events	16		17			

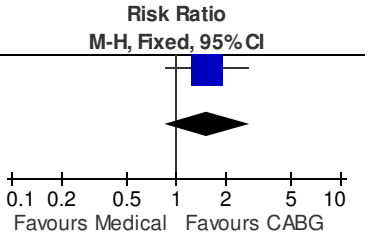
Heterogeneity: Not applicable
Test for overall effect: Z = 0.49 (P = 0.63)



3.11 Mortality- age 47-53 years

Study or Subgroup	Medical Events	Medical Total	CABG Events	CABG Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Alderman 1990 (CASS)	23	126	16	135	100.0%	1.54 [0.85, 2.78]
Total (95% CI)		**126**		**135**	**100.0%**	**1.54 [0.85, 2.78]**
Total events	23		16			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.43 (P = 0.15)

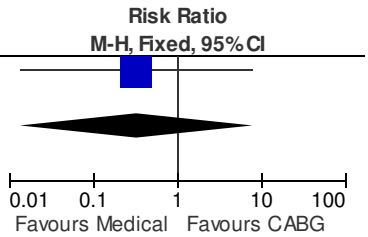


4 Single vessel disease- medium term follow-up (2-4 years)

4.1 Death

Study or Subgroup	Medical Events	Medical Total	CABG Events	CABG Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Hueb 1995 (MASS- I)	0	72	1	70	100.0%	0.32 [0.01, 7.83]
Total (95% CI)		**72**		**70**	**100.0%**	**0.32 [0.01, 7.83]**
Total events	0		1			

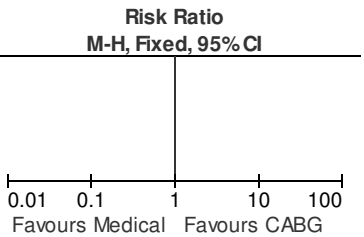
Heterogeneity: Not applicable
Test for overall effect: Z = 0.69 (P = 0.49)



4.2 Stroke

Study or Subgroup	Medical Events	Medical Total	CABG Events	CABG Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Hueb 1995 (MASS- I)	0	72	0	70		Not estimable
Total (95% CI)		**72**		**70**		**Not estimable**
Total events	0		0			

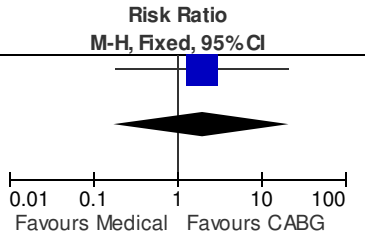
Heterogeneity: Not applicable
Test for overall effect: Not applicable



4.3 MI

Study or Subgroup	Medical Events	Medical Total	CABG Events	CABG Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Hueb 1995 (MASS- I)	2	72	1	70	100.0%	1.94 [0.18, 20.96]
Total (95% CI)		**72**		**70**	**100.0%**	**1.94 [0.18, 20.96]**
Total events	2		1			

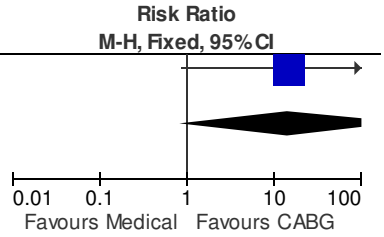
Heterogeneity: Not applicable
Test for overall effect: Z = 0.55 (P = 0.58)



4.4 Non protocol revascularisation

Study or Subgroup	Medical Events	Medical Total	CABG Events	CABG Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Hueb 1995 (MASS- I)	7	72	0	70	100.0%	14.59 [0.85, 250.71]
Total (95% CI)		**72**		**70**	**100.0%**	**14.59 [0.85, 250.71]**
Total events	7		0			

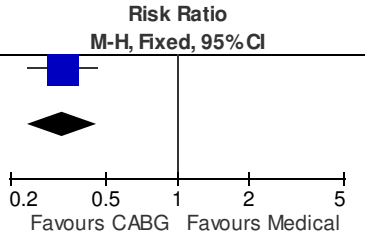
Heterogeneity: Not applicable
Test for overall effect: Z = 1.85 (P = 0.06)



4.5 Free of angina

Study or Subgroup	Medical Events	Medical Total	CABG Events	CABG Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Hueb 1995 (MASS- I)	23	72	68	70	100.0%	0.33 [0.23, 0.46]
Total (95% CI)		**72**		**70**	**100.0%**	**0.33 [0.23, 0.46]**
Total events	23		68			

Heterogeneity: Not applicable
Test for overall effect: Z = 6.42 (P < 0.00001)

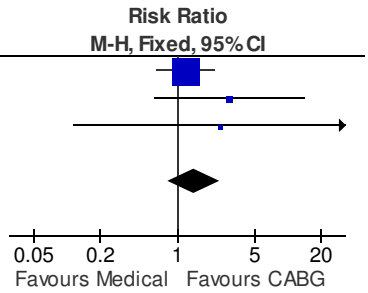


5 Single vessel disease -Long term follow-up (>4 years)

5.1 Death

Study or Subgroup	Medical Events	Medical Total	CABG Events	CABG Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Alderman 1990 (CASS)	19	107	16	107	86.1%	1.19 [0.65, 2.18]
Hueb 1999 (MASS-I)	6	72	2	70	10.9%	2.92 [0.61, 13.97]
Kloster 1979	1	10	0	8	3.0%	2.45 [0.11, 53.25]
Total (95% CI)		**189**		**185**	**100.0%**	**1.41 [0.81, 2.46]**
Total events	26		18			

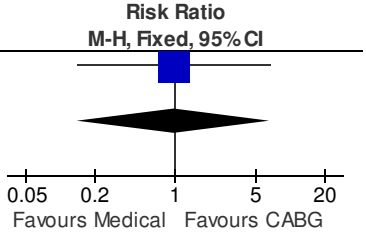
Heterogeneity: $Chi^2 = 1.26$, df = 2 (P = 0.53); $I^2 = 0\%$
Test for overall effect: Z = 1.23 (P = 0.22)



5.2 Cardiac death

Study or Subgroup	Medical Events	Medical Total	CABG Events	CABG Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Hueb 1999 (MASS-I)	2	72	2	70	100.0%	0.97 [0.14, 6.71]
Total (95% CI)		**72**		**70**	**100.0%**	**0.97 [0.14, 6.71]**
Total events	2		2			

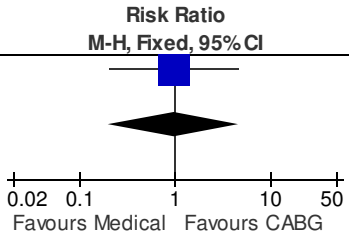
Heterogeneity: Not applicable
Test for overall effect: Z = 0.03 (P = 0.98)



5.3 MI

Study or Subgroup	Medical Events	Medical Total	CABG Events	CABG Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Hueb 1999 (MASS-I)	3	72	3	70	100.0%	0.97 [0.20, 4.66]
Total (95% CI)		**72**		**70**	**100.0%**	**0.97 [0.20, 4.66]**
Total events	3		3			

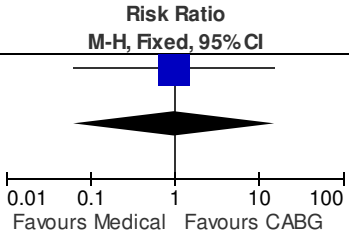
Heterogeneity: Not applicable
Test for overall effect: Z = 0.04 (P = 0.97)



5.4 Stroke

Study or Subgroup	Medical Events	Medical Total	CABG Events	CABG Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Hueb 1999 (MASS-I)	1	72	1	70	100.0%	0.97 [0.06, 15.24]
Total (95% CI)		**72**		**70**	**100.0%**	**0.97 [0.06, 15.24]**
Total events	1		1			

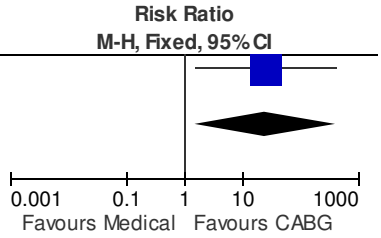
Heterogeneity: Not applicable
Test for overall effect: Z = 0.02 (P = 0.98)



5.5 Non protocol revascularisation

Study or Subgroup	Medical Events	Medical Total	CABG Events	CABG Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Hueb 1999 (MASS-I)	12	72	0	70	100.0%	24.32 [1.47, 402.97]
Total (95% CI)		**72**		**70**	**100.0%**	**24.32 [1.47, 402.97]**
Total events	12		0			

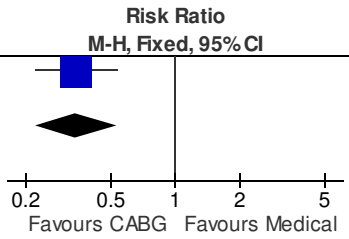
Heterogeneity: Not applicable
Test for overall effect: Z = 2.23 (P = 0.03)



5.6 Free of angina

Study or Subgroup	Medical Events	Medical Total	CABG Events	CABG Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Hueb 1999 (MASS-I)	17	72	48	70	100.0%	0.34 [0.22, 0.54]
Total (95% CI)		**72**		**70**	**100.0%**	**0.34 [0.22, 0.54]**
Total events	17		48			

Heterogeneity: Not applicable
Test for overall effect: Z = 4.70 (P < 0.00001)

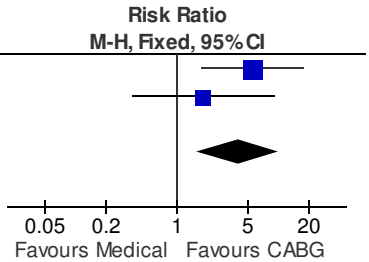


6 Left main stem disease- Medium term follow-up (2 to 4 years)

6.1 Death

Study or Subgroup	Medical Events	Medical Total	CABG Events	CABG Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Detre 1977 (VA study)	16	44	3	46	58.3%	5.58 [1.74, 17.82]
Varnauskas 1979 (ECSS)	4	31	2	28	41.7%	1.81 [0.36, 9.12]
Total (95% CI)		**75**		**74**	**100.0%**	**4.00 [1.60, 10.03]**
Total events	20		5			

Heterogeneity: $Chi^2 = 1.24$, df = 1 (P = 0.27); $I^2 = 19\%$
Test for overall effect: Z = 2.96 (P = 0.003)

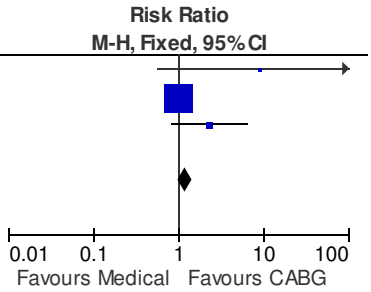


7 Left main stem disease- Long term follow-up (>4 years)

7.1 Death

Study or Subgroup	Medical Events	Medical Total	CABG Events	CABG Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Alderman 1990 (CASS)	3	6	0	8	1.0%	9.00 [0.55, 147.08]
Peduzzi 1998 (VA study)	38	43	43	48	89.8%	0.99 [0.85, 1.14]
Varnauskas 1982 (ECSS)	10	31	4	28	9.3%	2.26 [0.80, 6.39]
Total (95% CI)		**80**		**84**	**100.0%**	**1.18 [0.97, 1.43]**
Total events	51		47			

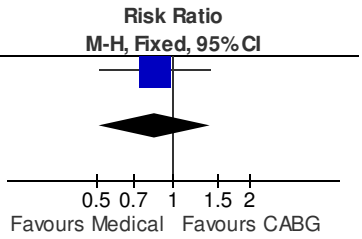
Heterogeneity: Chi² = 9.48, df = 2 (P = 0.009); I² = 79%
Test for overall effect: Z = 1.69 (P = 0.09)



7.2 MI

Study or Subgroup	Medical Events	Medical Total	CABG Events	CABG Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Peduzzi 1998 (VA study)	16	43	21	48	100.0%	0.85 [0.51, 1.41]
Total (95% CI)		**43**		**48**	**100.0%**	**0.85 [0.51, 1.41]**
Total events	16		21			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.63 (P = 0.53)

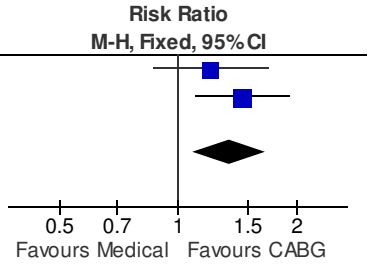


8 Left anterior descending artery - Long term follow-up (>4 years)

8.1 Death

Study or Subgroup	Medical Events	Medical Total	CABG Events	CABG Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Alderman 1990 (CASS)	60	275	50	277	45.3%	1.21 [0.86, 1.69]
Varnauaskas 1988 (ECSS)	84	240	63	262	54.7%	1.46 [1.10, 1.92]
Total (95% CI)		**515**		**539**	**100.0%**	**1.34 [1.09, 1.66]**
Total events	144		113			

Heterogeneity: Chi² = 0.70, df = 1 (P = 0.40); I² = 0%
Test for overall effect: Z = 2.72 (P = 0.007)

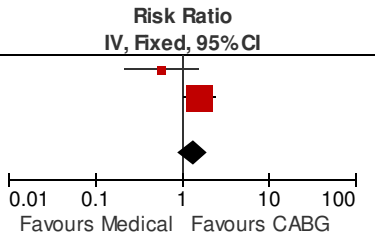


9 Sub group interaction

9.1 Sub group 2 vessel and 3 vessel (Death) - Multivessel medium term follow-up

Study or Subgroup	log[Risk Ratio]	SE	Weight	Risk Ratio IV, Fixed, 95% CI
meta analysis- 2 vessel	-0.5621189	0.508273	16.1%	0.57 [0.21, 1.54]
meta analysis- 3 vessel	0.45107562	0.222499	83.9%	1.57 [1.02, 2.43]
Total (95% CI)			**100.0%**	**1.33 [0.89, 1.99]**

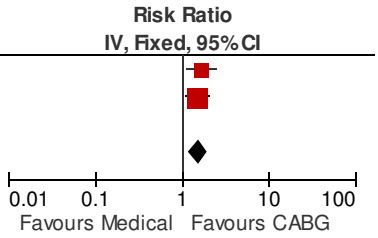
Heterogeneity: Chi² = 3.33, df = 1 (P = 0.07); I² = 70%
Test for overall effect: Z = 1.41 (P = 0.16)



9.2 Sub group 2 vessel and 3 vessel (Death) - Multivessel-long term follow-up

Study or Subgroup	log[Risk Ratio]	SE	Weight	Risk Ratio IV, Fixed, 95% CI
meta analysis- 2 vessel	0.49469624	0.20428	40.1%	1.64 [1.10, 2.45]
meta analysis- 3 vessel	0.39204209	0.167104	59.9%	1.48 [1.07, 2.05]
Total (95% CI)			**100.0%**	**1.54 [1.20, 1.99]**

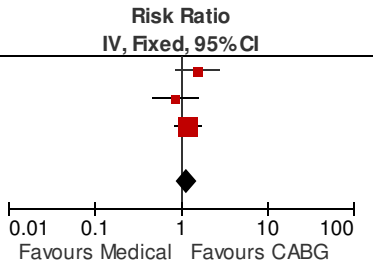
Heterogeneity: Chi² = 0.15, df = 1 (P = 0.70); I² = 0%
Test for overall effect: Z = 3.35 (P = 0.0008)



9.3 Sub group age <47, 47-53, >53 years (Death) - Multivessel -long term follow-up

Study or Subgroup	log[Risk Ratio]	SE	Weight	Risk Ratio IV, Fixed, 95% CI
meta analysis- 47-53	0.43178242	0.302288	22.0%	1.54 [0.85, 2.79]
meta analysis- age <47	-0.1508229	0.317993	19.9%	0.86 [0.46, 1.60]
meta analysis->53	0.16551444	0.18599	58.1%	1.18 [0.82, 1.70]
Total (95% CI)			**100.0%**	**1.17 [0.89, 1.55]**

Heterogeneity: Chi² = 1.76, df = 2 (P = 0.41); I² = 0%
Test for overall effect: Z = 1.14 (P = 0.26)

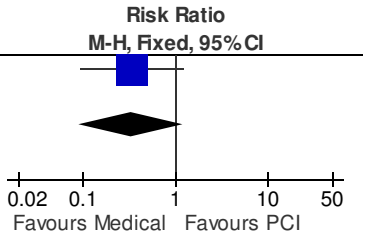


1 Multivessel disease - short term follow-up (1 year)

1.1 Death

Study or Subgroup	Medical Events	Medical Total	PCI Events	PCI Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Hueb 2004 (MASS-II)	3	203	9	205	100.0%	0.34 [0.09, 1.23]
Total (95% CI)		**203**		**205**	**100.0%**	**0.34 [0.09, 1.23]**
Total events	3		9			

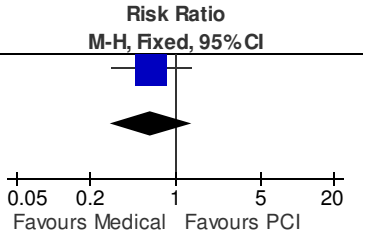
Heterogeneity: Not applicable
Test for overall effect: Z = 1.65 (P = 0.10)



1.2 Q wave MI

Study or Subgroup	Medical Events	Medical Total	PCI Events	PCI Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Hueb 2004 (MASS-II)	10	203	16	205	100.0%	0.63 [0.29, 1.36]
Total (95% CI)		**203**		**205**	**100.0%**	**0.63 [0.29, 1.36]**
Total events	10		16			

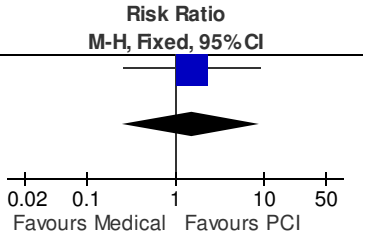
Heterogeneity: Not applicable
Test for overall effect: Z = 1.18 (P = 0.24)



1.3 Stroke

Study or Subgroup	Medical Events	Medical Total	PCI Events	PCI Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Hueb 2004 (MASS-II)	3	203	2	205	100.0%	1.51 [0.26, 8.97]
Total (95% CI)		**203**		**205**	**100.0%**	**1.51 [0.26, 8.97]**
Total events	3		2			

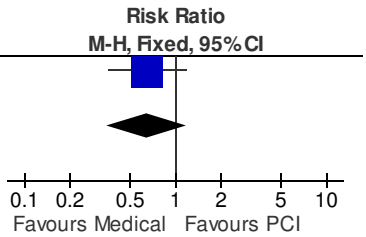
Heterogeneity: Not applicable
Test for overall effect: Z = 0.46 (P = 0.65)



1.4 Non protocol revascularisation

Study or Subgroup	Medical Events	Medical Total	PCI Events	PCI Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Hueb 2004 (MASS-II)	16	203	25	205	100.0%	0.65 [0.36, 1.17]
Total (95% CI)		**203**		**205**	**100.0%**	**0.65 [0.36, 1.17]**
Total events	16		25			

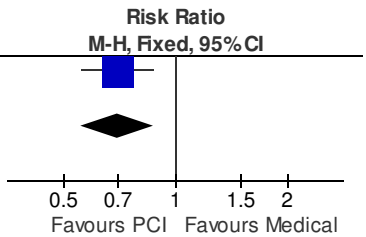
Heterogeneity: Not applicable
Test for overall effect: Z = 1.43 (P = 0.15)



1.5 Free of angina

Study or Subgroup	Medical Events	Medical Total	PCI Events	PCI Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Hueb 2004 (MASS-II)	74	203	107	205	100.0%	0.70 [0.56, 0.87]
Total (95% CI)		**203**		**205**	**100.0%**	**0.70 [0.56, 0.87]**
Total events	74		107			

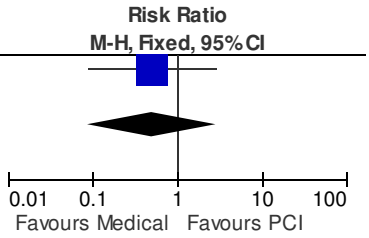
Heterogeneity: Not applicable
Test for overall effect: Z = 3.14 (P = 0.002)



1.6 Death- Sub group diabetes

Study or Subgroup	Medical Events	Medical Total	PCI Events	PCI Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Soares 2006 (MASS-II)	2	75	3	56	100.0%	0.50 [0.09, 2.88]
Total (95% CI)		**75**		**56**	**100.0%**	**0.50 [0.09, 2.88]**
Total events	2		3			

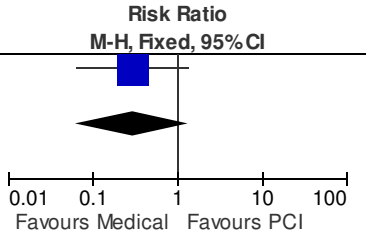
Heterogeneity: Not applicable
Test for overall effect: Z = 0.78 (P = 0.44)



1.7 Death- Subgroup no diabetes

Study or Subgroup	Medical Events	Medical Total	PCI Events	PCI Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Soares 2006 (MASS-II)	2	128	8	149	100.0%	0.29 [0.06, 1.35]
Total (95% CI)		**128**		**149**	**100.0%**	**0.29 [0.06, 1.35]**
Total events	2		8			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.58 (P = 0.11)

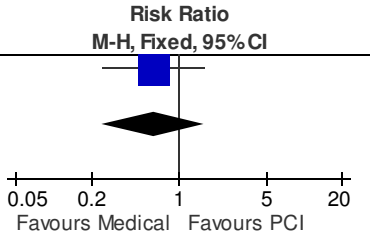


2 Multi vessel disease- medium term follow-up (2 to 4 years)

2.1 Death

Study or Subgroup	Medical Events	Medical Total	PCI Events	PCI Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Chamberlain 1997 (RITA-2)	7	514	11	504	100.0%	0.62 [0.24, 1.60]
Total (95% CI)		**514**		**504**	**100.0%**	**0.62 [0.24, 1.60]**
Total events	7		11			

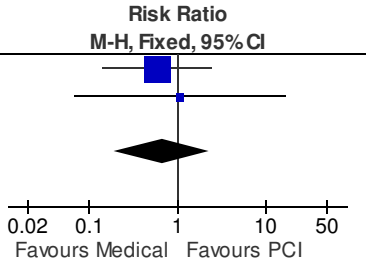
Heterogeneity: Not applicable
Test for overall effect: Z = 0.98 (P = 0.33)



2.2 cardiac death

Study or Subgroup	Medical Events	Medical Total	PCI Events	PCI Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Chamberlain 1997 (RITA-2)	3	514	5	504	84.0%	0.59 [0.14, 2.45]
Pitt 1999 (AVERT)	1	164	1	177	16.0%	1.08 [0.07, 17.11]
Total (95% CI)		**678**		**681**	**100.0%**	**0.67 [0.19, 2.35]**
Total events	4		6			

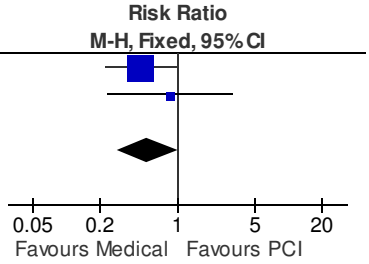
Heterogeneity: Chi² = 0.15, df = 1 (P = 0.70); I² = 0%
Test for overall effect: Z = 0.63 (P = 0.53)



2.3 Non fatal MI

Study or Subgroup	Medical Events	Medical Total	PCI Events	PCI Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Chamberlain 1997 (RITA-2)	10	514	21	504	81.5%	0.47 [0.22, 0.98]
Pitt 1999 (AVERT)	4	164	5	177	18.5%	0.86 [0.24, 3.16]
Total (95% CI)		**678**		**681**	**100.0%**	**0.54 [0.28, 1.02]**
Total events	14		26			

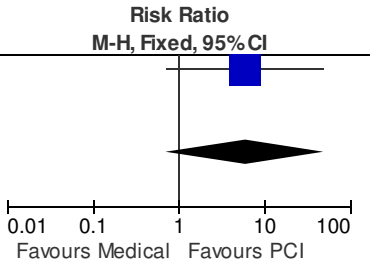
Heterogeneity: Chi² = 0.65, df = 1 (P = 0.42); I² = 0%
Test for overall effect: Z = 1.89 (P = 0.06)



2.4 Stroke

Study or Subgroup	Medical Events	Medical Total	PCI Events	PCI Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Chamberlain 1997 (RITA-2)	6	514	1	504	100.0%	5.88 [0.71, 48.69]
Pitt 1999 (AVERT)	0	164	0	164		Not estimable
Total (95% CI)		**678**		**668**	**100.0%**	**5.88 [0.71, 48.69]**
Total events	6		1			

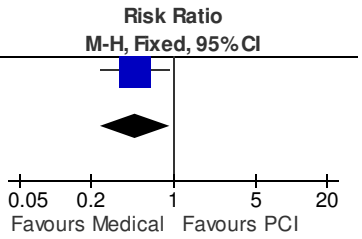
Heterogeneity: Not applicable
Test for overall effect: Z = 1.64 (P = 0.10)



2.5 Hospitalisation (for worsening of angina) no. of patients

Study or Subgroup	Medical Events	Medical Total	PCI Events	PCI Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Pitt 1999 (AVERT)	11	164	25	177	100.0%	0.47 [0.24, 0.93]
Total (95% CI)		**164**		**177**	**100.0%**	**0.47 [0.24, 0.93]**
Total events	11		25			

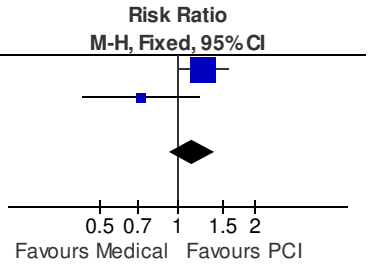
Heterogeneity: Not applicable
Test for overall effect: Z = 2.16 (P = 0.03)



2.6 Non protocol Revascularisation

Study or Subgroup	Medical Events	Medical Total	PCI Events	PCI Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Chamberlain 1997 (RITA-2)	131	514	102	504	78.1%	1.26 [1.00, 1.58]
Pitt 1999 (AVERT)	20	164	30	177	21.9%	0.72 [0.43, 1.22]
Total (95% CI)		**678**		**681**	**100.0%**	**1.14 [0.93, 1.40]**
Total events	151		132			

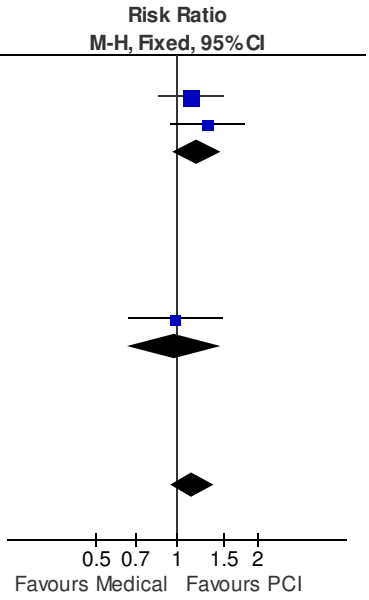
Heterogeneity: $Chi^2 = 3.69$, df = 1 (P = 0.05); $I^2 = 73\%$
Test for overall effect: Z = 1.24 (P = 0.21)



3 Multivessel disease-long term follow-up (> 4 years follow-up)

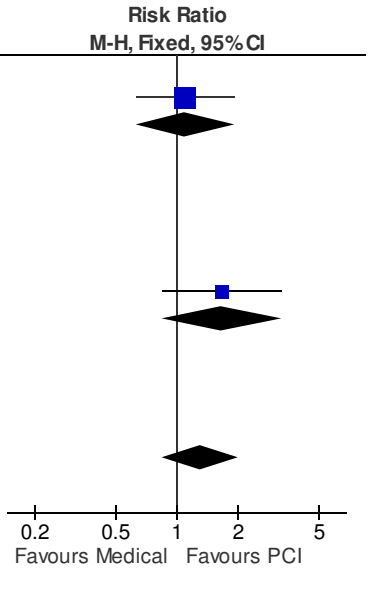
3.1 Death

Study or Subgroup	Medical Events	Medical Total	PCI Events	PCI Total	Weight	Risk Ratio M-H, Fixed, 95% CI
3.1.1 angioplasty and stents						
Boden 2007 (COURAGE)	95	1138	85	1149	47.9%	1.13 [0.85, 1.49]
Hueb 2010 (MASS-II)	63	203	49	205	27.6%	1.30 [0.94, 1.79]
Subtotal (95% CI)		**1341**		**1354**	**75.4%**	**1.19 [0.96, 1.47]**
Total events	158		134			
Heterogeneity: Chi² = 0.42, df = 1 (P = 0.52); I² = 0%						
Test for overall effect: Z = 1.61 (P = 0.11)						
3.1.2 angioplasty						
Henderson 2003 (RITA-2)	43	514	43	504	24.6%	0.98 [0.65, 1.47]
Subtotal (95% CI)		**514**		**504**	**24.6%**	**0.98 [0.65, 1.47]**
Total events	43		43			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.10 (P = 0.92)						
Total (95% CI)		**1855**		**1858**	**100.0%**	**1.14 [0.94, 1.37]**
Total events	201		177			
Heterogeneity: Chi² = 1.18, df = 2 (P = 0.55); I² = 0%						
Test for overall effect: Z = 1.36 (P = 0.17)						
Test for subgroup differences: Chi² = 0.69, df = 1 (P = 0.40), I² = 0%						



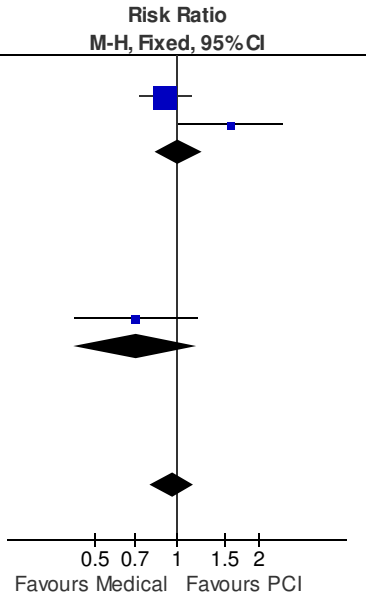
3.2 cardiac death

Study or Subgroup	Medical Events	Medical Total	PCI Events	PCI Total	Weight	Risk Ratio M-H, Fixed, 95% CI
3.2.1 angioplasty and stents						
Boden 2007 (COURAGE)	25	1138	23	1149	63.6%	1.10 [0.63, 1.92]
Subtotal (95% CI)		**1138**		**1149**	**63.6%**	**1.10 [0.63, 1.92]**
Total events	25		23			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.33 (P = 0.74)						
3.2.2 angioplasty						
Henderson 2003 (RITA-2)	22	514	13	504	36.4%	1.66 [0.85, 3.26]
Subtotal (95% CI)		**514**		**504**	**36.4%**	**1.66 [0.85, 3.26]**
Total events	22		13			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.47 (P = 0.14)						
Total (95% CI)		**1652**		**1653**	**100.0%**	**1.30 [0.85, 2.00]**
Total events	47		36			
Heterogeneity: Chi² = 0.85, df = 1 (P = 0.36); I² = 0%						
Test for overall effect: Z = 1.21 (P = 0.23)						
Test for subgroup differences: Chi² = 0.85, df = 1 (P = 0.36), I² = 0%						



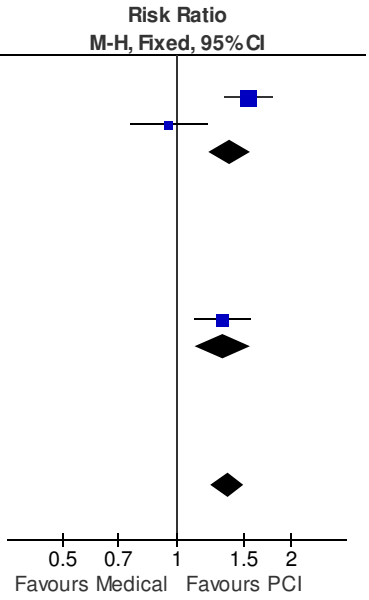
3.3 Non fatal MI

Study or Subgroup	Medical Events	Medical Total	PCI Events	PCI Total	Weight	Risk Ratio M-H, Fixed, 95% CI
3.3.1 angioplasty and Stents						
Boden 2007 (COURAGE)	128	1138	143	1149	70.6%	0.90 [0.72, 1.13]
Hueb 2010 (MASS-II)	42	203	27	205	13.3%	1.57 [1.01, 2.45]
Subtotal (95% CI)		**1341**		**1354**	**84.0%**	**1.01 [0.83, 1.23]**
Total events	170		170			
Heterogeneity: Chi² = 4.77, df = 1 (P = 0.03); I² = 79%						
Test for overall effect: Z = 0.10 (P = 0.92)						
3.3.2 angioplasty						
Henderson 2003 (RITA-2)	23	514	32	504	16.0%	0.70 [0.42, 1.19]
Subtotal (95% CI)		**514**		**504**	**16.0%**	**0.70 [0.42, 1.19]**
Total events	23		32			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.31 (P = 0.19)						
Total (95% CI)		**1855**		**1858**	**100.0%**	**0.96 [0.80, 1.16]**
Total events	193		202			
Heterogeneity: Chi² = 6.38, df = 2 (P = 0.04); I² = 69%						
Test for overall effect: Z = 0.42 (P = 0.67)						
Test for subgroup differences: Chi² = 1.59, df = 1 (P = 0.21), I² = 37.3%						



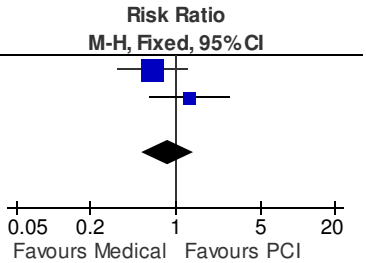
3.4 Non protocol Revascularisation

Study or Subgroup	Medical Events	Medical Total	PCI Events	PCI Total	Weight	Risk Ratio M-H, Fixed, 95% CI
3.4.1 angioplasty and stents						
Boden 2007 (COURAGE)	348	1138	228	1149	49.0%	1.54 [1.33, 1.78]
Hueb 2010 (MASS-II)	80	203	85	205	18.3%	0.95 [0.75, 1.20]
Subtotal (95% CI)		**1341**		**1354**	**67.3%**	**1.38 [1.22, 1.56]**
Total events	428		313			
Heterogeneity: Chi² = 11.83, df = 1 (P = 0.0006); I² = 92%						
Test for overall effect: Z = 5.10 (P < 0.00001)						
3.4.2 angioplasty						
Henderson 2003 (RITA-2)	202	514	150	504	32.7%	1.32 [1.11, 1.57]
Subtotal (95% CI)		**514**		**504**	**32.7%**	**1.32 [1.11, 1.57]**
Total events	202		150			
Heterogeneity: Not applicable						
Test for overall effect: Z = 3.17 (P = 0.002)						
Total (95% CI)		**1855**		**1858**	**100.0%**	**1.36 [1.23, 1.51]**
Total events	630		463			
Heterogeneity: Chi² = 11.84, df = 2 (P = 0.003); I² = 83%						
Test for overall effect: Z = 6.00 (P < 0.00001)						
Test for subgroup differences: Chi² = 0.17, df = 1 (P = 0.68), I² = 0%						



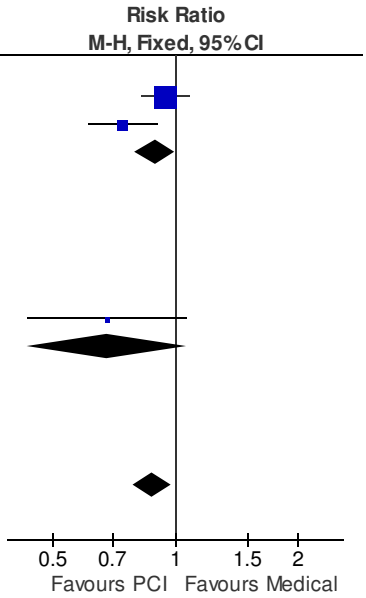
3.5 stroke

Study or Subgroup	Medical Events	Medical Total	PCI Events	PCI Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Boden 2007 (COURAGE)	14	1138	22	1149	66.7%	0.64 [0.33, 1.25]
Hueb 2010 (MASS-II)	14	203	11	205	33.3%	1.29 [0.60, 2.76]
Total (95% CI)		**1341**		**1354**	**100.0%**	**0.86 [0.52, 1.41]**
Total events	28		33			
Heterogeneity: Chi² = 1.80, df = 1 (P = 0.18); I² = 44%						
Test for overall effect: Z = 0.61 (P = 0.54)						



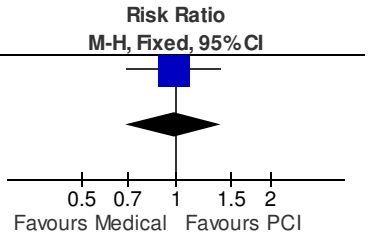
3.6 Free of angina

Study or Subgroup	Medical Events	Medical Total	PCI Events	PCI Total	Weight	Risk Ratio M-H, Fixed, 95% CI
3.6.1 angioplasty and stents						
Boden 2007 (COURAGE)	296	1138	316	1149	68.3%	0.95 [0.83, 1.08]
Hueb 2010 (MASS-II)	88	203	120	205	25.9%	0.74 [0.61, 0.90]
Subtotal (95% CI)		**1341**		**1354**	**94.2%**	**0.89 [0.79, 1.00]**
Total events	384		436			
Heterogeneity: Chi² = 4.18, df = 1 (P = 0.04); I² = 76%						
Test for overall effect: Z = 2.04 (P = 0.04)						
3.6.2 angioplasty						
Folland 1997 (ACME)	18	50	27	51	5.8%	0.68 [0.43, 1.07]
Subtotal (95% CI)		**50**		**51**	**5.8%**	**0.68 [0.43, 1.07]**
Total events	18		27			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.68 (P = 0.09)						
Total (95% CI)		**1391**		**1405**	**100.0%**	**0.88 [0.79, 0.98]**
Total events	402		463			
Heterogeneity: Chi² = 5.30, df = 2 (P = 0.07); I² = 62%						
Test for overall effect: Z = 2.35 (P = 0.02)						
Test for subgroup differences: Chi² = 1.28, df = 1 (P = 0.26), I² = 21.8%						



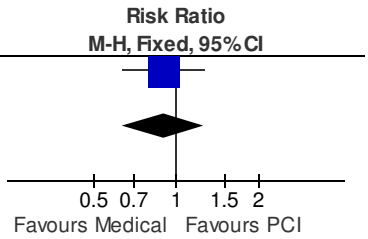
3.7 Death- sub group age >65 yrs

Study or Subgroup	Medical Events	Medical Total	PCI Events	PCI Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Teo 2009 (COURAGE)	54	444	57	460	100.0%	0.98 [0.69, 1.39]
Total (95% CI)		**444**		**460**	**100.0%**	**0.98 [0.69, 1.39]**
Total events	54		57			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.10 (P = 0.92)						



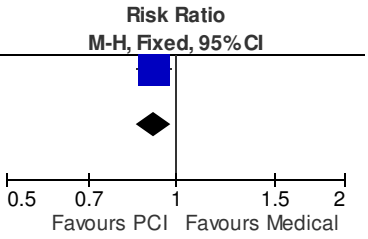
3.8 MI- sub group age >65 yrs

Study or Subgroup	Medical Events	Medical Total	PCI Events	PCI Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Teo 2009 (COURAGE)	52	444	60	460	100.0%	0.90 [0.63, 1.27]
Total (95% CI)		**444**		**460**	**100.0%**	**0.90 [0.63, 1.27]**
Total events	52		60			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.61 (P = 0.54)						



3.9 Free of angina- sub group age >65 yrs

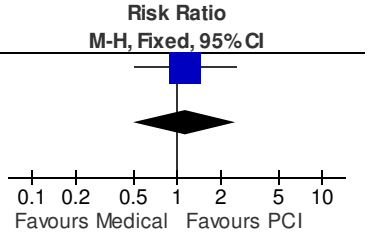
Study or Subgroup	Medical Events	Medical Total	PCI Events	PCI Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Teo 2009 (COURAGE)	324	444	368	460	100.0%	0.91 [0.85, 0.98]
Total (95% CI)		**444**		**460**	**100.0%**	**0.91 [0.85, 0.98]**
Total events	324		368			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.48 (P = 0.01)						



3.10 Death- sub group 2 vessel disease

Study or Subgroup	Medical Events	Medical Total	PCI Events	PCI Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Folland 1997 (ACME)	10	50	9	51	100.0%	1.13 [0.50, 2.55]
Total (95% CI)		**50**		**51**	**100.0%**	**1.13 [0.50, 2.55]**
Total events	10		9			

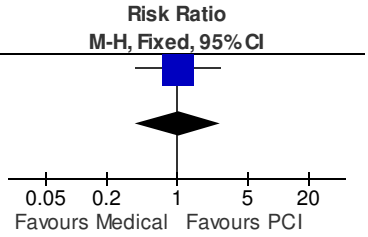
Heterogeneity: Not applicable
Test for overall effect: Z = 0.30 (P = 0.76)



3.11 Non fatal MI- sub group 2 vesel disease

Study or Subgroup	Medical Events	Medical Total	PCI Events	PCI Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Folland 1997 (ACME)	7	50	7	51	100.0%	1.02 [0.39, 2.70]
Total (95% CI)		**50**		**51**	**100.0%**	**1.02 [0.39, 2.70]**
Total events	7		7			

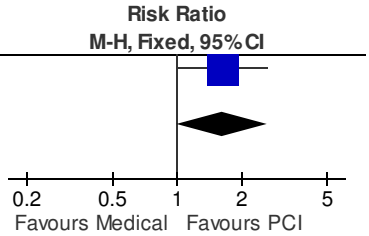
Heterogeneity: Not applicable
Test for overall effect: Z = 0.04 (P = 0.97)



3.12 Death- sub group age <65 yrs

Study or Subgroup	Medical Events	Medical Total	PCI Events	PCI Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Teo 2009 (COURAGE)	41	693	25	688	100.0%	1.63 [1.00, 2.65]
Total (95% CI)		**693**		**688**	**100.0%**	**1.63 [1.00, 2.65]**
Total events	41		25			

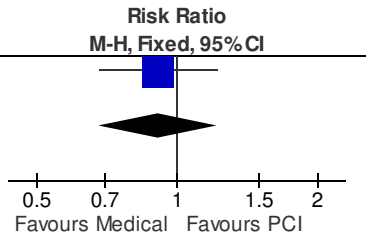
Heterogeneity: Not applicable
Test for overall effect: Z = 1.97 (P = 0.05)



3.13 MI - sub group age <65 yrs

Study or Subgroup	Medical Events	Medical Total	PCI Events	PCI Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Teo 2009 (COURAGE)	76	693	83	688	100.0%	0.91 [0.68, 1.22]
Total (95% CI)		**693**		**688**	**100.0%**	**0.91 [0.68, 1.22]**
Total events	76		83			

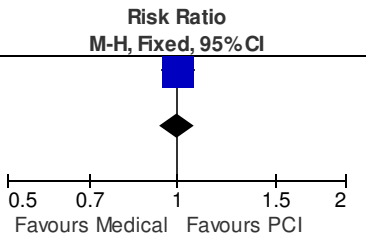
Heterogeneity: Not applicable
Test for overall effect: Z = 0.64 (P = 0.52)



3.14 Free of angina- sub group age<65 years

Study or Subgroup	Medical Events	Medical Total	PCI Events	PCI Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Teo 2009 (COURAGE)	485	693	481	688	100.0%	1.00 [0.93, 1.07]
Total (95% CI)		**693**		**688**	**100.0%**	**1.00 [0.93, 1.07]**
Total events	485		481			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.03 (P = 0.98)

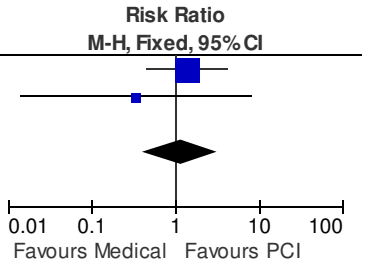


4 Single vessel disease - medium term follow-up (2 -4 years)

4.1 Death

Study or Subgroup	Medical Events	Medical Total	PCI Events	PCI Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Hartigan 1998 (ACME)	7	107	5	105	77.1%	1.37 [0.45, 4.19]
Hueb 1995 (MASS-I)	0	72	1	72	22.9%	0.33 [0.01, 8.05]
Total (95% CI)		**179**		**177**	**100.0%**	**1.14 [0.41, 3.17]**
Total events	7		6			

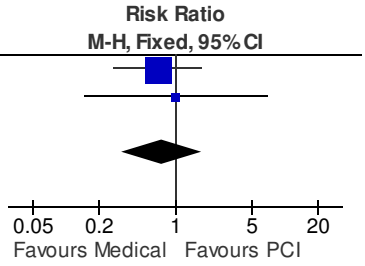
Heterogeneity: Chi² = 0.68, df = 1 (P = 0.41); I² = 0%
Test for overall effect: Z = 0.24 (P = 0.81)



4.2 MI

Study or Subgroup	Medical Events	Medical Total	PCI Events	PCI Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Hartigan 1998 (ACME)	7	107	10	105	83.5%	0.69 [0.27, 1.74]
Hueb 1995 (MASS-I)	2	72	2	72	16.5%	1.00 [0.14, 6.91]
Total (95% CI)		**179**		**177**	**100.0%**	**0.74 [0.32, 1.70]**
Total events	9		12			

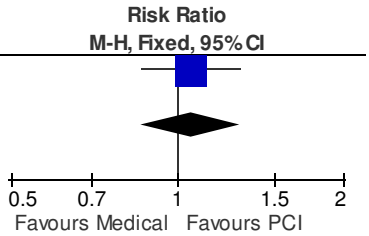
Heterogeneity: Chi² = 0.12, df = 1 (P = 0.73); I² = 0%
Test for overall effect: Z = 0.71 (P = 0.48)



4.3 Hospitalisation (no. of patients)

Study or Subgroup	Medical Events	Medical Total	PCI Events	PCI Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Hartigan 1998 (ACME)	69	107	64	105	100.0%	1.06 [0.86, 1.30]
Total (95% CI)		**107**		**105**	**100.0%**	**1.06 [0.86, 1.30]**
Total events	69		64			

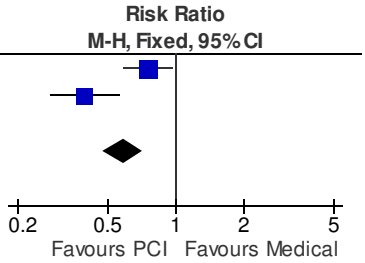
Heterogeneity: Not applicable
Test for overall effect: Z = 0.53 (P = 0.60)



4.4 Free of angina

Study or Subgroup	Medical Events	Medical Total	PCI Events	PCI Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Hartigan 1998 (ACME)	50	107	65	105	53.1%	0.75 [0.59, 0.97]
Hueb 1995 (MASS-I)	23	72	58	72	46.9%	0.40 [0.28, 0.57]
Total (95% CI)		**179**		**177**	**100.0%**	**0.59 [0.48, 0.72]**
Total events	73		123			

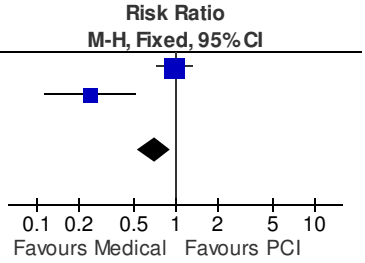
Heterogeneity: Chi² = 8.50, df = 1 (P = 0.004); I² = 88%
Test for overall effect: Z = 5.11 (P < 0.00001)



4.5 Non protocol revascularisation

Study or Subgroup	Medical Events	Medical Total	PCI Events	PCI Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Hartigan 1998 (ACME)	47	107	47	105	62.1%	0.98 [0.73, 1.33]
Hueb 1995 (MASS-I)	7	72	29	72	37.9%	0.24 [0.11, 0.52]
Total (95% CI)		**179**		**177**	**100.0%**	**0.70 [0.53, 0.93]**
Total events	54		76			

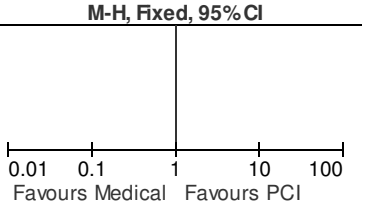
Heterogeneity: Chi² = 12.39, df = 1 (P = 0.0004); I² = 92%
Test for overall effect: Z = 2.50 (P = 0.01)



4.6 Stroke

Study or Subgroup	Medical Events	Medical Total	PCI Events	PCI Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Hueb 1995 (MASS-I)	0	72	0	72		Not estimable
Total (95% CI)		**72**		**72**		**Not estimable**
Total events	0		0			

Heterogeneity: Not applicable
Test for overall effect: Not applicable

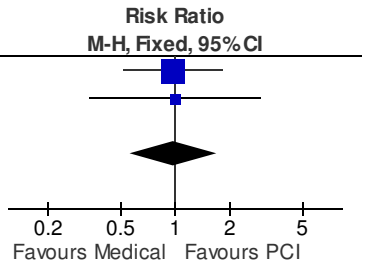


5 Single vessel disease - long term follow-up (>4 years)

5.1 Death

Study or Subgroup	Medical Events	Medical Total	PCI Events	PCI Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Folland 1997 (ACME)	16	112	17	115	73.7%	0.97 [0.51, 1.82]
Hueb 1999 (MASS-I)	6	72	6	72	26.3%	1.00 [0.34, 2.95]
Total (95% CI)		**184**		**187**	**100.0%**	**0.98 [0.57, 1.68]**
Total events	22		23			

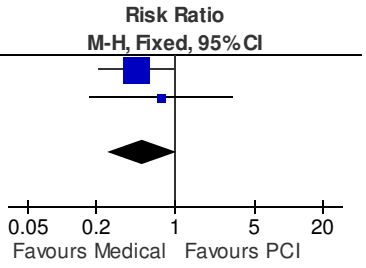
Heterogeneity: Chi² = 0.00, df = 1 (P = 0.96); I² = 0%
Test for overall effect: Z = 0.09 (P = 0.93)



5.2 Non fatal MI

Study or Subgroup	Medical Events	Medical Total	PCI Events	PCI Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Folland 1997 (ACME)	8	112	18	115	81.6%	0.46 [0.21, 1.01]
Hueb 1999 (MASS-I)	3	72	4	72	18.4%	0.75 [0.17, 3.23]
Total (95% CI)		**184**		**187**	**100.0%**	**0.51 [0.26, 1.02]**
Total events	11		22			

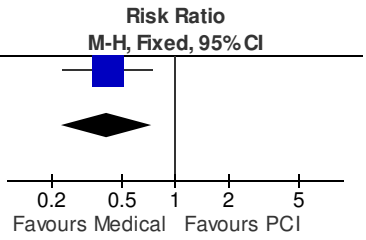
Heterogeneity: Chi² = 0.34, df = 1 (P = 0.56); I² = 0%
Test for overall effect: Z = 1.91 (P = 0.06)



5.3 Non protocol Revascularisation

Study or Subgroup	Medical Events	Medical Total	PCI Events	PCI Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Hueb 1999 (MASS-I)	12	72	29	72	100.0%	0.41 [0.23, 0.75]
Total (95% CI)		**72**		**72**	**100.0%**	**0.41 [0.23, 0.75]**
Total events	12		29			

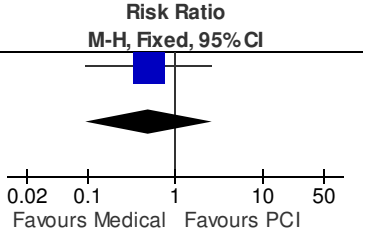
Heterogeneity: Not applicable
Test for overall effect: Z = 2.94 (P = 0.003)



5.4 cardiac death

Study or Subgroup	Medical Events	Medical Total	PCI Events	PCI Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Hueb 1999 (MASS-I)	2	72	4	72	100.0%	0.50 [0.09, 2.64]
Total (95% CI)		**72**		**72**	**100.0%**	**0.50 [0.09, 2.64]**
Total events	2		4			

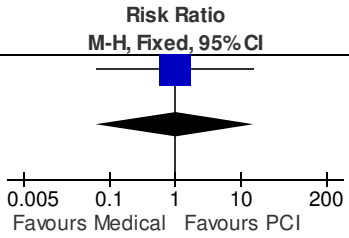
Heterogeneity: Not applicable
Test for overall effect: Z = 0.82 (P = 0.41)



5.5 stroke

Study or Subgroup	Medical Events	Medical Total	PCI Events	PCI Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Hueb 1999 (MASS-I)	1	72	1	72	100.0%	1.00 [0.06, 15.68]
Total (95% CI)		**72**		**72**	**100.0%**	**1.00 [0.06, 15.68]**
Total events	1		1			

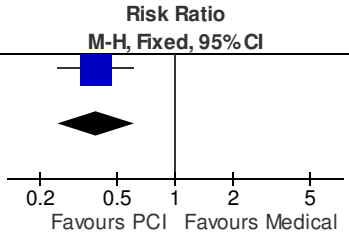
Heterogeneity: Not applicable
Test for overall effect: Z = 0.00 (P = 1.00)



5.6 Free of angina

Study or Subgroup	Medical Events	Medical Total	PCI Events	PCI Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Hueb 1999 (MASS-I)	17	72	44	72	100.0%	0.39 [0.25, 0.61]
Total (95% CI)		**72**		**72**	**100.0%**	**0.39 [0.25, 0.61]**
Total events	17		44			

Heterogeneity: Not applicable
Test for overall effect: Z = 4.10 (P < 0.0001)

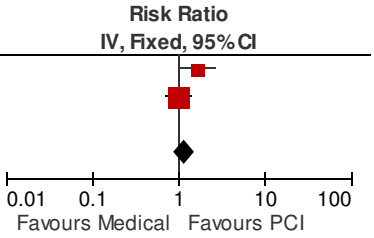


6 Sub group interaction

6.1 Age >and >65 yrs (Death) - Multivessel -LOng term follow-up

Study or Subgroup	log[Risk Ratio]	SE	Weight	Risk Ratio IV, Fixed, 95% CI
meta analysis- age<65	0.48858001	0.248612	34.1%	1.63 [1.00, 2.65]
meta analysis-age>65	-0.0202027	0.178665	65.9%	0.98 [0.69, 1.39]
Total (95% CI)			**100.0%**	**1.17 [0.88, 1.55]**

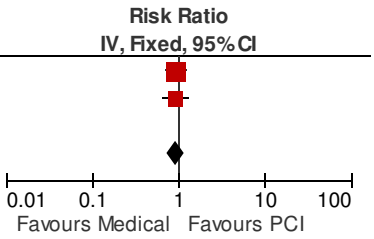
Heterogeneity: Chi² = 2.76, df = 1 (P = 0.10); I² = 64%
Test for overall effect: Z = 1.06 (P = 0.29)



6.2 Age < and >65 yrs (MI)-Multivessel -Long term follow-up

Study or Subgroup	log[Risk Ratio]	SE	Weight	Risk Ratio IV, Fixed, 95% CI
meta analysis- age<65	-0.0943107	0.149111	59.0%	0.91 [0.68, 1.22]
meta analysis-age>65	-0.1053605	0.17884	41.0%	0.90 [0.63, 1.28]
Total (95% CI)			**100.0%**	**0.91 [0.72, 1.13]**

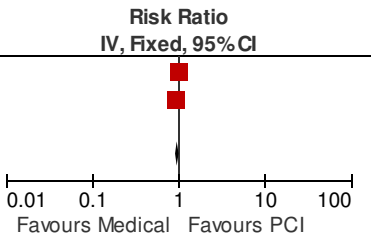
Heterogeneity: Chi² = 0.00, df = 1 (P = 0.96); I² = 0%
Test for overall effect: Z = 0.86 (P = 0.39)



6.3 Age <65 and >65 yrs (Free of angina)- Multivessel- Long term follow-up)

Study or Subgroup	log[Risk Ratio]	SE	Weight	Risk Ratio IV, Fixed, 95% CI
meta analysis- age<65	0	0.035773	50.7%	1.00 [0.93, 1.07]
meta analysis-age>65	-0.0943107	0.036305	49.3%	0.91 [0.85, 0.98]
Total (95% CI)			**100.0%**	**0.95 [0.91, 1.00]**

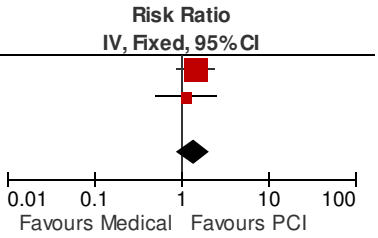
Heterogeneity: Chi² = 3.42, df = 1 (P = 0.06); I² = 71%
Test for overall effect: Z = 1.82 (P = 0.07)



6.4 Single vessel and 2 vessel (Death)- Long term follow-up

Study or Subgroup	log[Risk Ratio]	SE	Weight	Risk Ratio IV, Fixed, 95% CI
meta analysis- single ves	0.37156356	0.255944	72.5%	1.45 [0.88, 2.39]
meta analysis-2 vessel	0.12221763	0.415623	27.5%	1.13 [0.50, 2.55]
Total (95% CI)			**100.0%**	**1.35 [0.88, 2.08]**

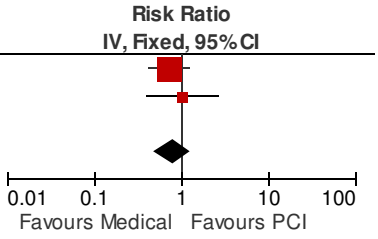
Heterogeneity: Chi² = 0.26, df = 1 (P = 0.61); I² = 0%
Test for overall effect: Z = 1.39 (P = 0.16)



6.5 Single vessel and 2 vessel (MI)- Long term follow-up

Study or Subgroup	log[Risk Ratio]	SE	Weight	Risk Ratio IV, Fixed, 95% CI
meta analysis- single ves	-0.3285041	0.278226	75.9%	0.72 [0.42, 1.24]
meta analysis-2 vessel	0.01980263	0.493587	24.1%	1.02 [0.39, 2.68]
Total (95% CI)			**100.0%**	**0.78 [0.49, 1.26]**

Heterogeneity: Chi² = 0.38, df = 1 (P = 0.54); I² = 0%
Test for overall effect: Z = 1.01 (P = 0.31)

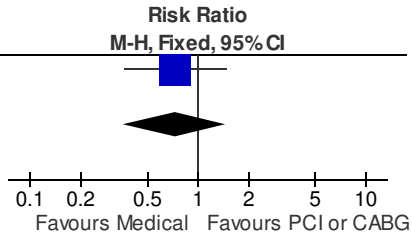


1 Multivessel disease- short term follow-up (1 year)

1.1 Death

Study or Subgroup	Medical Events	Total	PCI or CABG Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Pfisterer 2003 (TIME)	12	148	17	153	100.0%	0.73 [0.36, 1.47]
Total (95% CI)		**148**		**153**	**100.0%**	**0.73 [0.36, 1.47]**
Total events	12		17			

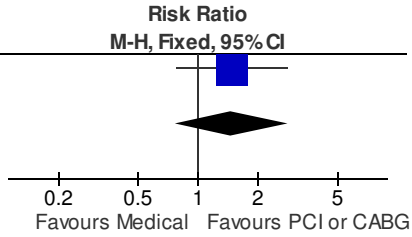
Heterogeneity: Not applicable
Test for overall effect: Z = 0.88 (P = 0.38)



1.2 MI

Study or Subgroup	Medical Events	Total	PCI or CABG Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Pfisterer 2003 (TIME)	20	148	14	153	100.0%	1.48 [0.78, 2.81]
Total (95% CI)		**148**		**153**	**100.0%**	**1.48 [0.78, 2.81]**
Total events	20		14			

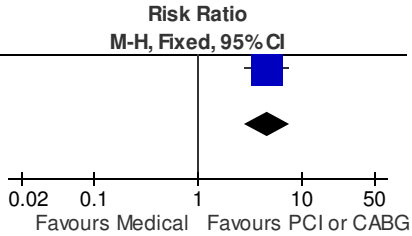
Heterogeneity: Not applicable
Test for overall effect: Z = 1.19 (P = 0.24)



1.3 Non protocol revascularisation

Study or Subgroup	Medical Events	Total	PCI or CABG Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Pfisterer 2003 (TIME)	71	148	16	153	100.0%	4.59 [2.80, 7.51]
Total (95% CI)		**148**		**153**	**100.0%**	**4.59 [2.80, 7.51]**
Total events	71		16			

Heterogeneity: Not applicable
Test for overall effect: Z = 6.06 (P < 0.00001)

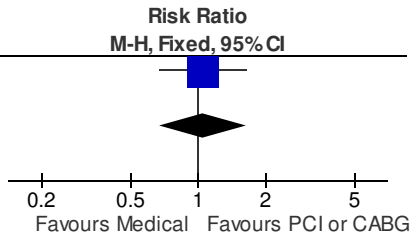


2 Multi vessel disease- medium term follow-up (2 to 4 years)

2.1 Death

Study or Subgroup	Medical Events	Total	PCI or CABG Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Pfisterer 2004 (TIME)	31	139	29	137	100.0%	1.05 [0.67, 1.65]
Total (95% CI)		**139**		**137**	**100.0%**	**1.05 [0.67, 1.65]**
Total events	31		29			

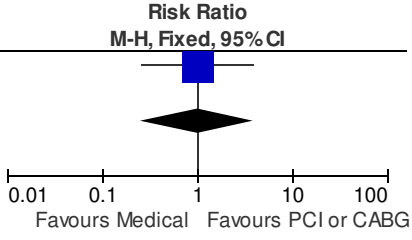
Heterogeneity: Not applicable
Test for overall effect: Z = 0.23 (P = 0.82)



2.2 Non protocol revascularisation

Study or Subgroup	Medical Events	Total	PCI or CABG Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Pfisterer 2004 (TIME)	4	139	4	137	100.0%	0.99 [0.25, 3.86]
Total (95% CI)		**139**		**137**	**100.0%**	**0.99 [0.25, 3.86]**
Total events	4		4			

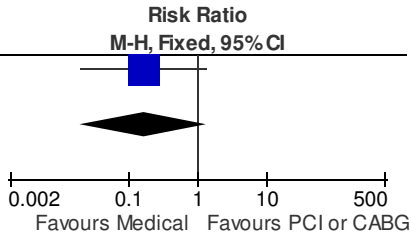
Heterogeneity: Not applicable
Test for overall effect: Z = 0.02 (P = 0.98)



2.3 Non fatal MI

Study or Subgroup	Medical Events	Medical Total	PCI or CABG Events	PCI or CABG Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Pfisterer 2004 (TIME)	1	139	6	137	100.0%	0.16 [0.02, 1.35]
Total (95% CI)		**139**		**137**	**100.0%**	**0.16 [0.02, 1.35]**
Total events	1		6			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.68 (P = 0.09)

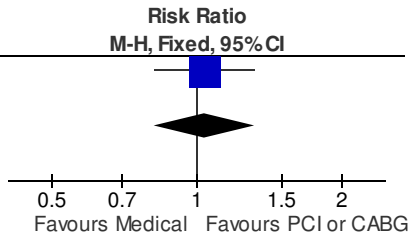


3 Multi vessel disease- Long term follow-up (5 years)

3.1 Death (all patients with type 2 diabetes)

Study or Subgroup	Medical Events	Medical Total	PCI or CABG Events	PCI or CABG Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Frye et al 2009 (BARI-2D)	121	991	112	953	100.0%	1.04 [0.82, 1.32]
Total (95% CI)		**991**		**953**	**100.0%**	**1.04 [0.82, 1.32]**
Total events	121		112			

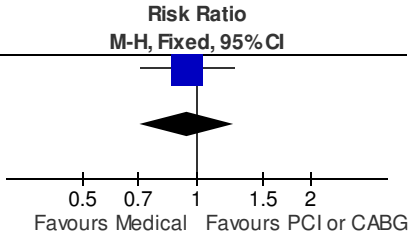
Heterogeneity: Not applicable
Test for overall effect: Z = 0.31 (P = 0.76)



3.2 Death (in PCI stratum in BARI-2D)

Study or Subgroup	Medical Events	Medical Total	PCI Events	PCI Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Frye et al 2009 (BARI-2D)	82	807	86	798	100.0%	0.94 [0.71, 1.26]
Total (95% CI)		**807**		**798**	**100.0%**	**0.94 [0.71, 1.26]**
Total events	82		86			

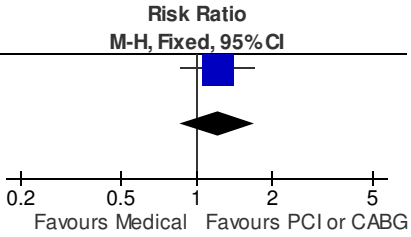
Heterogeneity: Not applicable
Test for overall effect: Z = 0.40 (P = 0.69)



3.3 Death (in CABG stratum in BARI-2D)

Study or Subgroup	Medical Events	Medical Total	CABG Events	CABG Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Frye et al 2009 (BARI-2D)	63	385	51	378	100.0%	1.21 [0.86, 1.71]
Total (95% CI)		**385**		**378**	**100.0%**	**1.21 [0.86, 1.71]**
Total events	63		51			

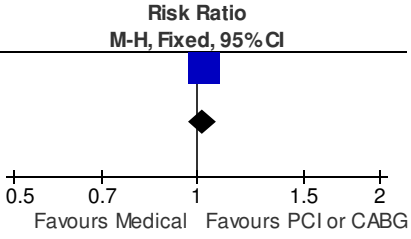
Heterogeneity: Not applicable
Test for overall effect: Z = 1.11 (P = 0.27)



3.4 Freedom from CV events (death, MI or stroke) - PCI stratum (BARI-2D)

Study or Subgroup	Medical Events	Medical Total	PCI Events	PCI Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Frye et al 2009 (BARI-2D)	637	807	614	798	100.0%	1.03 [0.97, 1.08]
Total (95% CI)		**807**		**798**	**100.0%**	**1.03 [0.97, 1.08]**
Total events	637		614			

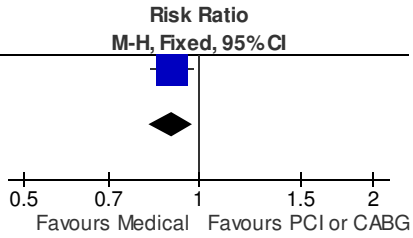
Heterogeneity: Not applicable
Test for overall effect: Z = 0.96 (P = 0.34)



3.5 Freedom from CV events (death, MI or stroke)- CABG stratum(BARI-2D)

Study or Subgroup	Medical Events	Medical Total	CABG Events	CABG Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Frye et al 2009 (BARI-2D)	268	385	293	378	100.0%	0.90 [0.82, 0.98]
Total (95% CI)		**385**		**378**	**100.0%**	**0.90 [0.82, 0.98]**
Total events	268		293			

Heterogeneity: Not applicable
Test for overall effect: Z = 2.47 (P = 0.01)

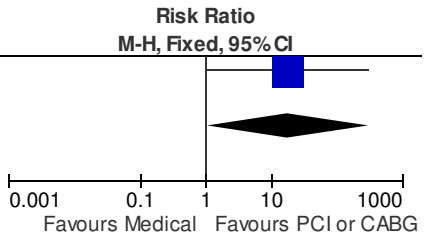


4 Angiography prior randomisation - Multivessel disease short term

4.1 Death

Study or Subgroup	Medical Events	Medical Total	PCI or CABG Events	PCI or CABG Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Rogers 1995 (ACIP)	8	183	0	192	100.0%	17.83 [1.04, 306.73]
Total (95% CI)		**183**		**192**	**100.0%**	**17.83 [1.04, 306.73]**
Total events	8		0			

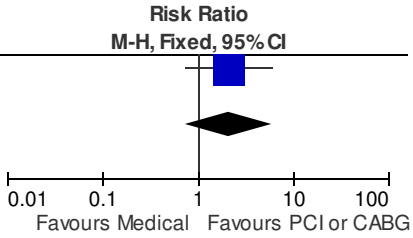
Heterogeneity: Not applicable
Test for overall effect: Z = 1.98 (P = 0.05)



4.2 MI

Study or Subgroup	Medical Events	Medical Total	PCI or CABG Events	PCI or CABG Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Rogers 1995 (ACIP)	10	183	5	192	100.0%	2.10 [0.73, 6.02]
Total (95% CI)		**183**		**192**	**100.0%**	**2.10 [0.73, 6.02]**
Total events	10		5			

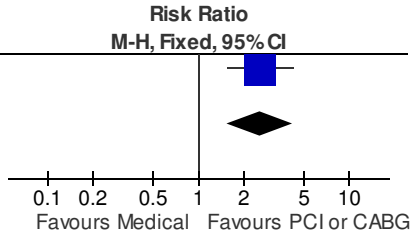
Heterogeneity: Not applicable
Test for overall effect: Z = 1.38 (P = 0.17)



4.3 Non protocol revascularisation

Study or Subgroup	Medical Events	Medical Total	PCI or CABG Events	PCI or CABG Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Rogers 1995 (ACIP)	44	183	18	192	100.0%	2.56 [1.54, 4.27]
Total (95% CI)		**183**		**192**	**100.0%**	**2.56 [1.54, 4.27]**
Total events	44		18			

Heterogeneity: Not applicable
Test for overall effect: Z = 3.62 (P = 0.0003)

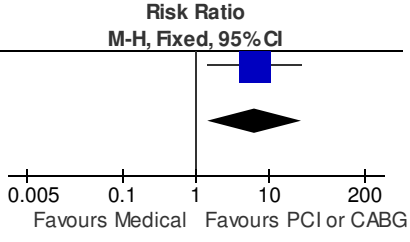


5 Angiography prior randomisation- Multivessel disease medium term follow-up

5.1 Death

Study or Subgroup	Medical Events	Medical Total	PCI or CABG Events	PCI or CABG Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Davies 1997 (ACIP)	12	183	2	192	100.0%	6.30 [1.43, 27.74]
Total (95% CI)		**183**		**192**	**100.0%**	**6.30 [1.43, 27.74]**
Total events	12		2			

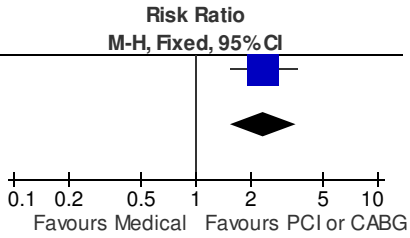
Heterogeneity: Not applicable
Test for overall effect: Z = 2.43 (P = 0.02)



5.2 Non protocol revascularisation

Study or Subgroup	Medical Events	Medical Total	PCI or CABG Events	PCI or CABG Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Davies 1997 (ACIP)	56	183	25	192	100.0%	2.35 [1.54, 3.60]
Total (95% CI)		**183**		**192**	**100.0%**	**2.35 [1.54, 3.60]**
Total events	56		25			

Heterogeneity: Not applicable
Test for overall effect: Z = 3.93 (P < 0.0001)

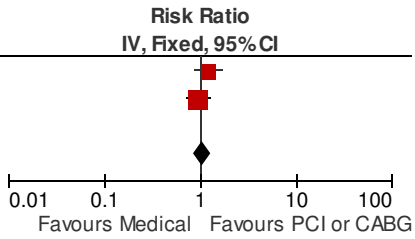


6 Interaction between study group assignment (BARI-2D trial)

6.1 Death in PCI stratum and CABG startum

Study or Subgroup	log[Risk Ratio]	SE	Weight	Risk Ratio IV, Fixed, 95% CI
CABG stratum-BARI 2D	0.19062036	0.175336	41.1%	1.21 [0.86, 1.71]
PCI stratum- BARI 2D	-0.0618754	0.146327	58.9%	0.94 [0.71, 1.25]
Total (95% CI)			**100.0%**	**1.04 [0.84, 1.30]**

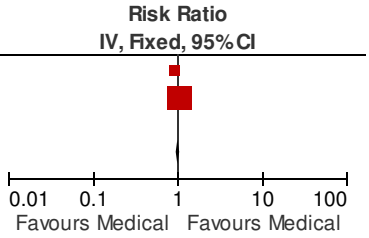
Heterogeneity: Chi² = 1.22, df = 1 (P = 0.27); I² = 18%
Test for overall effect: Z = 0.37 (P = 0.71)



6.2 Freedom from CV events- PCI stratum and CABG stratum

Study or Subgroup	log[Risk Ratio]	SE	Weight	Risk Ratio IV, Fixed, 95% CI
CABG stratum-BARI 2D	-0.1053605	0.045471	26.6%	0.90 [0.82, 0.98]
PCI stratum- BARI 2D	0.0295588	0.027403	73.4%	1.03 [0.98, 1.09]
Total (95% CI)			**100.0%**	**0.99 [0.95, 1.04]**

Heterogeneity: Chi² = 6.46, df = 1 (P = 0.01); I² = 85%
Test for overall effect: Z = 0.27 (P = 0.79)

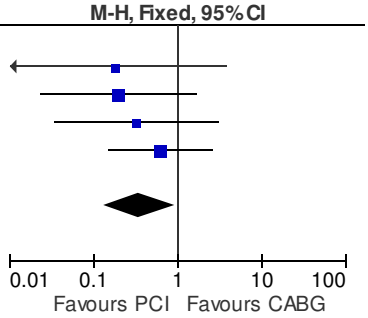


1 Multi vessel disease - Immediate follow-up

1.1 Stroke

Study or Subgroup	PCI Events	PCI Total	CABG Events	CABG Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Eefting 2003	0	138	0	142		Not estimable
Hamm 1994 (GABI)	0	176	2	161	16.7%	0.18 [0.01, 3.78]
Hampton 1993 (RITA)	1	509	5	498	32.3%	0.20 [0.02, 1.67]
King 1994 (EAST)	1	198	3	194	19.4%	0.33 [0.03, 3.11]
Zhang 2006 (SOS)	3	488	5	500	31.6%	0.61 [0.15, 2.56]
Total (95% CI)		**1509**		**1495**	**100.0%**	**0.35 [0.13, 0.92]**
Total events	5		15			

Heterogeneity: Chi² = 1.06, df = 3 (P = 0.79); I² = 0%
Test for overall effect: Z = 2.12 (P = 0.03)

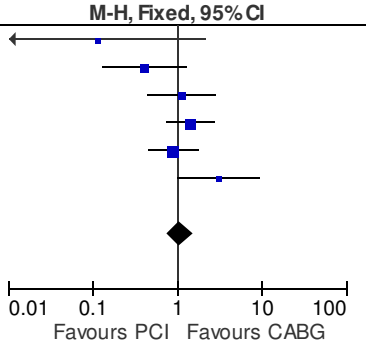


2 Multivessel disease -Short term follow-up (1 yr)

2.1 Death (all causes)

Study or Subgroup	PCI Events	PCI Total	CABG Events	CABG Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Eefting 2003	0	138	4	142	7.8%	0.11 [0.01, 2.10]
Hamm 1994 (GABI)	4	155	9	139	16.6%	0.40 [0.13, 1.27]
Hueb 2004 (MASS- II)	9	205	8	203	14.1%	1.11 [0.44, 2.83]
Rickards 1995 (CABRI)	21	541	14	513	25.1%	1.42 [0.73, 2.77]
Serruys 2001 (ARTS)	15	600	17	605	29.6%	0.89 [0.45, 1.77]
Sigwart 2002 (SOS)	12	488	4	500	6.9%	3.07 [1.00, 9.46]
Total (95% CI)		**2127**		**2102**	**100.0%**	**1.06 [0.75, 1.52]**
Total events	61		56			

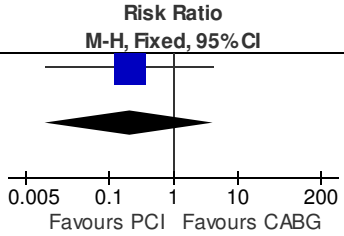
Heterogeneity: Chi² = 9.45, df = 5 (P = 0.09); I² = 47%
Test for overall effect: Z = 0.34 (P = 0.73)



2.2 Cardiac mortality

Study or Subgroup	PCI Events	PCI Total	CABG Events	CABG Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Eefting 2003	0	138	2	142	100.0%	0.21 [0.01, 4.25]
Total (95% CI)		**138**		**142**	**100.0%**	**0.21 [0.01, 4.25]**
Total events	0		2			

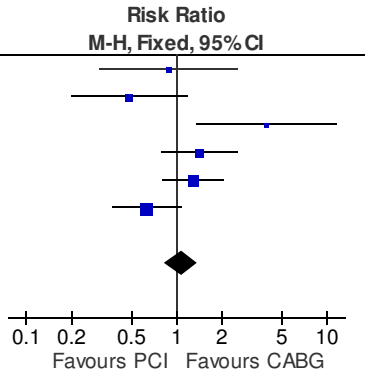
Heterogeneity: Not applicable
Test for overall effect: Z = 1.02 (P = 0.31)



2.3 Non fatal MI

Study or Subgroup	PCI Events	PCI Total	CABG Events	CABG Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Eefting 2003	6	138	7	142	6.5%	0.88 [0.30, 2.56]
Hamm 1994 (GABI)	7	155	13	139	13.0%	0.48 [0.20, 1.18]
Hueb 2004 (MASS- II)	16	205	4	203	3.8%	3.96 [1.35, 11.64]
Rickards 1995 (CABRI)	27	541	18	513	17.5%	1.42 [0.79, 2.55]
Serruys 2001 (ARTS)	37	600	29	605	27.4%	1.29 [0.80, 2.06]
Sigwart 2002 (SOS)	21	488	34	500	31.8%	0.63 [0.37, 1.07]
Total (95% CI)		**2127**		**2102**	**100.0%**	**1.07 [0.83, 1.39]**
Total events	114		105			

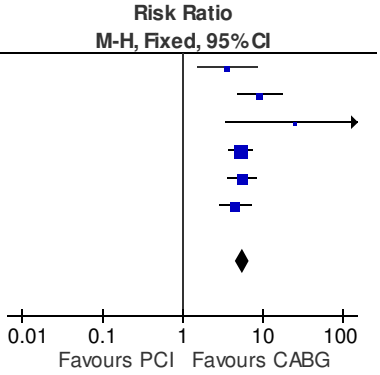
Heterogeneity: Chi² = 14.14, df = 5 (P = 0.01); I² = 65%
Test for overall effect: Z = 0.54 (P = 0.59)



2.4 Repeat revascularisation

Study or Subgroup	PCI Events	PCI Total	CABG Events	CABG Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Eefting 2003	21	138	6	142	6.3%	3.60 [1.50, 8.65]
Hamm 1994 (GABI)	91	155	9	139	10.1%	9.07 [4.76, 17.29]
Hueb 2004 (MASS- II)	25	205	1	203	1.1%	24.76 [3.39, 180.98]
Rickards 1995 (CABRI)	182	541	33	513	36.1%	5.23 [3.68, 7.43]
Serruys 2001 (ARTS)	126	600	23	605	24.4%	5.52 [3.59, 8.49]
Sigwart 2002 (SOS)	93	488	21	500	22.1%	4.54 [2.87, 7.16]
Total (95% CI)		**2127**		**2102**	**100.0%**	**5.64 [4.57, 6.97]**
Total events	538		93			

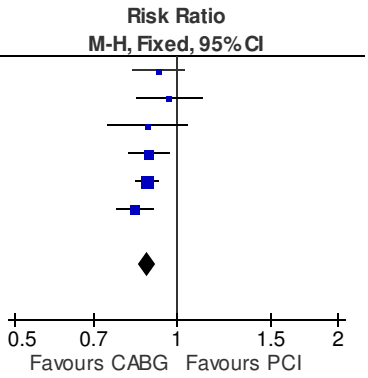
Heterogeneity: Chi² = 6.27, df = 5 (P = 0.28); I² = 20%
Test for overall effect: Z = 16.07 (P < 0.00001)



2.5 Free of angina

Study or Subgroup	PCI Events	PCI Total	CABG Events	CABG Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Eefting 2003	108	138	120	142	7.3%	0.93 [0.83, 1.04]
Hamm 1994 (GABI)	110	155	102	139	6.6%	0.97 [0.84, 1.11]
Hueb 2004 (MASS- II)	107	205	120	203	7.4%	0.88 [0.74, 1.05]
Rickards 1995 (CABRI)	328	541	350	513	22.1%	0.89 [0.81, 0.97]
Serruys 2001 (ARTS)	473	600	541	605	33.2%	0.88 [0.84, 0.93]
Sigwart 2002 (SOS)	309	471	387	493	23.3%	0.84 [0.77, 0.91]
Total (95% CI)		**2110**		**2095**	**100.0%**	**0.88 [0.85, 0.91]**
Total events	1435		1620			

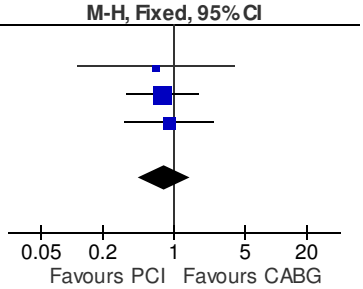
Heterogeneity: Chi² = 4.11, df = 5 (P = 0.53); I² = 0%
Test for overall effect: Z = 6.76 (P < 0.00001)



2.6 Stroke

Study or Subgroup	PCI Events	PCI Total	CABG Events	CABG Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Eefting 2003	0	138	0	142		Not estimable
Hueb 2004 (MASS- II)	2	205	3	203	12.6%	0.66 [0.11, 3.91]
Serruys 2001 (ARTS)	10	600	13	605	54.3%	0.78 [0.34, 1.76]
Sigwart 2002 (SOS)	7	488	8	500	33.1%	0.90 [0.33, 2.45]
Total (95% CI)		**1431**		**1450**	**100.0%**	**0.80 [0.44, 1.45]**
Total events	19		24			

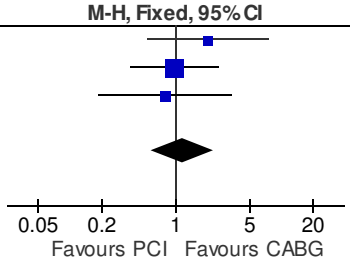
Heterogeneity: Chi² = 0.10, df = 2 (P = 0.95); I² = 0%
Test for overall effect: Z = 0.73 (P = 0.47)



2.7 Subgroup-diabetes- Death (all causes)

Study or Subgroup	PCI Events	PCI Total	CABG Events	CABG Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Abizaid 2001 (ARTS)	7	112	3	96	21.2%	2.00 [0.53, 7.52]
Kapur 2009 (CARDia trial)	8	254	8	248	53.2%	0.98 [0.37, 2.56]
Soares 2006 (MASS-II)	3	56	4	59	25.6%	0.79 [0.19, 3.37]
Total (95% CI)		**422**		**403**	**100.0%**	**1.15 [0.58, 2.25]**
Total events	18		15			

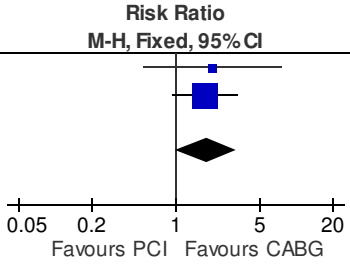
Heterogeneity: Chi² = 1.04, df = 2 (P = 0.60); I² = 0%
Test for overall effect: Z = 0.39 (P = 0.69)



2.8 Subgroup diabetes-MI

Study or Subgroup	PCI Events	PCI Total	CABG Events	CABG Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Abizaid 2001 (ARTS)	7	112	3	96	18.6%	2.00 [0.53, 7.52]
Kapur 2009 (CARDia trial)	25	254	14	248	81.4%	1.74 [0.93, 3.28]
Total (95% CI)		**366**		**344**	**100.0%**	**1.79 [1.01, 3.17]**
Total events	32		17			

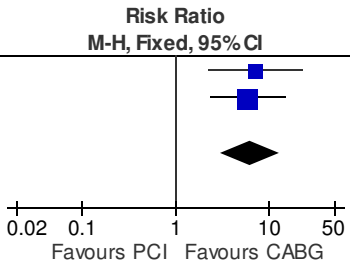
Heterogeneity: Chi² = 0.03, df = 1 (P = 0.85); I² = 0%
Test for overall effect: Z = 2.01 (P = 0.04)



2.9 Subgroup diabetes- Repeat revascularisation

Study or Subgroup	PCI Events	PCI Total	CABG Events	CABG Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Abizaid 2001 (ARTS)	25	112	3	96	39.0%	7.14 [2.23, 22.93]
Kapur 2009 (CARDia trial)	30	254	5	248	61.0%	5.86 [2.31, 14.85]
Total (95% CI)		**366**		**344**	**100.0%**	**6.36 [3.07, 13.16]**
Total events	55		8			

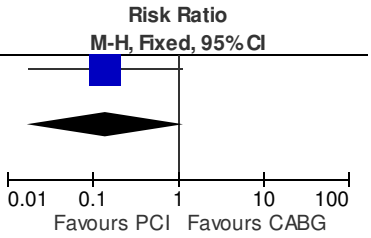
Heterogeneity: Chi² = 0.07, df = 1 (P = 0.79); I² = 0%
Test for overall effect: Z = 4.98 (P < 0.00001)



2.10 Sub group diabetes- Non fatal stroke

Study or Subgroup	PCI Events	PCI Total	CABG Events	CABG Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Kapur 2009 (CARDia trial)	1	254	7	248	100.0%	0.14 [0.02, 1.13]
Total (95% CI)		**254**		**248**	**100.0%**	**0.14 [0.02, 1.13]**
Total events	1		7			

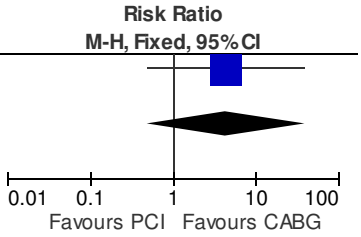
Heterogeneity: Not applicable
Test for overall effect: Z = 1.85 (P = 0.06)



2.11 Subgroup age>65 yrs- Death (all causes)

Study or Subgroup	PCI Events	PCI Total	CABG Events	CABG Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Zhang 2006 (SOS)	4	190	1	205	100.0%	4.32 [0.49, 38.27]
Total (95% CI)		**190**		**205**	**100.0%**	**4.32 [0.49, 38.27]**
Total events	4		1			

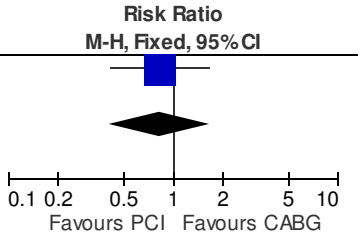
Heterogeneity: Not applicable
Test for overall effect: Z = 1.31 (P = 0.19)



2.12 subgroup age>65 yrs-MI

Study or Subgroup	PCI Events	PCI Total	CABG Events	CABG Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Zhang 2006 (SOS)	13	190	17	205	100.0%	0.83 [0.41, 1.65]
Total (95% CI)		**190**		**205**	**100.0%**	**0.83 [0.41, 1.65]**
Total events	13		17			

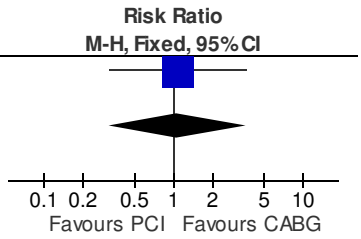
Heterogeneity: Not applicable
Test for overall effect: Z = 0.54 (P = 0.59)



2.13 Subgroup age>65 yrs- stroke

Study or Subgroup	PCI Events	PCI Total	CABG Events	CABG Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Zhang 2006 (SOS)	5	190	5	205	100.0%	1.08 [0.32, 3.67]
Total (95% CI)		**190**		**205**	**100.0%**	**1.08 [0.32, 3.67]**
Total events	5		5			

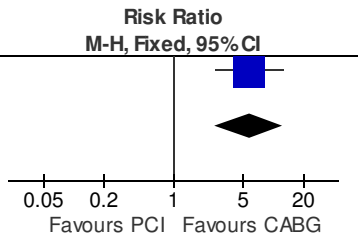
Heterogeneity: Not applicable
Test for overall effect: Z = 0.12 (P = 0.90)



2.14 subgroup age>65 yrs- repeat revascularisation

Study or Subgroup	PCI Events	PCI Total	CABG Events	CABG Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Zhang 2006 (SOS)	37	190	7	205	100.0%	5.70 [2.61, 12.48]
Total (95% CI)		**190**		**205**	**100.0%**	**5.70 [2.61, 12.48]**
Total events	37		7			

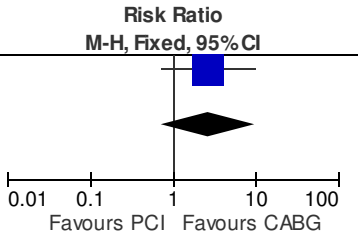
Heterogeneity: Not applicable
Test for overall effect: Z = 4.36 (P < 0.0001)



2.15 Sub group age <65 yrs- Death

Study or Subgroup	PCI Events	PCI Total	CABG Events	CABG Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Zhang 2006 (SOS)	8	298	3	295	100.0%	2.64 [0.71, 9.85]
Total (95% CI)		**298**		**295**	**100.0%**	**2.64 [0.71, 9.85]**
Total events	8		3			

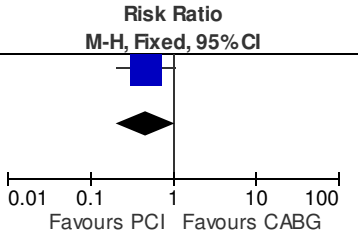
Heterogeneity: Not applicable
Test for overall effect: Z = 1.44 (P = 0.15)



2.16 Sub group age <65 yrs-MI

Study or Subgroup	PCI Events	PCI Total	CABG Events	CABG Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Zhang 2006 (SOS)	8	298	17	295	100.0%	0.47 [0.20, 1.06]
Total (95% CI)		**298**		**295**	**100.0%**	**0.47 [0.20, 1.06]**
Total events	8		17			

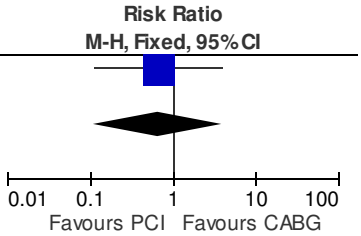
Heterogeneity: Not applicable
Test for overall effect: Z = 1.82 (P = 0.07)



2.17 Sub group age<65 yrs- Stroke

Study or Subgroup	PCI Events	PCI Total	CABG Events	CABG Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Zhang 2006 (SOS)	2	298	3	295	100.0%	0.66 [0.11, 3.92]
Total (95% CI)		**298**		**295**	**100.0%**	**0.66 [0.11, 3.92]**
Total events	2		3			

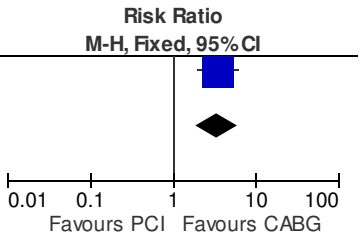
Heterogeneity: Not applicable
Test for overall effect: Z = 0.46 (P = 0.65)



2.18 Sub group age<65 yrs- Repeat revascularisation

Study or Subgroup	PCI Events	PCI Total	CABG Events	CABG Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Zhang 2006 (SOS)	48	298	14	295	100.0%	3.39 [1.91, 6.02]
Total (95% CI)		**298**		**295**	**100.0%**	**3.39 [1.91, 6.02]**
Total events	48		14			

Heterogeneity: Not applicable
Test for overall effect: Z = 4.18 (P < 0.0001)

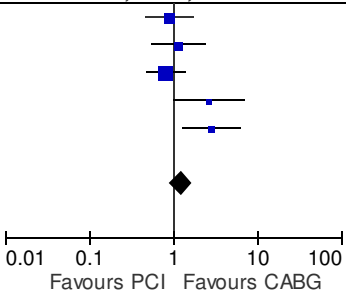


3 Multi vessel disease - Medium term follow-up (>1-4 yrs)

3.1 Death (all causes)

Study or Subgroup	PCI Events	PCI Total	CABG Events	CABG Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Hampton 1993 (RITA)	16	510	18	501	25.4%	0.87 [0.45, 1.69]
King 1994 (EAST)	14	198	12	194	17.0%	1.14 [0.54, 2.41]
Legrand 2004 (ARTS)	22	600	28	605	39.0%	0.79 [0.46, 1.37]
Martuscelli 2008 (CABRI)	15	120	5	103	7.5%	2.58 [0.97, 6.84]
Sigwart 2002 (SOS)	22	488	8	500	11.1%	2.82 [1.27, 6.27]
Total (95% CI)		**1916**		**1903**	**100.0%**	**1.23 [0.91, 1.67]**
Total events	89		71			

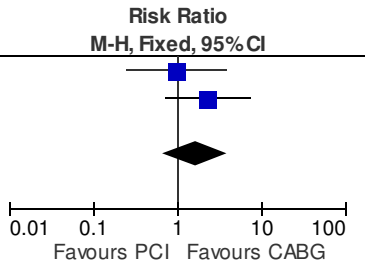
Heterogeneity: Chi² = 9.88, df = 4 (P = 0.04); I² = 60%
Test for overall effect: Z = 1.33 (P = 0.18)



3.2 Cardiac mortality

Study or Subgroup	PCI Events	PCI Total	CABG Events	CABG Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Hampton 1993 (RITA)	4	510	4	501	50.5%	0.98 [0.25, 3.91]
Sigwart 2002 (SOS)	9	488	4	500	49.5%	2.31 [0.71, 7.44]
Total (95% CI)		**998**		**1001**	**100.0%**	**1.64 [0.68, 3.92]**
Total events	13		8			

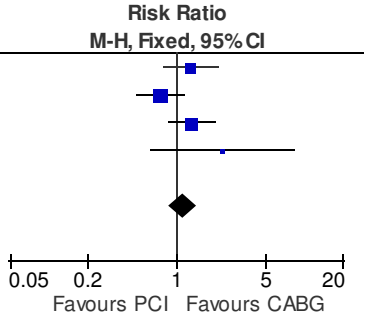
Heterogeneity: Chi² = 0.85, df = 1 (P = 0.36); I² = 0%
Test for overall effect: Z = 1.10 (P = 0.27)



3.3 Non fatal MI

Study or Subgroup	PCI Events	PCI Total	CABG Events	CABG Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Hampton 1993 (RITA)	34	510	26	501	25.8%	1.28 [0.78, 2.11]
King 1994 (EAST)	29	198	38	194	37.7%	0.75 [0.48, 1.16]
Legrand 2004 (ARTS)	44	600	34	605	33.3%	1.30 [0.85, 2.01]
Martuscelli 2008 (CABRI)	8	120	3	103	3.2%	2.29 [0.62, 8.40]
Total (95% CI)		**1428**		**1403**	**100.0%**	**1.12 [0.87, 1.45]**
Total events	115		101			

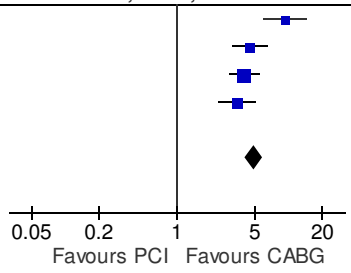
Heterogeneity: Chi² = 5.16, df = 3 (P = 0.16); I² = 42%
Test for overall effect: Z = 0.88 (P = 0.38)



3.4 Repeat revascularisation

Study or Subgroup	PCI Events	PCI Total	CABG Events	CABG Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Hampton 1993 (RITA)	189	510	20	501	16.7%	9.28 [5.95, 14.47]
King 1994 (EAST)	125	198	27	194	22.6%	4.54 [3.15, 6.54]
Legrand 2004 (ARTS)	175	600	44	605	36.2%	4.01 [2.94, 5.47]
Sigwart 2002 (SOS)	101	488	30	500	24.5%	3.45 [2.34, 5.08]
Total (95% CI)		**1796**		**1800**	**100.0%**	**4.87 [4.06, 5.85]**
Total events	590		121			

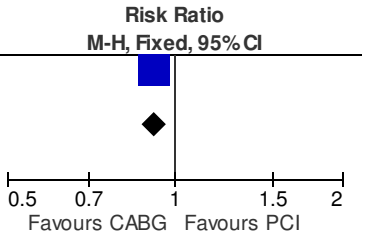
Heterogeneity: Chi² = 12.79, df = 3 (P = 0.005); I² = 77%
Test for overall effect: Z = 16.92 (P < 0.00001)



3.5 Free of angina

Study or Subgroup	PCI Events	PCI Total	CABG Events	CABG Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Unger 2003 (ARTS)	478	600	527	605	100.0%	0.91 [0.87, 0.96]
Total (95% CI)		**600**		**605**	**100.0%**	**0.91 [0.87, 0.96]**
Total events	478		527			

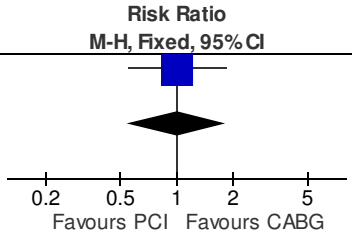
Heterogeneity: Not applicable
Test for overall effect: Z = 3.45 (P = 0.0006)



3.6 Stroke

Study or Subgroup	PCI Events	PCI Total	CABG Events	CABG Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Legrand 2004 (ARTS)	20	600	20	605	100.0%	1.01 [0.55, 1.85]
Total (95% CI)		**600**		**605**	**100.0%**	**1.01 [0.55, 1.85]**
Total events	20		20			

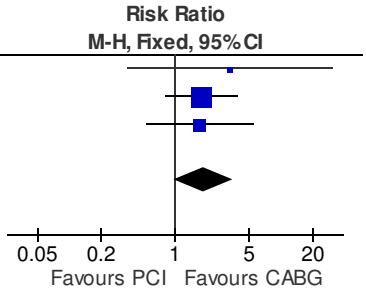
Heterogeneity: Not applicable
Test for overall effect: Z = 0.03 (P = 0.98)



3.7 Sub group diabetes- Mortality

Study or Subgroup	PCI Events	PCI Total	CABG Events	CABG Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Booth 2008 (SOS)	3	68	1	74	7.3%	3.26 [0.35, 30.64]
Kurbaan 2001 (CABRI)	14	62	8	63	60.1%	1.78 [0.80, 3.94]
Legrand 2004 (ARTS)	8	112	4	96	32.6%	1.71 [0.53, 5.52]
Total (95% CI)		**242**		**233**	**100.0%**	**1.87 [0.99, 3.50]**
Total events	25		13			

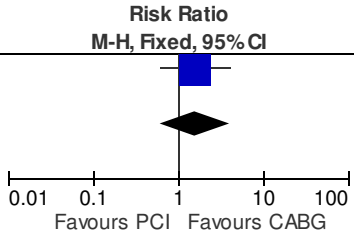
Heterogeneity: Chi² = 0.27, df = 2 (P = 0.87); I² = 0%
Test for overall effect: Z = 1.94 (P = 0.05)



3.8 Sub group diabetes- MI

Study or Subgroup	PCI Events	PCI Total	CABG Events	CABG Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Legrand 2004 (ARTS)	11	112	6	96	100.0%	1.57 [0.60, 4.09]
Total (95% CI)		**112**		**96**	**100.0%**	**1.57 [0.60, 4.09]**
Total events	11		6			

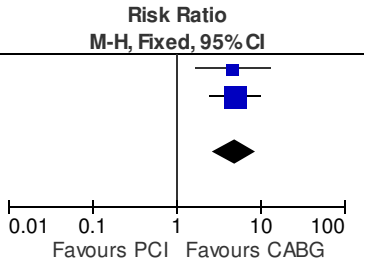
Heterogeneity: Not applicable
Test for overall effect: Z = 0.93 (P = 0.35)



3.9 Sub group diabetes- Repeat revascularisation

Study or Subgroup	PCI Events	PCI Total	CABG Events	CABG Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Booth 2008 (SOS)	17	68	4	74	30.8%	4.63 [1.64, 13.06]
Legrand 2004 (ARTS)	46	112	8	96	69.2%	4.93 [2.45, 9.92]
Total (95% CI)		**180**		**170**	**100.0%**	**4.84 [2.71, 8.64]**
Total events	63		12			

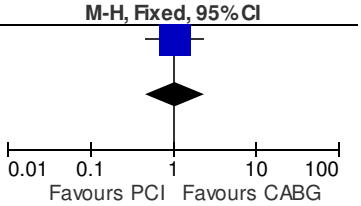
Heterogeneity: Chi² = 0.01, df = 1 (P = 0.92); I² = 0%
Test for overall effect: Z = 5.32 (P < 0.00001)



3.10 Sub group- Left Anterior descending coronary artery proximally- Death

Study or Subgroup	PCI Events	PCI Total	CABG Events	CABG Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Aoki 2004 (ARTS)	11	246	11	253	100.0%	1.03 [0.45, 2.33]
Total (95% CI)		**246**		**253**	**100.0%**	**1.03 [0.45, 2.33]**
Total events	11		11			

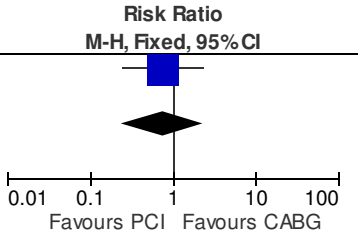
Heterogeneity: Not applicable
Test for overall effect: Z = 0.07 (P = 0.95)



3.11 Sub group LAD artery- Stroke

Study or Subgroup	PCI Events	PCI Total	CABG Events	CABG Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Aoki 2004 (ARTS)	5	246	7	253	100.0%	0.73 [0.24, 2.28]
Total (95% CI)		**246**		**253**	**100.0%**	**0.73 [0.24, 2.28]**
Total events	5		7			

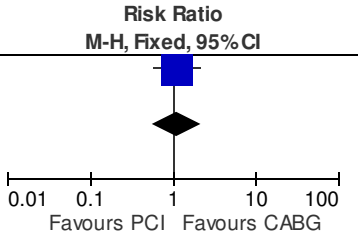
Heterogeneity: Not applicable
Test for overall effect: Z = 0.53 (P = 0.59)



3.12 Sub group LAD artery- MI

Study or Subgroup	PCI Events	PCI Total	CABG Events	CABG Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Aoki 2004 (ARTS)	17	246	16	253	100.0%	1.09 [0.56, 2.11]
Total (95% CI)		**246**		**253**	**100.0%**	**1.09 [0.56, 2.11]**
Total events	17		16			

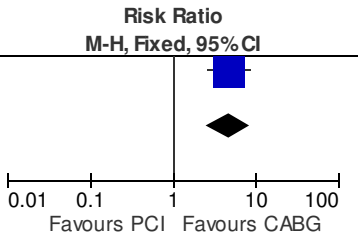
Heterogeneity: Not applicable
Test for overall effect: Z = 0.26 (P = 0.79)



3.13 Sub group LAD artery- Repeat revascularisation

Study or Subgroup	PCI Events	PCI Total	CABG Events	CABG Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Aoki 2004 (ARTS)	54	246	12	253	100.0%	4.63 [2.54, 8.44]
Total (95% CI)		**246**		**253**	**100.0%**	**4.63 [2.54, 8.44]**
Total events	54		12			

Heterogeneity: Not applicable
Test for overall effect: Z = 5.00 (P < 0.00001)

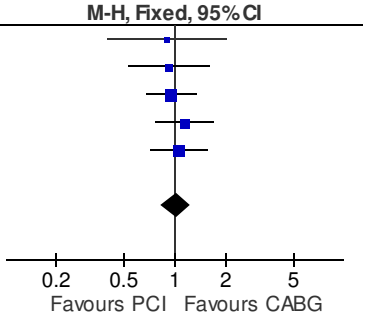


4 Multi vessel disease - Long term follow-up (> 5 yrs)

4.1 Death (all causes)

Study or Subgroup	PCI Events	PCI Total	CABG Events	CABG Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Buszman 2009 (SOS)	9	50	10	50	6.0%	0.90 [0.40, 2.02]
Henderson 1998 (RITA)	22	277	24	279	14.4%	0.92 [0.53, 1.61]
Hueb 2010 (MASS-II)	49	205	51	203	30.8%	0.95 [0.68, 1.34]
Kaehler (GABI 2005)	41	164	35	160	21.3%	1.14 [0.77, 1.70]
Serruys2005 (ARTS)	48	600	46	605	27.5%	1.05 [0.71, 1.55]
Total (95% CI)		**1296**		**1297**	**100.0%**	**1.01 [0.83, 1.23]**
Total events	169		166			

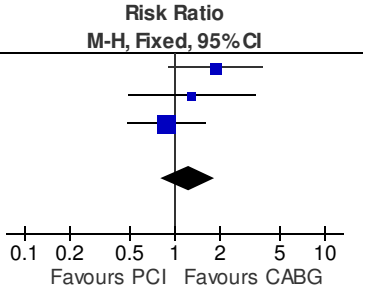
Heterogeneity: Chi² = 0.71, df = 4 (P = 0.95); I² = 0%
Test for overall effect: Z = 0.13 (P = 0.90)



4.2 Cardiac mortality

Study or Subgroup	PCI Events	PCI Total	CABG Events	CABG Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Booth 2008 (SOS)	20	488	11	500	28.5%	1.86 [0.90, 3.85]
Henderson 1998 (RITA)	9	277	7	279	18.3%	1.29 [0.49, 3.43]
Kaehler (GABI 2005)	18	164	20	160	53.2%	0.88 [0.48, 1.60]
Total (95% CI)		**929**		**939**	**100.0%**	**1.24 [0.82, 1.87]**
Total events	47		38			

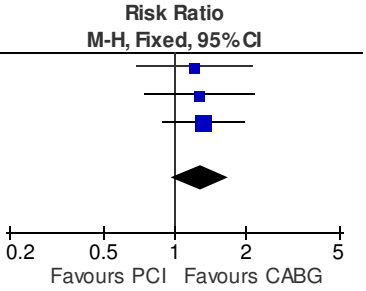
Heterogeneity: Chi² = 2.49, df = 2 (P = 0.29); I² = 20%
Test for overall effect: Z = 1.01 (P = 0.31)



4.3 Non fatal MI

Study or Subgroup	PCI Events	PCI Total	CABG Events	CABG Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Henderson 1998 (RITA)	24	277	20	279	25.0%	1.21 [0.68, 2.14]
Hueb 2010 (MASS-II)	27	205	21	203	26.4%	1.27 [0.74, 2.18]
Serruys2005 (ARTS)	51	600	39	605	48.6%	1.32 [0.88, 1.97]
Total (95% CI)		**1082**		**1087**	**100.0%**	**1.28 [0.97, 1.69]**
Total events	102		80			

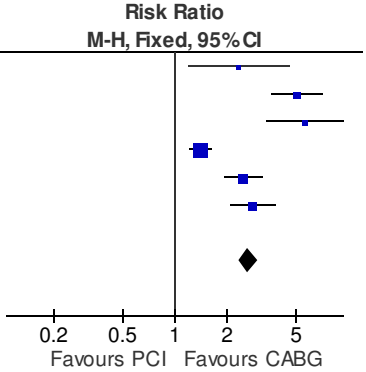
Heterogeneity: Chi² = 0.06, df = 2 (P = 0.97); I² = 0%
Test for overall effect: Z = 1.72 (P = 0.08)



4.4 Repeat revascularisation

Study or Subgroup	PCI Events	PCI Total	CABG Events	CABG Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Buszman 2009 (SOS)	21	50	9	50	3.6%	2.33 [1.19, 4.58]
Henderson 1998 (RITA)	161	277	32	279	12.6%	5.07 [3.60, 7.13]
Hueb 2010 (MASS-II)	85	205	15	203	6.0%	5.61 [3.36, 9.38]
Kaehler (GABI 2005)	136	164	94	160	37.7%	1.41 [1.22, 1.64]
King 2000 (EAST)	129	198	51	194	20.4%	2.48 [1.92, 3.20]
Serruys2005 (ARTS)	139	600	50	605	19.7%	2.80 [2.07, 3.79]
Total (95% CI)		**1494**		**1491**	**100.0%**	**2.65 [2.35, 2.98]**
Total events	671		251			

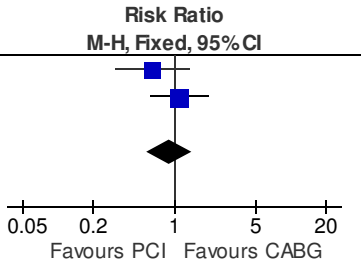
Heterogeneity: Chi² = 92.87, df = 5 (P < 0.00001); I² = 95%
Test for overall effect: Z = 16.12 (P < 0.00001)



4.5 Stroke

Study or Subgroup	PCI Events	PCI Total	CABG Events	CABG Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Hueb 2010 (MASS-II)	11	205	17	203	45.0%	0.64 [0.31, 1.33]
Serruys2005 (ARTS)	23	600	21	605	55.0%	1.10 [0.62, 1.97]
Total (95% CI)		**805**		**808**	**100.0%**	**0.90 [0.57, 1.41]**
Total events	34		38			

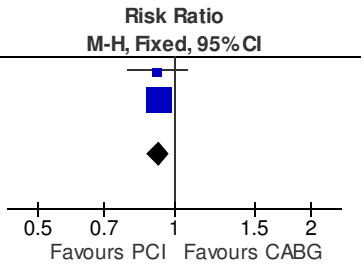
Heterogeneity: Chi² = 1.30, df = 1 (P = 0.25); I² = 23%
Test for overall effect: Z = 0.48 (P = 0.63)



4.6 Free of angina

Study or Subgroup	PCI Events	PCI Total	CABG Events	CABG Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Hueb 2010 (MASS-II)	120	205	130	203	20.4%	0.91 [0.78, 1.07]
Serruys2005 (ARTS)	467	600	511	605	79.6%	0.92 [0.87, 0.97]
Total (95% CI)		**805**		**808**	**100.0%**	**0.92 [0.87, 0.97]**
Total events	587		641			

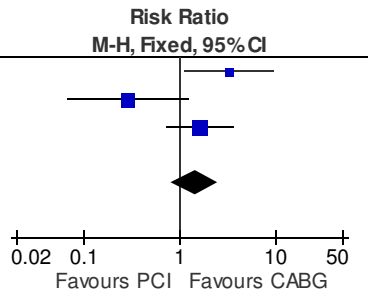
Heterogeneity: Chi² = 0.01, df = 1 (P = 0.92); I² = 0%
Test for overall effect: Z = 3.04 (P = 0.002)



4.7 Sub group diabetes - Death (all causes)

Study or Subgroup	PCI Events	PCI Total	CABG Events	CABG Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Booth 2008 (SOS)	12	68	4	74	19.2%	3.26 [1.11, 9.64]
Henderson 1998 (RITA)	2	29	8	33	37.6%	0.28 [0.07, 1.23]
Serruys2005 (ARTS)	15	112	8	96	43.2%	1.61 [0.71, 3.63]
Total (95% CI)		**209**		**203**	**100.0%**	**1.43 [0.83, 2.47]**
Total events	29		20			

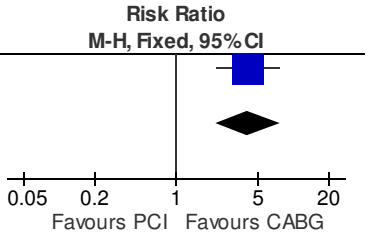
Heterogeneity: Chi² = 6.97, df = 2 (P = 0.03); I² = 71%
Test for overall effect: Z = 1.28 (P = 0.20)



4.8 Sub group diabetes- Repeat revascularisation

Study or Subgroup	PCI Events	PCI Total	CABG Events	CABG Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Serruys2005 (ARTS)	48	112	10	96	100.0%	4.11 [2.20, 7.68]
Total (95% CI)		**112**		**96**	**100.0%**	**4.11 [2.20, 7.68]**
Total events	48		10			

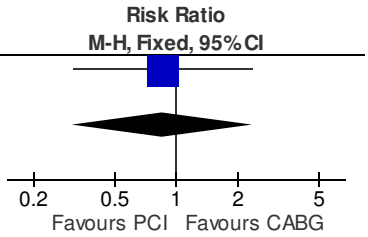
Heterogeneity: Not applicable
Test for overall effect: Z = 4.44 (P < 0.00001)



4.9 Sub group diabetes- stroke

Study or Subgroup	PCI Events	PCI Total	CABG Events	CABG Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Serruys2005 (ARTS)	7	112	7	96	100.0%	0.86 [0.31, 2.36]
Total (95% CI)		**112**		**96**	**100.0%**	**0.86 [0.31, 2.36]**
Total events	7		7			

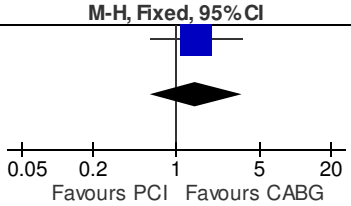
Heterogeneity: Not applicable
Test for overall effect: Z = 0.30 (P = 0.77)



4.10 Sub group diabetes- MI

Study or Subgroup	PCI Events	PCI Total	CABG Events	CABG Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Serruys2005 (ARTS)	12	112	7	96	100.0%	1.47 [0.60, 3.58]
Total (95% CI)		**112**		**96**	**100.0%**	**1.47 [0.60, 3.58]**
Total events	12		7			

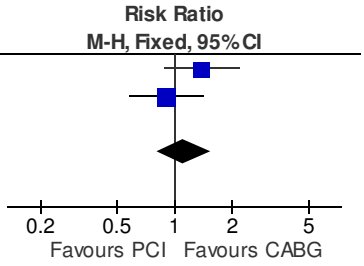
Heterogeneity: Not applicable
Test for overall effect: Z = 0.85 (P = 0.40)



4.11 Sub group-no diabetes -Death (all causes)

Study or Subgroup	PCI Events	PCI Total	CABG Events	CABG Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Booth 2008 (SOS)	41	420	30	426	44.5%	1.39 [0.88, 2.18]
Serruys2005 (ARTS)	33	488	38	509	55.5%	0.91 [0.58, 1.42]
Total (95% CI)		**908**		**935**	**100.0%**	**1.12 [0.82, 1.54]**
Total events	74		68			

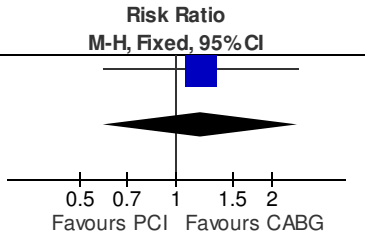
Heterogeneity: Chi² = 1.71, df = 1 (P = 0.19); I² = 42%
Test for overall effect: Z = 0.70 (P = 0.49)



4.12 Sub group no diabetes- stroke

Study or Subgroup	PCI Events	PCI Total	CABG Events	CABG Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Serruys2005 (ARTS)	16	488	14	509	100.0%	1.19 [0.59, 2.42]
Total (95% CI)		**488**		**509**	**100.0%**	**1.19 [0.59, 2.42]**
Total events	16		14			

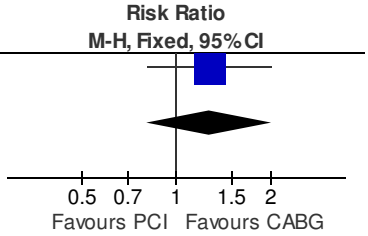
Heterogeneity: Not applicable
Test for overall effect: Z = 0.49 (P = 0.63)



4.13 Sub group no diabetes- MI

Study or Subgroup	PCI Events	PCI Total	CABG Events	CABG Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Serruys2005 (ARTS)	38	488	31	509	100.0%	1.28 [0.81, 2.02]
Total (95% CI)		**488**		**509**	**100.0%**	**1.28 [0.81, 2.02]**
Total events	38		31			

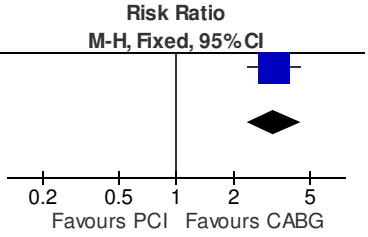
Heterogeneity: Not applicable
Test for overall effect: Z = 1.05 (P = 0.29)



4.14 Sub group no diabetes- Repeat revascularisation

Study or Subgroup	PCI Events	PCI Total	CABG Events	CABG Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Serruys2005 (ARTS)	134	488	43	509	100.0%	3.25 [2.36, 4.48]
Total (95% CI)		**488**		**509**	**100.0%**	**3.25 [2.36, 4.48]**
Total events	134		43			

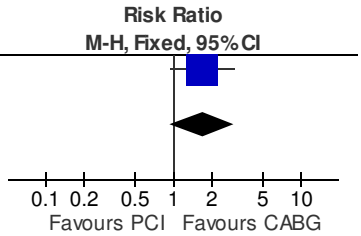
Heterogeneity: Not applicable
Test for overall effect: Z = 7.21 (P < 0.00001)



4.15 Sub group 2 vessel- Death

Study or Subgroup	PCI Events	PCI Total	CABG Events	CABG Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Booth 2008 (SOS)	31	305	16	264	100.0%	1.68 [0.94, 3.00]
Total (95% CI)		**305**		**264**	**100.0%**	**1.68 [0.94, 3.00]**
Total events	31		16			

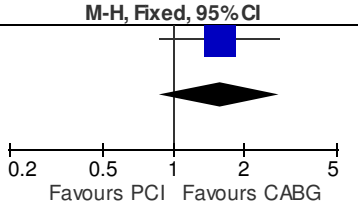
Heterogeneity: Not applicable
Test for overall effect: Z = 1.75 (P = 0.08)



4.16 Sub group 3 vessel -Death

Study or Subgroup	PCI Events	PCI Total	CABG Events	CABG Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Booth 2008 (SOS)	22	183	18	236	100.0%	1.58 [0.87, 2.85]
Total (95% CI)		**183**		**236**	**100.0%**	**1.58 [0.87, 2.85]**
Total events	22		18			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.51 (P = 0.13)

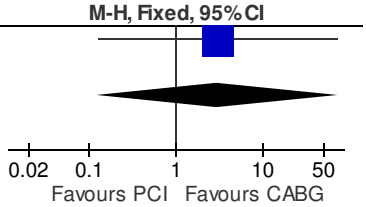


5 Single vessel disease - Short term follow-up (1 yr)

5.1 Death (all causes)

Study or Subgroup	PCI Events	PCI Total	CABG Events	CABG Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Cisowski et al 2002	1	50	0	50	100.0%	3.00 [0.13, 71.92]
Total (95% CI)		**50**		**50**	**100.0%**	**3.00 [0.13, 71.92]**
Total events	1		0			

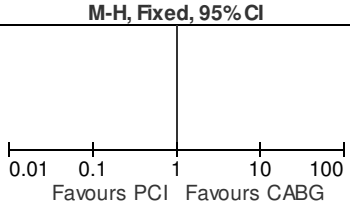
Heterogeneity: Not applicable
Test for overall effect: Z = 0.68 (P = 0.50)



5.2 MI

Study or Subgroup	PCI Events	PCI Total	CABG Events	CABG Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Cisowski et al 2002	0	50	0	50		Not estimable
Total (95% CI)		**50**		**50**		**Not estimable**
Total events	0		0			

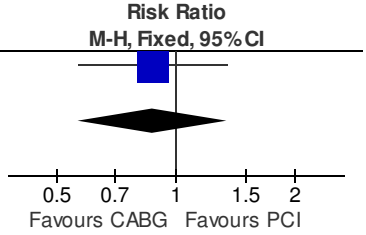
Heterogeneity: Not applicable
Test for overall effect: Not applicable



5.3 Free of angina

Study or Subgroup	PCI Events	PCI Total	CABG Events	CABG Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Cisowski et al 2002	21	50	24	50	100.0%	0.88 [0.57, 1.35]
Total (95% CI)		**50**		**50**	**100.0%**	**0.88 [0.57, 1.35]**
Total events	21		24			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.60 (P = 0.55)

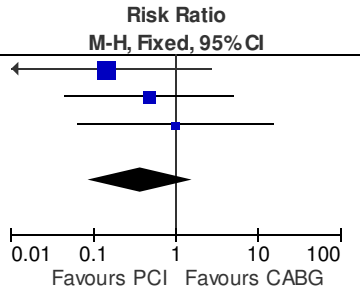


6 Single vessel disease - Medium term follow-up (>1-4 yrs)

6.1 Death (all causes)

Study or Subgroup	PCI Events	PCI Total	CABG Events	CABG Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Drenth et al 2004	0	51	3	51	53.3%	0.14 [0.01, 2.70]
Goy et al 2000 (SIMA)	1	62	2	59	31.2%	0.48 [0.04, 5.11]
Hueb 1995 (MASS-I)	1	72	1	70	15.4%	0.97 [0.06, 15.24]
Total (95% CI)		**185**		**180**	**100.0%**	**0.37 [0.09, 1.60]**
Total events	2		6			

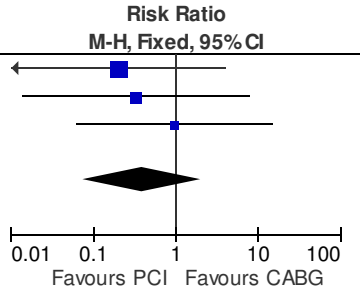
Heterogeneity: Chi² = 0.91, df = 2 (P = 0.63); I² = 0%
Test for overall effect: Z = 1.33 (P = 0.18)



6.2 Cardiac death

Study or Subgroup	PCI Events	PCI Total	CABG Events	CABG Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Drenth et al 2004	0	51	2	51	49.5%	0.20 [0.01, 4.07]
Goy et al 1994	0	68	1	66	30.2%	0.32 [0.01, 7.81]
Goy et al 2000 (SIMA)	1	62	1	59	20.3%	0.95 [0.06, 14.87]
Total (95% CI)		**181**		**176**	**100.0%**	**0.39 [0.08, 2.00]**
Total events	1		4			

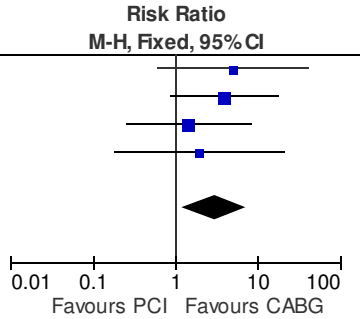
Heterogeneity: Chi² = 0.61, df = 2 (P = 0.74); I² = 0%
Test for overall effect: Z = 1.13 (P = 0.26)



6.3 MI

Study or Subgroup	PCI Events	PCI Total	CABG Events	CABG Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Drenth et al 2004	5	51	1	51	16.4%	5.00 [0.61, 41.31]
Goy et al 1994	8	68	2	66	33.3%	3.88 [0.86, 17.61]
Goy et al 2000 (SIMA)	3	62	2	59	33.6%	1.43 [0.25, 8.24]
Hueb 1995 (MASS-I)	2	72	1	70	16.6%	1.94 [0.18, 20.96]
Total (95% CI)		**253**		**246**	**100.0%**	**2.92 [1.18, 7.21]**
Total events	18		6			

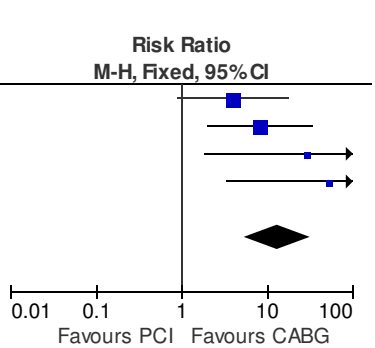
Heterogeneity: Chi² = 1.14, df = 3 (P = 0.77); I² = 0%
Test for overall effect: Z = 2.32 (P = 0.02)



6.4 Repeat revascularisation

Study or Subgroup	PCI Events	PCI Total	CABG Events	CABG Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Drenth et al 2004	8	51	2	51	39.6%	4.00 [0.89, 17.93]
Goy et al 1994	17	68	2	66	40.2%	8.25 [1.98, 34.32]
Goy et al 2000 (SIMA)	15	62	0	59	10.1%	29.52 [1.81, 482.55]
Hueb 1995 (MASS-I)	27	72	0	70	10.0%	53.49 [3.33, 860.32]
Total (95% CI)		**253**		**246**	**100.0%**	**13.27 [5.41, 32.51]**
Total events	67		4			

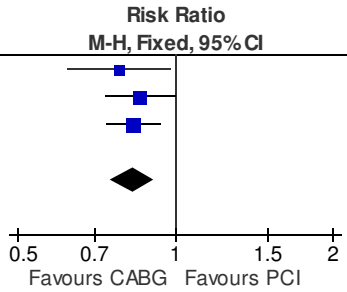
Heterogeneity: Chi² = 4.16, df = 3 (P = 0.24); I² = 28%
Test for overall effect: Z = 5.65 (P < 0.00001)



6.5 Free of angina

Study or Subgroup	PCI Events	PCI Total	CABG Events	CABG Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Drenth et al 2004	34	51	41	48	24.7%	0.78 [0.62, 0.98]
Goy et al 1994	52	68	59	66	35.0%	0.86 [0.73, 1.00]
Hueb 1995 (MASS-I)	58	72	68	70	40.3%	0.83 [0.74, 0.94]
Total (95% CI)		**191**		**184**	**100.0%**	**0.83 [0.75, 0.91]**
Total events	144		168			

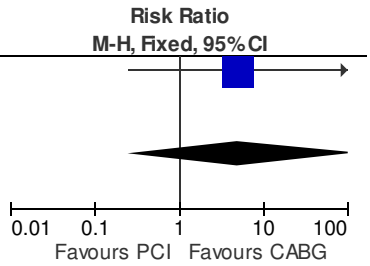
Heterogeneity: Chi² = 0.44, df = 2 (P = 0.80); I² = 0%
Test for overall effect: Z = 4.08 (P < 0.0001)



6.6 Stroke

Study or Subgroup	PCI Events	PCI Total	CABG Events	CABG Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Drenth et al 2004	2	51	0	51	100.0%	5.00 [0.25, 101.63]
Goy et al 2000 (SIMA)	0	62	0	59		Not estimable
Total (95% CI)		**113**		**110**	**100.0%**	**5.00 [0.25, 101.63]**
Total events	2		0			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.05 (P = 0.29)

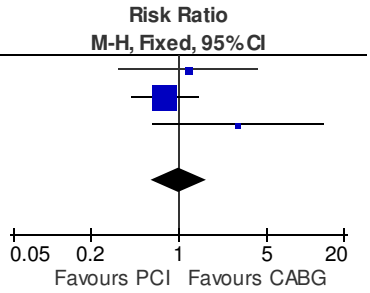


7 Single vessel disease - Long term follow-up (>5 yrs)

7.1 Death (all causes)

Study or Subgroup	PCI Events	PCI Total	CABG Events	CABG Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Goy 2008 (SIMA)	5	62	4	59	14.8%	1.19 [0.34, 4.22]
Henderson 1998 (RITA)	17	233	21	222	77.8%	0.77 [0.42, 1.42]
Hueb 1999 (MASS-I)	6	72	2	70	7.3%	2.92 [0.61, 13.97]
Total (95% CI)		**367**		**351**	**100.0%**	**0.99 [0.60, 1.65]**
Total events	28		27			

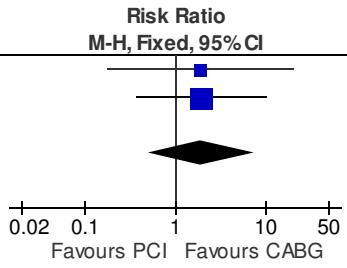
Heterogeneity: Chi² = 2.55, df = 2 (P = 0.28); I² = 22%
Test for overall effect: Z = 0.04 (P = 0.97)



7.2 Cardiac death

Study or Subgroup	PCI Events	PCI Total	CABG Events	CABG Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Goy 2008 (SIMA)	2	62	1	59	33.6%	1.90 [0.18, 20.44]
Hueb 1999 (MASS-I)	4	72	2	70	66.4%	1.94 [0.37, 10.28]
Total (95% CI)		**134**		**129**	**100.0%**	**1.93 [0.49, 7.55]**
Total events	6		3			

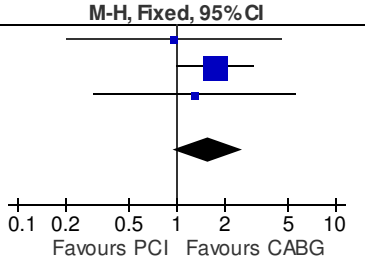
Heterogeneity: Chi² = 0.00, df = 1 (P = 0.99); I² = 0%
Test for overall effect: Z = 0.95 (P = 0.34)



7.3 MI

Study or Subgroup	PCI Events	PCI Total	CABG Events	CABG Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Goy 2008 (SIMA)	3	62	3	59	13.1%	0.95 [0.20, 4.53]
Henderson 1998 (RITA)	31	233	17	222	74.0%	1.74 [0.99, 3.05]
Hueb 1999 (MASS-I)	4	72	3	70	12.9%	1.30 [0.30, 5.58]
Total (95% CI)		**367**		**351**	**100.0%**	**1.58 [0.96, 2.59]**
Total events	38		23			

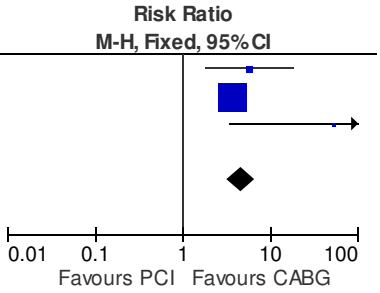
Heterogeneity: Chi² = 0.59, df = 2 (P = 0.75); I² = 0%
Test for overall effect: Z = 1.81 (P = 0.07)



7.4 Repeat revascularisation

Study or Subgroup	PCI Events	PCI Total	CABG Events	CABG Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Goy 2008 (SIMA)	18	62	3	59	9.2%	5.71 [1.77, 18.38]
Henderson 1998 (RITA)	111	233	29	222	89.2%	3.65 [2.53, 5.25]
Hueb 1999 (MASS-I)	27	72	0	70	1.5%	53.49 [3.33, 860.32]
Total (95% CI)		**367**		**351**	**100.0%**	**4.60 [3.25, 6.50]**
Total events	156		32			

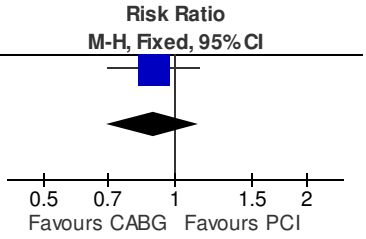
Heterogeneity: Chi² = 4.67, df = 2 (P = 0.10); I² = 57%
Test for overall effect: Z = 8.65 (P < 0.00001)



7.5 Free of angina

Study or Subgroup	PCI Events	PCI Total	CABG Events	CABG Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Hueb 1999 (MASS-I)	44	72	48	70	100.0%	0.89 [0.70, 1.14]
Total (95% CI)		**72**		**70**	**100.0%**	**0.89 [0.70, 1.14]**
Total events	44		48			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.93 (P = 0.35)

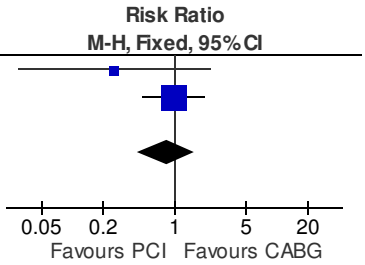


8 Left main coronary disease - Short term follow-up (1 yr)

8.1 Death

Study or Subgroup	PCI Events	PCI Total	CABG Events	CABG Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Buszman 2008 (LE MANS)	1	52	4	53	20.7%	0.25 [0.03, 2.20]
Morice 2010 (SYNTAX)	15	357	15	348	79.3%	0.97 [0.48, 1.96]
Total (95% CI)		**409**		**401**	**100.0%**	**0.83 [0.43, 1.59]**
Total events	16		19			

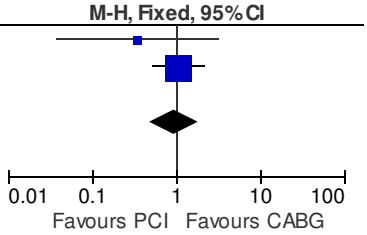
Heterogeneity: Chi² = 1.36, df = 1 (P = 0.24); I² = 26%
Test for overall effect: Z = 0.57 (P = 0.57)



8.2 non fatal MI

Study or Subgroup	PCI Events	PCI Total	CABG Events	CABG Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Buszman 2008 (LE MANS)	1	52	3	53	17.3%	0.34 [0.04, 3.16]
Morice 2010 (SYNTAX)	15	357	14	348	82.7%	1.04 [0.51, 2.13]
Total (95% CI)		**409**		**401**	**100.0%**	**0.92 [0.47, 1.80]**
Total events	16		17			

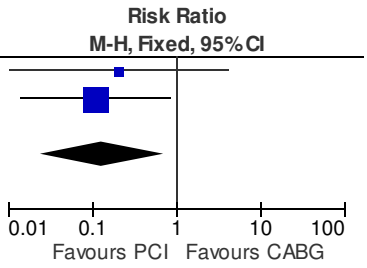
Heterogeneity: Chi² = 0.89, df = 1 (P = 0.35); I² = 0%
Test for overall effect: Z = 0.24 (P = 0.81)



8.3 Stroke

Study or Subgroup	PCI Events	PCI Total	CABG Events	CABG Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Buszman 2008 (LE MANS)	0	52	2	53	21.4%	0.20 [0.01, 4.14]
Morice 2010 (SYNTAX)	1	357	9	348	78.6%	0.11 [0.01, 0.85]
Total (95% CI)		**409**		**401**	**100.0%**	**0.13 [0.02, 0.70]**
Total events	1		11			

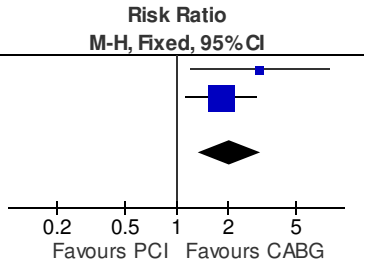
Heterogeneity: Chi² = 0.12, df = 1 (P = 0.73); I² = 0%
Test for overall effect: Z = 2.37 (P = 0.02)



8.4 Repeat revascularisation

Study or Subgroup	PCI Events	PCI Total	CABG Events	CABG Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Buszman 2008 (LE MANS)	15	52	5	53	17.5%	3.06 [1.20, 7.80]
Morice 2010 (SYNTAX)	43	357	23	348	82.5%	1.82 [1.12, 2.96]
Total (95% CI)		**409**		**401**	**100.0%**	**2.04 [1.33, 3.13]**
Total events	58		28			

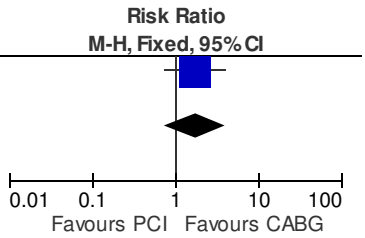
Heterogeneity: Chi² = 0.92, df = 1 (P = 0.34); I² = 0%
Test for overall effect: Z = 3.26 (P = 0.001)



8.5 Cardiac death

Study or Subgroup	PCI Events	PCI Total	CABG Events	CABG Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Morice 2010 (SYNTAX)	14	357	8	348	100.0%	1.71 [0.72, 4.02]
Total (95% CI)		**357**		**348**	**100.0%**	**1.71 [0.72, 4.02]**
Total events	14		8			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.22 (P = 0.22)

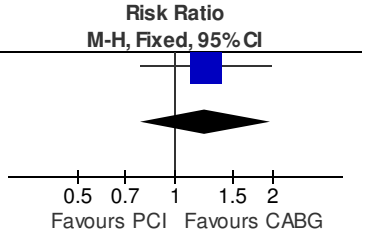


9 Left main coronary artery or 3 vessel disease -Short term follow-up (1yr)

9.1 Death (all causes)

Study or Subgroup	PCI Events	PCI Total	CABG Events	CABG Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Serruys 2009 (SYNTAX)	39	891	30	849	100.0%	1.24 [0.78, 1.98]
Total (95% CI)		**891**		**849**	**100.0%**	**1.24 [0.78, 1.98]**
Total events	39		30			

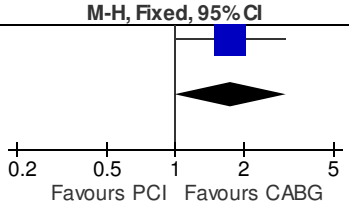
Heterogeneity: Not applicable
Test for overall effect: Z = 0.90 (P = 0.37)



9.2 cardiac mortality

Study or Subgroup	PCI Events	PCI Total	CABG Events	CABG Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Serruys 2009 (SYNTAX)	33	891	18	849	100.0%	1.75 [0.99, 3.08]
Total (95% CI)		**891**		**849**	**100.0%**	**1.75 [0.99, 3.08]**
Total events	33		18			

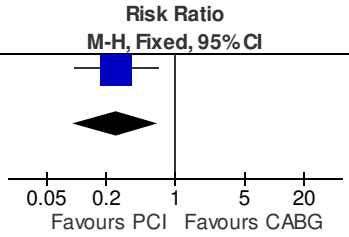
Heterogeneity: Not applicable
Test for overall effect: Z = 1.93 (P = 0.05)



9.3 Stroke

Study or Subgroup	PCI Events	PCI Total	CABG Events	CABG Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Serruys 2009 (SYNTAX)	5	891	19	849	100.0%	0.25 [0.09, 0.67]
Total (95% CI)		**891**		**849**	**100.0%**	**0.25 [0.09, 0.67]**
Total events	5		19			

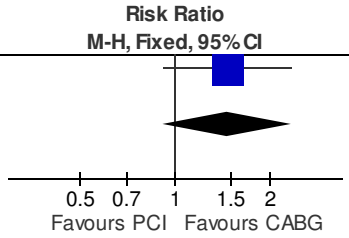
Heterogeneity: Not applicable
Test for overall effect: Z = 2.76 (P = 0.006)



9.4 MI

Study or Subgroup	PCI Events	PCI Total	CABG Events	CABG Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Serruys 2009 (SYNTAX)	43	891	28	849	100.0%	1.46 [0.92, 2.33]
Total (95% CI)		**891**		**849**	**100.0%**	**1.46 [0.92, 2.33]**
Total events	43		28			

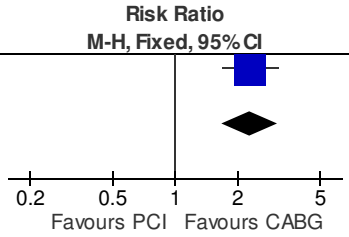
Heterogeneity: Not applicable
Test for overall effect: Z = 1.60 (P = 0.11)



9.5 Repeat revascularisation

Study or Subgroup	PCI Events	PCI Total	CABG Events	CABG Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Serruys 2009 (SYNTAX)	120	891	50	849	100.0%	2.29 [1.67, 3.14]
Total (95% CI)		**891**		**849**	**100.0%**	**2.29 [1.67, 3.14]**
Total events	120		50			

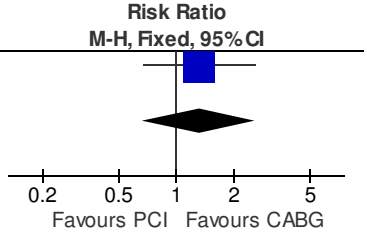
Heterogeneity: Not applicable
Test for overall effect: Z = 5.13 (P < 0.00001)



9.6 Sub group diabetes (Death)

Study or Subgroup	PCI Events	PCI Total	CABG Events	CABG Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Banning 2010 (SYNTAX)	19	227	13	204	100.0%	1.31 [0.67, 2.59]
Total (95% CI)		**227**		**204**	**100.0%**	**1.31 [0.67, 2.59]**
Total events	19		13			

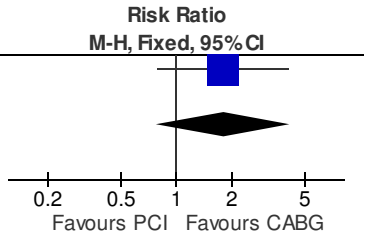
Heterogeneity: Not applicable
Test for overall effect: Z = 0.79 (P = 0.43)



9.7 Sub group diabetes (cardiac death)

Study or Subgroup	PCI Events	PCI Total	CABG Events	CABG Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Banning 2010 (SYNTAX)	16	227	8	204	100.0%	1.80 [0.79, 4.11]
Total (95% CI)		**227**		**204**	**100.0%**	**1.80 [0.79, 4.11]**
Total events	16		8			

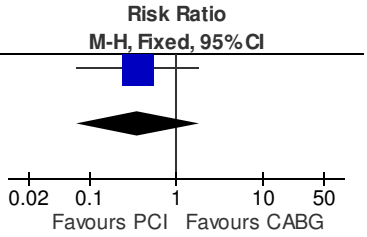
Heterogeneity: Not applicable
Test for overall effect: Z = 1.39 (P = 0.16)



9.8 Sub group diabetes (stroke)

Study or Subgroup	PCI Events	PCI Total	CABG Events	CABG Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Banning 2010 (SYNTAX)	2	227	5	204	100.0%	0.36 [0.07, 1.83]
Total (95% CI)		**227**		**204**	**100.0%**	**0.36 [0.07, 1.83]**
Total events	2		5			

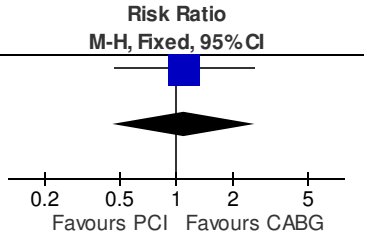
Heterogeneity: Not applicable
Test for overall effect: Z = 1.23 (P = 0.22)



9.9 Sub group diabetes (MI)

Study or Subgroup	PCI Events	PCI Total	CABG Events	CABG Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Banning 2010 (SYNTAX)	11	227	9	204	100.0%	1.10 [0.46, 2.60]
Total (95% CI)		**227**		**204**	**100.0%**	**1.10 [0.46, 2.60]**
Total events	11		9			

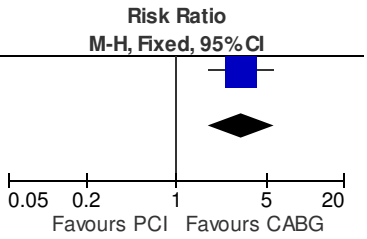
Heterogeneity: Not applicable
Test for overall effect: Z = 0.21 (P = 0.83)



9.10 Sub group diabetes (Repeat revascularisation)

Study or Subgroup	PCI Events	PCI Total	CABG Events	CABG Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Banning 2010 (SYNTAX)	46	227	13	204	100.0%	3.18 [1.77, 5.71]
Total (95% CI)		**227**		**204**	**100.0%**	**3.18 [1.77, 5.71]**
Total events	46		13			

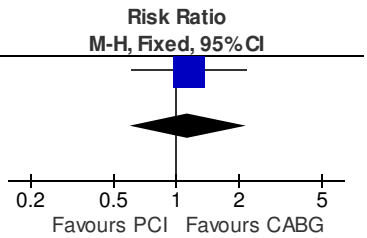
Heterogeneity: Not applicable
Test for overall effect: Z = 3.87 (P = 0.0001)



9.11 Sub group no diabetes (Death)

Study or Subgroup	PCI Events	PCI Total	CABG Events	CABG Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Banning 2010 (SYNTAX)	20	664	17	645	100.0%	1.14 [0.60, 2.16]
Total (95% CI)		**664**		**645**	**100.0%**	**1.14 [0.60, 2.16]**
Total events	20		17			

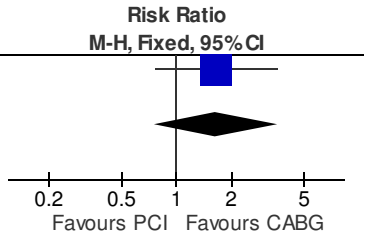
Heterogeneity: Not applicable
Test for overall effect: Z = 0.41 (P = 0.68)



9.12 Sub group no diabetes (cardiac death)

Study or Subgroup	PCI Events	PCI Total	CABG Events	CABG Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Banning 2010 (SYNTAX)	17	664	10	645	100.0%	1.65 [0.76, 3.58]
Total (95% CI)		**664**		**645**	**100.0%**	**1.65 [0.76, 3.58]**
Total events	17		10			

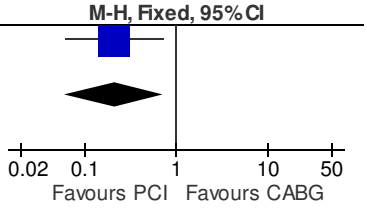
Heterogeneity: Not applicable
Test for overall effect: Z = 1.27 (P = 0.20)



9.13 Sub group no diabetes (stroke)

Study or Subgroup	PCI Events	PCI Total	CABG Events	CABG Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Banning 2010 (SYNTAX)	3	664	14	645	100.0%	0.21 [0.06, 0.72]
Total (95% CI)		**664**		**645**	**100.0%**	**0.21 [0.06, 0.72]**
Total events	3		14			

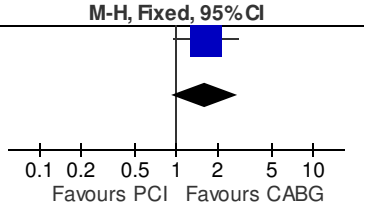
Heterogeneity: Not applicable
Test for overall effect: Z = 2.48 (P = 0.01)



9.14 Sub group no diabetes (MI)

Study or Subgroup	PCI Events	PCI Total	CABG Events	CABG Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Banning 2010 (SYNTAX)	32	664	19	645	100.0%	1.64 [0.94, 2.86]
Total (95% CI)		**664**		**645**	**100.0%**	**1.64 [0.94, 2.86]**
Total events	32		19			

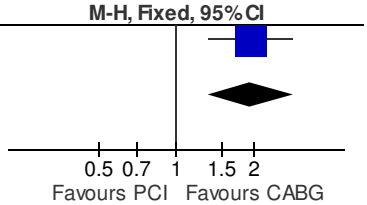
Heterogeneity: Not applicable
Test for overall effect: Z = 1.73 (P = 0.08)



9.15 Sub group no diabetes (Repeat revasc)

Study or Subgroup	PCI Events	PCI Total	CABG Events	CABG Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Banning 2010 (SYNTAX)	74	664	37	645	100.0%	1.94 [1.33, 2.84]
Total (95% CI)		**664**		**645**	**100.0%**	**1.94 [1.33, 2.84]**
Total events	74		37			

Heterogeneity: Not applicable
Test for overall effect: Z = 3.43 (P = 0.0006)

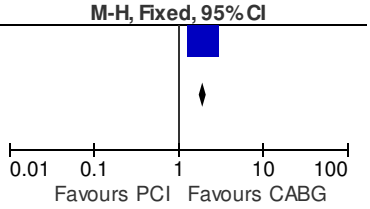


10 IPD meta analyses

10.1 Prevalance of angina

Study or Subgroup	PCI Events	PCI Total	CABG Events	CABG Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Hlatky et al 2009 (IPD)	856	3240	439	3228	100.0%	1.94 [1.75, 2.16]
Total (95% CI)		**3240**		**3228**	**100.0%**	**1.94 [1.75, 2.16]**
Total events	856		439			

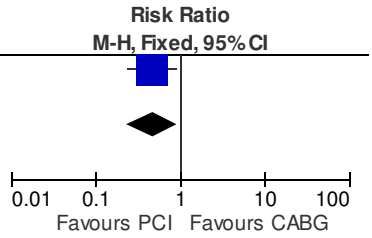
Heterogeneity: Not applicable
Test for overall effect: Z = 12.49 (P < 0.00001)



10.2 Stroke (90 days)

Study or Subgroup	PCI Events	PCI Total	CABG Events	CABG Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Hlatky et al 2009 (IPD)	12	2269	26	2268	100.0%	0.46 [0.23, 0.91]
Total (95% CI)		**2269**		**2268**	**100.0%**	**0.46 [0.23, 0.91]**
Total events	12		26			

Heterogeneity: Not applicable
Test for overall effect: Z = 2.22 (P = 0.03)

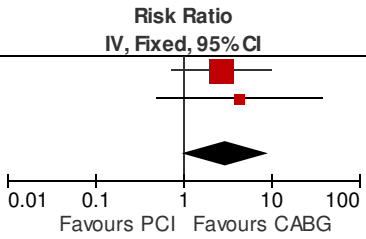


11 Sub group interaction

11.1 Age >65 yrs and age <65 yrs (Death) (Multi vessel short term)

Study or Subgroup	log[Risk Ratio]	SE	Weight	Risk Ratio IV, Fixed, 95% CI
meta analysis age <65 yrs	0.97077892	0.670909	73.3%	2.64 [0.71, 9.83]
meta analysis age >65 yrs	1.4632554	1.111739	26.7%	4.32 [0.49, 38.18]
Total (95% CI)			**100.0%**	**3.01 [0.98, 9.28]**

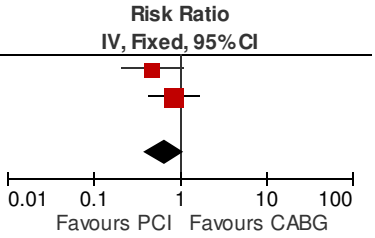
Heterogeneity: Chi² = 0.14, df = 1 (P = 0.70); I² = 0%
Test for overall effect: Z = 1.92 (P = 0.05)



11.2 Age >65 yrs and age <65 yrs (MI) (Multi vessel short term)

Study or Subgroup	log[Risk Ratio]	SE	Weight	Risk Ratio IV, Fixed, 95% CI
meta analysis age <65 yrs	-0.7550226	0.425435	41.1%	0.47 [0.20, 1.08]
meta analysis age >65 yrs	-0.1863296	0.355197	58.9%	0.83 [0.41, 1.67]
Total (95% CI)			**100.0%**	**0.66 [0.39, 1.12]**

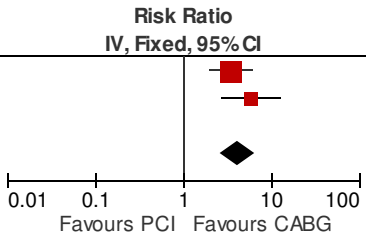
Heterogeneity: Chi² = 1.05, df = 1 (P = 0.30); I² = 5%
Test for overall effect: Z = 1.54 (P = 0.12)



11.3 Age >65 yrs and age <65 yrs (Repeat revasc) (Multi vessel short term)

Study or Subgroup	log[Risk Ratio]	SE	Weight	Risk Ratio IV, Fixed, 95% CI
meta analysis age <65 yrs	1.22082992	0.292853	65.0%	3.39 [1.91, 6.02]
meta analysis age >65 yrs	1.74046617	0.399178	35.0%	5.70 [2.61, 12.46]
Total (95% CI)			**100.0%**	**4.07 [2.56, 6.46]**

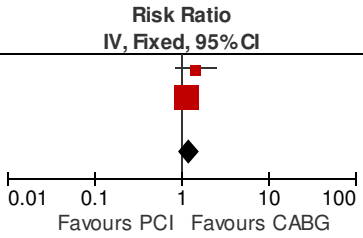
Heterogeneity: Chi² = 1.10, df = 1 (P = 0.29); I² = 9%
Test for overall effect: Z = 5.94 (P < 0.00001)



11.4 Diabetes and no diabetes (Death) (Multi vessel Long term)

Study or Subgroup	log[Risk Ratio]	SE	Weight	Risk Ratio IV, Fixed, 95% CI
meta analysis - diabetes	0.35767444	0.278201	25.0%	1.43 [0.83, 2.47]
meta analysis-no diabetes	0.11332869	0.160774	75.0%	1.12 [0.82, 1.53]
Total (95% CI)			**100.0%**	**1.19 [0.91, 1.56]**

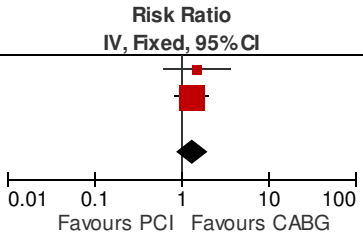
Heterogeneity: Chi² = 0.58, df = 1 (P = 0.45); I² = 0%
Test for overall effect: Z = 1.25 (P = 0.21)



11.5 Diabetes and no diabetes (MI) (Multi vessel long term)

Study or Subgroup	log[Risk Ratio]	SE	Weight	Risk Ratio IV, Fixed, 95% CI
meta analysis - diabetes	0.3852624	0.45566	20.7%	1.47 [0.60, 3.59]
meta analysis-no diabetes	0.24686008	0.233117	79.3%	1.28 [0.81, 2.02]
Total (95% CI)			**100.0%**	**1.32 [0.88, 1.98]**

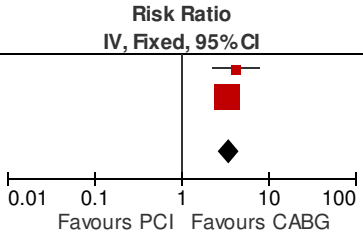
Heterogeneity: Chi² = 0.07, df = 1 (P = 0.79); I² = 0%
Test for overall effect: Z = 1.33 (P = 0.18)



11.6 Diabetes and no diabetes (Repeat revasc) (Multi vessel long term)

Study or Subgroup	log[Risk Ratio]	SE	Weight	Risk Ratio IV, Fixed, 95% CI
meta analysis - diabetes	1.41342303	0.318919	20.8%	4.11 [2.20, 7.68]
meta analysis-no diabetes	1.178655	0.163511	79.2%	3.25 [2.36, 4.48]
Total (95% CI)			**100.0%**	**3.41 [2.57, 4.54]**

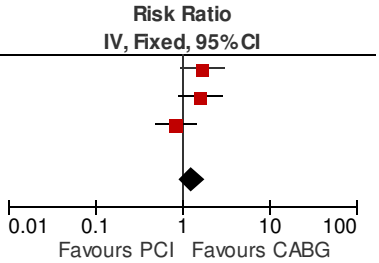
Heterogeneity: Chi² = 0.43, df = 1 (P = 0.51); I² = 0%
Test for overall effect: Z = 8.44 (P < 0.00001)



11.7 Single, 2 vessel and 3 vessel (Death) (long term)

Study or Subgroup	log[Risk Ratio]	SE	Weight	Risk Ratio IV, Fixed, 95% CI
meta analysis - 2 vessel	0.51879379	0.296043	32.7%	1.68 [0.94, 3.00]
meta analysis -3 vessel	0.45742485	0.302699	31.3%	1.58 [0.87, 2.86]
meta analysis -single ves	-0.1743534	0.282024	36.0%	0.84 [0.48, 1.46]
Total (95% CI)			**100.0%**	**1.28 [0.92, 1.79]**

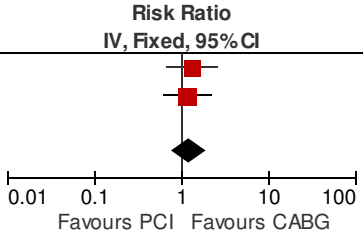
Heterogeneity: Chi² = 3.56, df = 2 (P = 0.17); I² = 44%
Test for overall effect: Z = 1.48 (P = 0.14)



11.8 Diabetes and no diabetes (Death) (LMD or 3 vessel-short term)

Study or Subgroup	log[Risk Ratio]	SE	Weight	Risk Ratio IV, Fixed, 95% CI
meta analysis - diabetes	0.27002714	0.344933	47.3%	1.31 [0.67, 2.58]
meta analysis-no diabetes	0.13102826	0.326769	52.7%	1.14 [0.60, 2.16]
Total (95% CI)			**100.0%**	**1.22 [0.76, 1.94]**

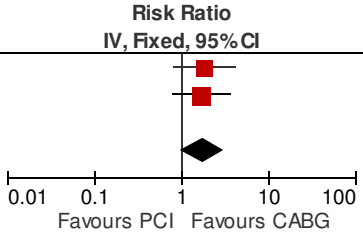
Heterogeneity: Chi² = 0.09, df = 1 (P = 0.77); I² = 0%
Test for overall effect: Z = 0.83 (P = 0.41)



11.9 Diabetes and no diabetes (cardiac Death) (LMD or 3 ves sel -s

Study or Subgroup	log[Risk Ratio]	SE	Weight	Risk Ratio IV, Fixed, 95% CI
meta analysis - diabetes	0.58778666	0.4207	46.9%	1.80 [0.79, 4.11]
meta analysis-no diabetes	0.50077529	0.395357	53.1%	1.65 [0.76, 3.58]
Total (95% CI)			**100.0%**	**1.72 [0.98, 3.02]**

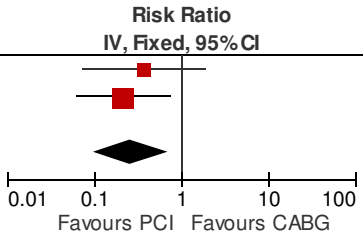
Heterogeneity: Chi² = 0.02, df = 1 (P = 0.88); I² = 0%
Test for overall effect: Z = 1.88 (P = 0.06)



11.10 Diabetes and no diabetes (stroke) (LMD or 3 vessel short term)

Study or Subgroup	log[Risk Ratio]	SE	Weight	Risk Ratio IV, Fixed, 95% CI
meta analysis - diabetes	-1.0216512	0.832545	36.7%	0.36 [0.07, 1.84]
meta analysis-no diabetes	-1.5606477	0.633905	63.3%	0.21 [0.06, 0.73]
Total (95% CI)			**100.0%**	**0.26 [0.10, 0.69]**

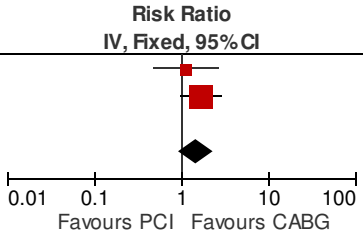
Heterogeneity: Chi² = 0.27, df = 1 (P = 0.61); I² = 0%
Test for overall effect: Z = 2.70 (P = 0.007)



11.11 Diabetes and no diabetes (MI) (LMD or 3 vessel short term)

Study or Subgroup	log[Risk Ratio]	SE	Weight	Risk Ratio IV, Fixed, 95% CI
meta analysis - diabetes	0.09531018	0.441847	29.2%	1.10 [0.46, 2.62]
meta analysis-no diabetes	0.49469624	0.283851	70.8%	1.64 [0.94, 2.86]
Total (95% CI)			**100.0%**	**1.46 [0.91, 2.33]**

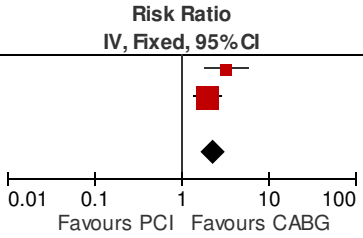
Heterogeneity: Chi² = 0.58, df = 1 (P = 0.45); I² = 0%
Test for overall effect: Z = 1.58 (P = 0.11)



11.12 Diabetes and no diabetes (repeat revasc) (LMD or 3 vessel short term)

Study or Subgroup	log[Risk Ratio]	SE	Weight	Risk Ratio IV, Fixed, 95% CI
meta analysis - diabetes	1.1568812	0.298786	29.6%	3.18 [1.77, 5.71]
meta analysis-no diabetes	0.66268797	0.193527	70.4%	1.94 [1.33, 2.83]
Total (95% CI)			**100.0%**	**2.25 [1.63, 3.09]**

Heterogeneity: Chi² = 1.93, df = 1 (P = 0.17); I² = 48%
Test for overall effect: Z = 4.98 (P < 0.00001)

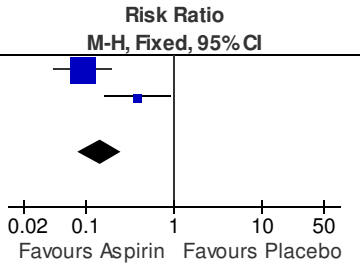


1 Aspirin vs. Placebo

1.1 Non fatal MI (follow-up 50-60 months)

Study or Subgroup	Aspirin Events	Aspirin Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Moller 1992 (SAPAT trial)	7	1009	78	1026	81.9%	0.09 [0.04, 0.20]
Ridker 1991	7	178	16	155	18.1%	0.38 [0.16, 0.90]
Total (95% CI)		**1187**		**1181**	**100.0%**	**0.14 [0.08, 0.25]**
Total events	14		94			

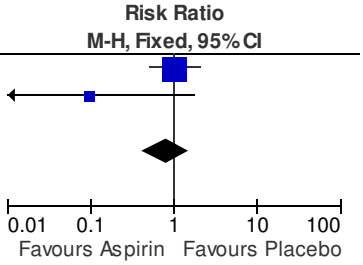
Heterogeneity: Chi² = 6.26, df = 1 (P = 0.01); I² = 84%
Test for overall effect: Z = 6.76 (P < 0.00001)



1.2 Fatal MI (follow-up 50-60 months)

Study or Subgroup	Aspirin Events	Aspirin Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Moller 1992 (SAPAT trial)	15	1009	15	1026	75.6%	1.02 [0.50, 2.07]
Ridker 1991	0	178	4	155	24.4%	0.10 [0.01, 1.78]
Total (95% CI)		**1187**		**1181**	**100.0%**	**0.79 [0.41, 1.53]**
Total events	15		19			

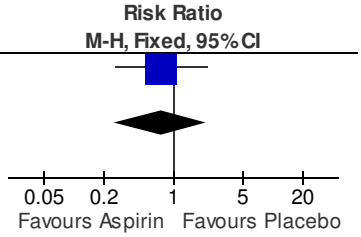
Heterogeneity: Chi² = 2.47, df = 1 (P = 0.12); I² = 60%
Test for overall effect: Z = 0.70 (P = 0.49)



1.3 Cardiovascular death (follow-up 60.2 months)

Study or Subgroup	Aspirin Events	Aspirin Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Ridker 1991	6	178	7	155	100.0%	0.75 [0.26, 2.17]
Total (95% CI)		**178**		**155**	**100.0%**	**0.75 [0.26, 2.17]**
Total events	6		7			

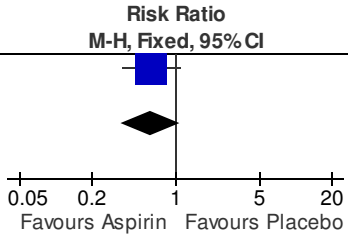
Heterogeneity: Not applicable
Test for overall effect: Z = 0.54 (P = 0.59)



1.4 Sudden death (follow-up median 50 months)

Study or Subgroup	Aspirin Events	Aspirin Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Moller 1992 (SAPAT trial)	19	1009	31	1026	100.0%	0.62 [0.35, 1.10]
Total (95% CI)		**1009**		**1026**	**100.0%**	**0.62 [0.35, 1.10]**
Total events	19		31			

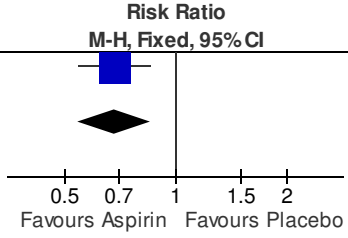
Heterogeneity: Not applicable
Test for overall effect: Z = 1.64 (P = 0.10)



1.5 Vascular events (follow-up median 50 months)

Study or Subgroup	Aspirin Events	Aspirin Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Moller 1992 (SAPAT trial)	108	1009	161	1026	100.0%	0.68 [0.54, 0.86]
Total (95% CI)		**1009**		**1026**	**100.0%**	**0.68 [0.54, 0.86]**
Total events	108		161			

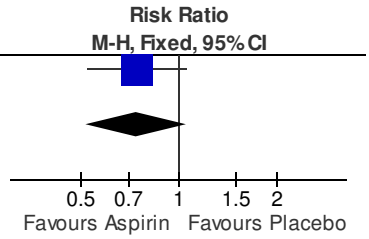
Heterogeneity: Not applicable
Test for overall effect: Z = 3.29 (P = 0.0010)



1.6 Vascular deaths (follow-up median 50 months)

Study or Subgroup	Aspirin Events	Aspirin Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Moller 1992 (SAPAT trial)	51	1009	70	1026	100.0%	0.74 [0.52, 1.05]
Total (95% CI)		**1009**		**1026**	**100.0%**	**0.74 [0.52, 1.05]**
Total events	51		70			

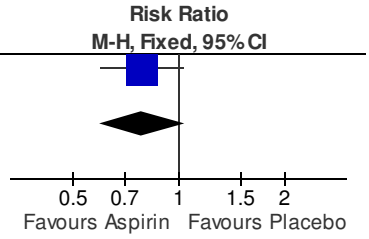
Heterogeneity: Not applicable
Test for overall effect: Z = 1.68 (P = 0.09)



1.7 All cause mortality (follow-up median 50 months)

Study or Subgroup	Aspirin Events	Aspirin Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Moller 1992 (SAPAT trial)	82	1009	106	1026	100.0%	0.79 [0.60, 1.04]
Total (95% CI)		**1009**		**1026**	**100.0%**	**0.79 [0.60, 1.04]**
Total events	82		106			

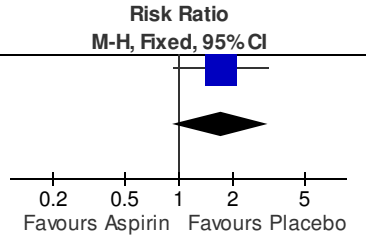
Heterogeneity: Not applicable
Test for overall effect: Z = 1.71 (P = 0.09)



1.8 Haemorrhagic adverse events (follow-up median 50 months)

Study or Subgroup	Aspirin Events	Aspirin Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Moller 1992 (SAPAT trial)	27	1009	16	1026	100.0%	1.72 [0.93, 3.17]
Total (95% CI)		**1009**		**1026**	**100.0%**	**1.72 [0.93, 3.17]**
Total events	27		16			

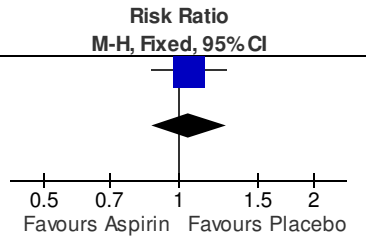
Heterogeneity: Not applicable
Test for overall effect: Z = 1.73 (P = 0.08)



1.9 Non haemorrhagic adverse events (follow-up median 50 months)

Study or Subgroup	Aspirin Events	Aspirin Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Moller 1992 (SAPAT trial)	174	1009	168	1026	100.0%	1.05 [0.87, 1.28]
Total (95% CI)		**1009**		**1026**	**100.0%**	**1.05 [0.87, 1.28]**
Total events	174		168			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.53 (P = 0.60)

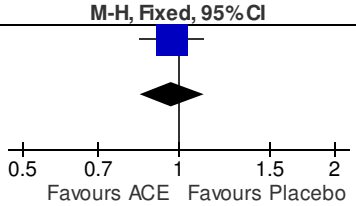


1 ACE +background medication vs. Placebo +background medication

1.1 Combined (death from cv causes or non fatal MI)

Study or Subgroup	ACE Events	ACE Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Braunwald 2004(PEACE)	344	4158	352	4132	100.0%	0.97 [0.84, 1.12]
Total (95% CI)		**4158**		**4132**	**100.0%**	**0.97 [0.84, 1.12]**
Total events	344		352			

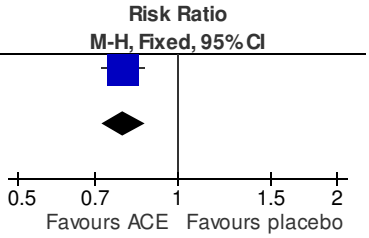
Heterogeneity: Not applicable
Test for overall effect: Z = 0.40 (P = 0.69)



1.2 Combined (MI, stroke, or death from CV causes)

Study or Subgroup	ACE Events	ACE Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Yusuf 2000 (HOPE trial)	651	4645	826	4652	100.0%	0.79 [0.72, 0.87]
Total (95% CI)		**4645**		**4652**	**100.0%**	**0.79 [0.72, 0.87]**
Total events	651		826			

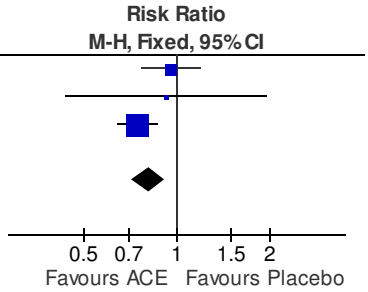
Heterogeneity: Not applicable
Test for overall effect: Z = 4.92 (P < 0.00001)



1.3 Death from cardio vascular causes

Study or Subgroup	ACE Events	ACE Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Braunwald 2004(PEACE)	146	4158	152	4132	28.1%	0.95 [0.76, 1.19]
Pitt 2001 (QUIET)	13	878	14	872	2.6%	0.92 [0.44, 1.95]
Yusuf 2000 (HOPE trial)	282	4645	377	4652	69.3%	0.75 [0.65, 0.87]
Total (95% CI)		**9681**		**9656**	**100.0%**	**0.81 [0.72, 0.92]**
Total events	441		543			

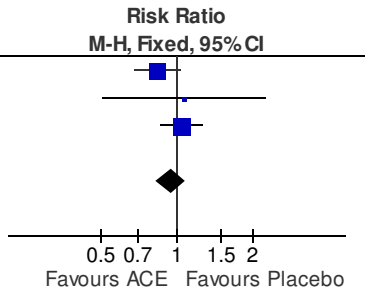
Heterogeneity: Chi² = 3.26, df = 2 (P = 0.20); I² = 39%
Test for overall effect: Z = 3.36 (P = 0.0008)



1.4 Death from non cardiovascular or unknown causes

Study or Subgroup	ACE Events	ACE Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Braunwald 2004(PEACE)	153	4158	182	4132	47.1%	0.84 [0.68, 1.03]
Pitt 2001 (QUIET)	14	878	13	872	3.4%	1.07 [0.51, 2.26]
Yusuf 2000 (HOPE trial)	200	4645	192	4652	49.5%	1.04 [0.86, 1.27]
Total (95% CI)		**9681**		**9656**	**100.0%**	**0.95 [0.82, 1.09]**
Total events	367		387			

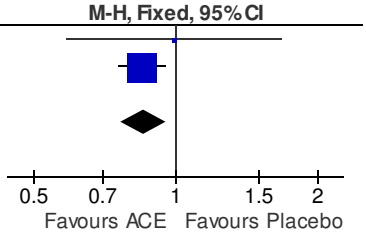
Heterogeneity: Chi² = 2.42, df = 2 (P = 0.30); I² = 17%
Test for overall effect: Z = 0.77 (P = 0.44)



1.5 All causes death

Study or Subgroup	ACE Events	ACE Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Pitt 2001 (QUIET)	27	878	27	872	4.5%	0.99 [0.59, 1.68]
Yusuf 2000 (HOPE trial)	482	4645	569	4652	95.5%	0.85 [0.76, 0.95]
Total (95% CI)		**5523**		**5524**	**100.0%**	**0.85 [0.76, 0.96]**
Total events	509		596			

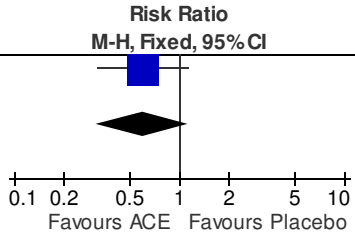
Heterogeneity: Chi² = 0.33, df = 1 (P = 0.57); I² = 0%
Test for overall effect: Z = 2.75 (P = 0.006)



1.6 Death from CHF

Study or Subgroup	ACE Events	ACE Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Braunwald 2004(PEACE)	15	4158	25	4132	100.0%	0.60 [0.31, 1.13]
Total (95% CI)		**4158**		**4132**	**100.0%**	**0.60 [0.31, 1.13]**
Total events	15		25			

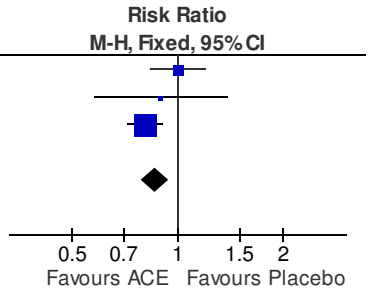
Heterogeneity: Not applicable
Test for overall effect: Z = 1.59 (P = 0.11)



1.7 Non fatal MI (MI in HOPE trial)

Study or Subgroup	ACE Events	ACE Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Braunwald 2004(PEACE)	222	4158	220	4132	26.6%	1.00 [0.84, 1.20]
Pitt 2001 (QUIET)	36	878	40	872	4.8%	0.89 [0.58, 1.39]
Yusuf 2000 (HOPE trial)	459	4645	570	4652	68.6%	0.81 [0.72, 0.91]
Total (95% CI)		**9681**		**9656**	**100.0%**	**0.86 [0.78, 0.95]**
Total events	717		830			

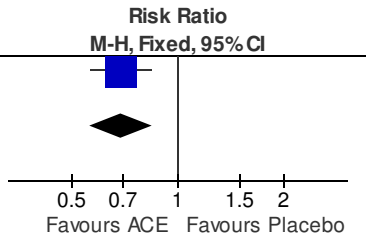
Heterogeneity: Chi² = 3.96, df = 2 (P = 0.14); I² = 50%
Test for overall effect: Z = 3.03 (P = 0.002)



1.8 Stroke

Study or Subgroup	ACE Events	ACE Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Yusuf 2000 (HOPE trial)	156	4645	226	4652	100.0%	0.69 [0.57, 0.84]
Total (95% CI)		**4645**		**4652**	**100.0%**	**0.69 [0.57, 0.84]**
Total events	156		226			

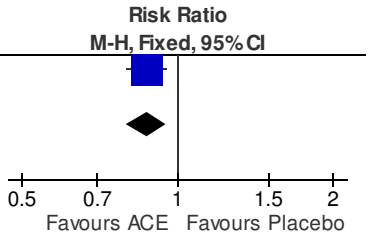
Heterogeneity: Not applicable
Test for overall effect: Z = 3.62 (P = 0.0003)



1.9 Revascularisation

Study or Subgroup	ACE Events	ACE Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Yusuf 2000 (HOPE trial)	742	4645	852	4652	100.0%	0.87 [0.80, 0.95]
Total (95% CI)		**4645**		**4652**	**100.0%**	**0.87 [0.80, 0.95]**
Total events	742		852			

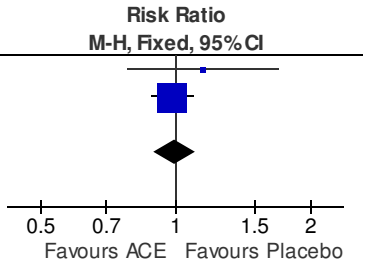
Heterogeneity: Not applicable
Test for overall effect: Z = 2.99 (P = 0.003)



1.10 Hospitalised with unstable angina

Study or Subgroup	ACE Events	ACE Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Pitt 2001 (QUIET)	52	878	45	872	7.4%	1.15 [0.78, 1.69]
Yusuf 2000 (HOPE trial)	554	4645	565	4652	92.6%	0.98 [0.88, 1.10]
Total (95% CI)		**5523**		**5524**	**100.0%**	**0.99 [0.89, 1.11]**
Total events	606		610			

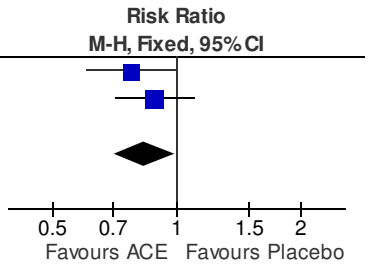
Heterogeneity: Chi² = 0.57, df = 1 (P = 0.45); I² = 0%
Test for overall effect: Z = 0.11 (P = 0.92)



1.11 Hospitalisation due to CHF

Study or Subgroup	ACE Events	ACE Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Braunwald 2004(PEACE)	105	4158	134	4132	45.7%	0.78 [0.61, 1.00]
Yusuf 2000 (HOPE trial)	141	4645	160	4652	54.3%	0.88 [0.71, 1.10]
Total (95% CI)		**8803**		**8784**	**100.0%**	**0.84 [0.71, 0.99]**
Total events	246		294			

Heterogeneity: Chi² = 0.53, df = 1 (P = 0.47); I² = 0%
Test for overall effect: Z = 2.12 (P = 0.03)

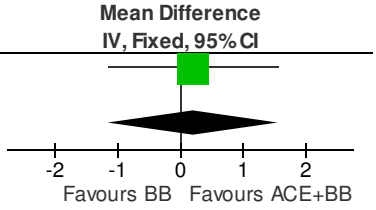


2 ACE+BB vs. BB

2.1 Exercise time (min)

Study or Subgroup	ACE Mean	ACE SD	ACE Total	BB Mean	BB SD	BB Total	Weight	Mean Difference IV, Fixed, 95% CI
Klein 1990	9.6	2.35	23	9.4	2.35	23	100.0%	0.20 [-1.16, 1.56]
Total (95% CI)			**23**			**23**	**100.0%**	**0.20 [-1.16, 1.56]**

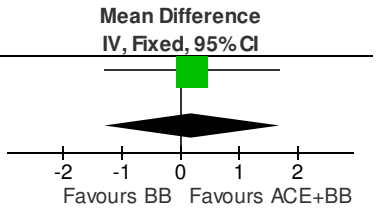
Heterogeneity: Not applicable
Test for overall effect: Z = 0.29 (P = 0.77)



2.2 Time to 1mm ST segment depression (min)

Study or Subgroup	ACE Mean	ACE SD	ACE Total	BB Mean	BB SD	BB Total	Weight	Mean Difference IV, Fixed, 95% CI
Klein 1990	8.1	2.82	23	7.9	2.35	23	100.0%	0.20 [-1.30, 1.70]
Total (95% CI)			**23**			**23**	**100.0%**	**0.20 [-1.30, 1.70]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.26 (P = 0.79)

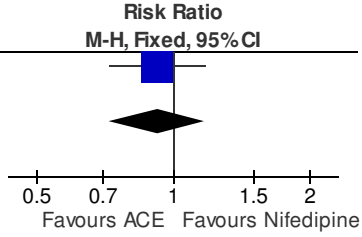


3 ACE +background medication vs. Nifedipine + background medication

3.1 Combined Cardiac events

Study or Subgroup	ACE Events	ACE Total	Nifedipine Events	Nifedipine Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Yui 200 (JMIC-B)	106	822	116	828	100.0%	0.92 [0.72, 1.18]
Total (95% CI)		**822**		**828**	**100.0%**	**0.92 [0.72, 1.18]**
Total events	106		116			

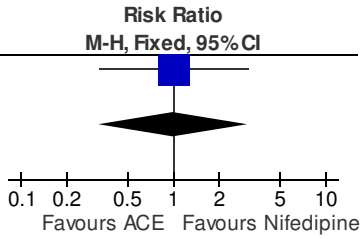
Heterogeneity: Not applicable
Test for overall effect: Z = 0.66 (P = 0.51)



3.2 sudden death or cardiac death

Study or Subgroup	ACE Events	Total	Nifedipine Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Yui 200 (JMIC-B)	6	822	6	828	100.0%	1.01 [0.33, 3.11]
Total (95% CI)		**822**		**828**	**100.0%**	**1.01 [0.33, 3.11]**
Total events	6		6			

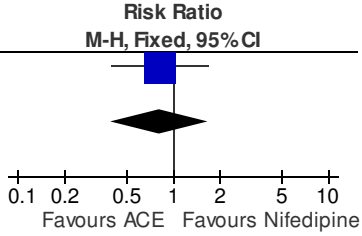
Heterogeneity: Not applicable
Test for overall effect: Z = 0.01 (P = 0.99)



3.3 MI

Study or Subgroup	ACE Events	Total	Nifedipine Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Yui 200 (JMIC-B)	13	822	16	828	100.0%	0.82 [0.40, 1.69]
Total (95% CI)		**822**		**828**	**100.0%**	**0.82 [0.40, 1.69]**
Total events	13		16			

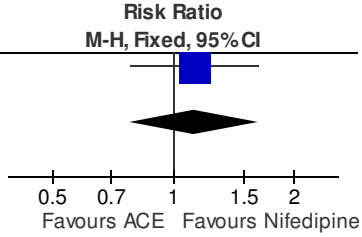
Heterogeneity: Not applicable
Test for overall effect: Z = 0.54 (P = 0.59)



3.4 Hospitalisation for angina pectoris

Study or Subgroup	ACE Events	Total	Nifedipine Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Yui 200 (JMIC-B)	56	822	50	828	100.0%	1.13 [0.78, 1.63]
Total (95% CI)		**822**		**828**	**100.0%**	**1.13 [0.78, 1.63]**
Total events	56		50			

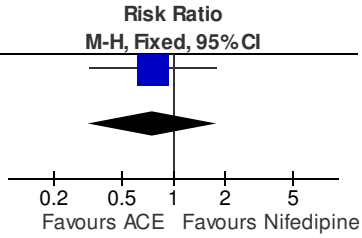
Heterogeneity: Not applicable
Test for overall effect: Z = 0.64 (P = 0.52)



3.5 Hospitalisation for HF

Study or Subgroup	ACE Events	Total	Nifedipine Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Yui 200 (JMIC-B)	9	822	12	828	100.0%	0.76 [0.32, 1.78]
Total (95% CI)		**822**		**828**	**100.0%**	**0.76 [0.32, 1.78]**
Total events	9		12			

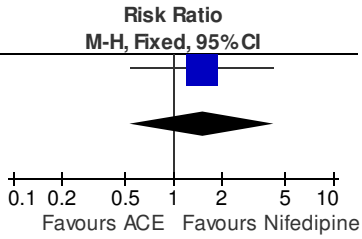
Heterogeneity: Not applicable
Test for overall effect: Z = 0.64 (P = 0.52)



3.6 Non cardiac death

Study or Subgroup	ACE Events	Total	Nifedipine Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Yui 200 (JMIC-B)	9	822	6	828	100.0%	1.51 [0.54, 4.23]
Total (95% CI)		**822**		**828**	**100.0%**	**1.51 [0.54, 4.23]**
Total events	9		6			

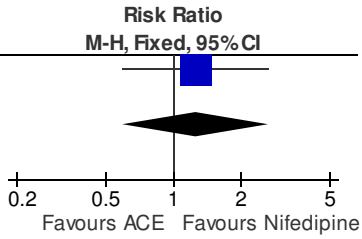
Heterogeneity: Not applicable
Test for overall effect: Z = 0.79 (P = 0.43)



3.7 Total mortality

Study or Subgroup	ACE Events	ACE Total	Nifedipine Events	Nifedipine Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Yui 200 (JMIC-B)	15	822	12	828	100.0%	1.26 [0.59, 2.67]
Total (95% CI)		**822**		**828**	**100.0%**	**1.26 [0.59, 2.67]**
Total events	15		12			

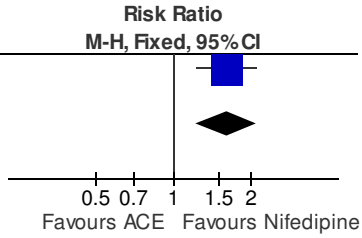
Heterogeneity: Not applicable
Test for overall effect: Z = 0.60 (P = 0.55)



3.8 Adverse events

Study or Subgroup	ACE Events	ACE Total	Nifedipine Events	Nifedipine Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Yui 200 (JMIC-B)	121	822	76	828	100.0%	1.60 [1.22, 2.10]
Total (95% CI)		**822**		**828**	**100.0%**	**1.60 [1.22, 2.10]**
Total events	121		76			

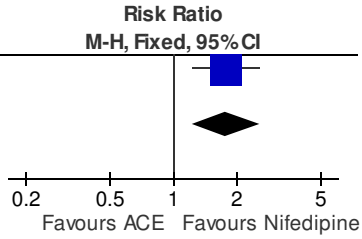
Heterogeneity: Not applicable
Test for overall effect: Z = 3.43 (P = 0.0006)



3.9 Withdrawal due to adverse effects

Study or Subgroup	ACE Events	ACE Total	Nifedipine Events	Nifedipine Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Yui 200 (JMIC-B)	72	822	41	828	100.0%	1.77 [1.22, 2.56]
Total (95% CI)		**822**		**828**	**100.0%**	**1.77 [1.22, 2.56]**
Total events	72		41			

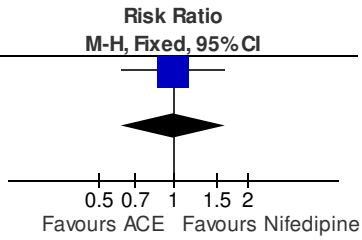
Heterogeneity: Not applicable
Test for overall effect: Z = 3.01 (P = 0.003)



3.10 Diabetes sub group (combined cardiac events)

Study or Subgroup	ACE Events	ACE Total	Nifedipine Events	Nifedipine Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Yui 2004 (JMIC-B)	26	173	30	199	100.0%	1.00 [0.61, 1.62]
Total (95% CI)		**173**		**199**	**100.0%**	**1.00 [0.61, 1.62]**
Total events	26		30			

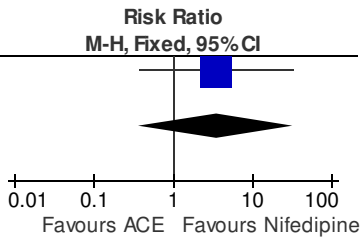
Heterogeneity: Not applicable
Test for overall effect: Z = 0.01 (P = 0.99)



3.11 Diabetes sub group (cardiac death or sudden death)

Study or Subgroup	ACE Events	ACE Total	Nifedipine Events	Nifedipine Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Yui 2004 (JMIC-B)	3	173	1	199	100.0%	3.45 [0.36, 32.87]
Total (95% CI)		**173**		**199**	**100.0%**	**3.45 [0.36, 32.87]**
Total events	3		1			

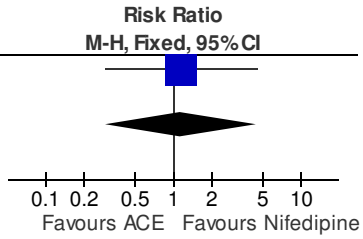
Heterogeneity: Not applicable
Test for overall effect: Z = 1.08 (P = 0.28)



3.12 Diabetes sub group (MI)

Study or Subgroup	ACE Events	Total	Nifedipine Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Yui 2004 (JMIC-B)	4	173	4	199	100.0%	1.15 [0.29, 4.53]
Total (95% CI)		**173**		**199**	**100.0%**	**1.15 [0.29, 4.53]**
Total events	4		4			

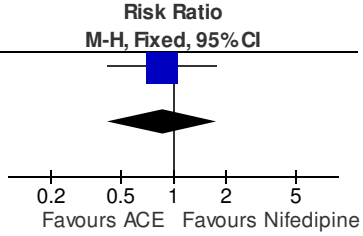
Heterogeneity: Not applicable
Test for overall effect: Z = 0.20 (P = 0.84)



3.13 Diabetes sub group (hospitalisation for angina pectoris)

Study or Subgroup	ACE Events	Total	Nifedipine Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Yui 2004 (JMIC-B)	12	173	16	199	100.0%	0.86 [0.42, 1.77]
Total (95% CI)		**173**		**199**	**100.0%**	**0.86 [0.42, 1.77]**
Total events	12		16			

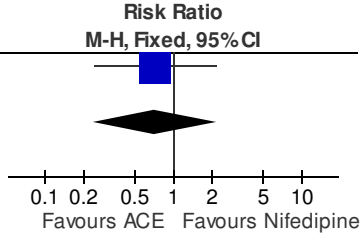
Heterogeneity: Not applicable
Test for overall effect: Z = 0.40 (P = 0.69)



3.14 Diabetes sub group (Hospitalisation for HF)

Study or Subgroup	ACE Events	Total	Nifedipine Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Yui 2004 (JMIC-B)	5	173	8	199	100.0%	0.72 [0.24, 2.16]
Total (95% CI)		**173**		**199**	**100.0%**	**0.72 [0.24, 2.16]**
Total events	5		8			

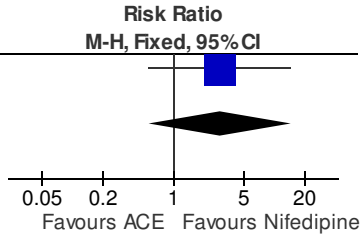
Heterogeneity: Not applicable
Test for overall effect: Z = 0.59 (P = 0.56)



3.15 Diabetes sub group (Total mortality)

Study or Subgroup	ACE Events	Total	Nifedipine Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Yui 2004 (JMIC-B)	5	173	2	199	100.0%	2.88 [0.57, 14.64]
Total (95% CI)		**173**		**199**	**100.0%**	**2.88 [0.57, 14.64]**
Total events	5		2			

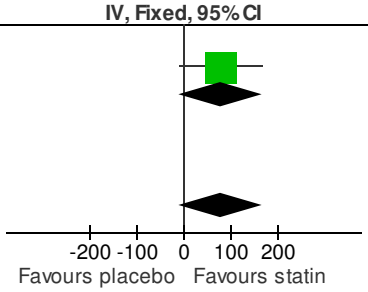
Heterogeneity: Not applicable
Test for overall effect: Z = 1.27 (P = 0.20)



1 Statins vs. Placebo

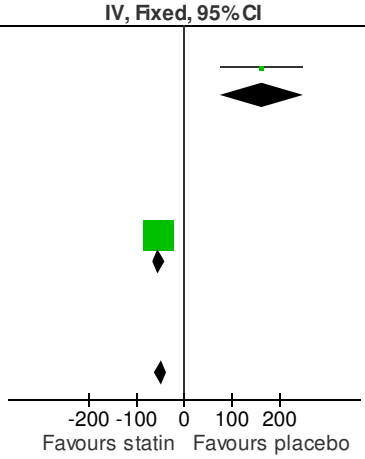
1.1 Total exercise time (Sec)

Study or Subgroup	Statin Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
1.1.1 Pravastatin vs. placebo								
Kayikcioglu 2005	585	165	19	507	110	19	100.0%	78.00 [-11.17, 167.17]
Subtotal (95% CI)			**19**			**19**	**100.0%**	**78.00 [-11.17, 167.17]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.71 (P = 0.09)								
Total (95% CI)			**19**			**19**	**100.0%**	**78.00 [-11.17, 167.17]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.71 (P = 0.09)								
Test for subgroup differences: Not applicable								



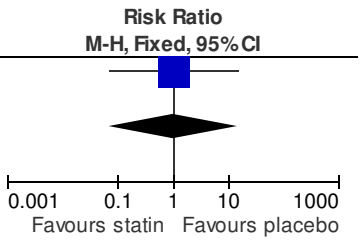
1.2 Time to 1mm ST depression (Sec)

Study or Subgroup	Statin Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
1.2.1 Pravastatin vs. Placebo								
Kayikcioglu 2005	419	162	19	256	102	19	2.1%	163.00 [76.92, 249.08]
Subtotal (95% CI)			**19**			**19**	**2.1%**	**163.00 [76.92, 249.08]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 3.71 (P = 0.0002)								
1.2.2 Simvastatin vs. Placebo								
Fabian 2004	267	23.4	20	319.8	16.2	20	97.9%	-52.80 [-65.27, -40.33]
Subtotal (95% CI)			**20**			**20**	**97.9%**	**-52.80 [-65.27, -40.33]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 8.30 (P < 0.00001)								
Total (95% CI)			**39**			**39**	**100.0%**	**-48.36 [-60.71, -36.02]**
Heterogeneity: Chi² = 23.65, df = 1 (P < 0.00001); I² = 96%								
Test for overall effect: Z = 7.68 (P < 0.00001)								
Test for subgroup differences: Chi² = 23.65, df = 1 (P < 0.00001), I² = 95.8%								



1.3 Hospitalisation for worsening of angina

Study or Subgroup	Statin Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Kayikcioglu 2005	1	19	1	19	100.0%	1.00 [0.07, 14.85]
Total (95% CI)		**19**		**19**	**100.0%**	**1.00 [0.07, 14.85]**
Total events	1		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.00 (P = 1.00)						

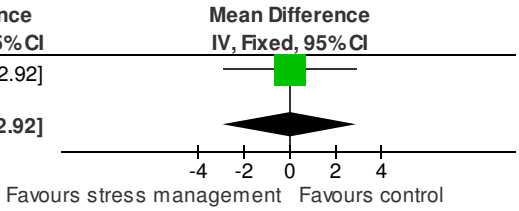


1 Stress management vs. routine care control

1.1 Frequency of angina (average no. of. daily attacks) (8 weeks)

Study or Subgroup	stress management Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Bundy 1998	7.4	4.7	42	7.4	5.2	16	100.0%	0.00 [-2.92, 2.92]
Total (95% CI)			**42**			**16**	**100.0%**	**0.00 [-2.92, 2.92]**

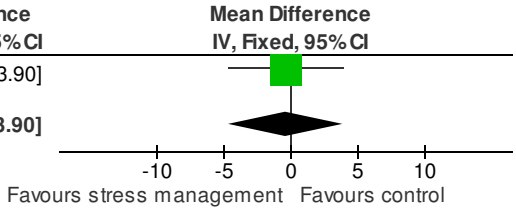
Heterogeneity: Not applicable
Test for overall effect: Z = 0.00 (P = 1.00)



1.2 Average duration of angina per attack (mins) (8 weeks)

Study or Subgroup	stress management Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Bundy 1998	11	7.4	42	11.4	7.5	16	100.0%	-0.40 [-4.70, 3.90]
Total (95% CI)			**42**			**16**	**100.0%**	**-0.40 [-4.70, 3.90]**

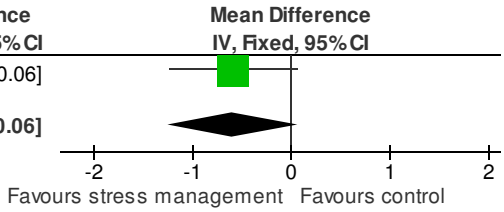
Heterogeneity: Not applicable
Test for overall effect: Z = 0.18 (P = 0.86)



1.3 Frequency of chest pain at rest (days per fortnight) (6 months)

Study or Subgroup	stress management Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Gallacher 1997	1.83	2.92	158	2.42	3.19	179	100.0%	-0.59 [-1.24, 0.06]
Total (95% CI)			**158**			**179**	**100.0%**	**-0.59 [-1.24, 0.06]**

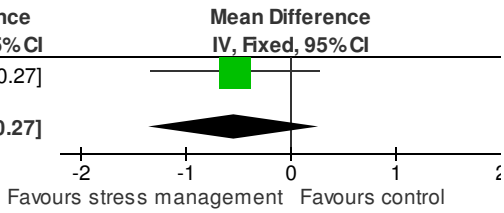
Heterogeneity: Not applicable
Test for overall effect: Z = 1.77 (P = 0.08)



1.4 Frequency of chest pain on exertion (days per fortnight) (6 months)

Study or Subgroup	stress management Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Gallacher 1997	3.42	3.71	158	3.96	3.86	179	100.0%	-0.54 [-1.35, 0.27]
Total (95% CI)			**158**			**179**	**100.0%**	**-0.54 [-1.35, 0.27]**

Heterogeneity: Not applicable
Test for overall effect: Z = 1.31 (P = 0.19)

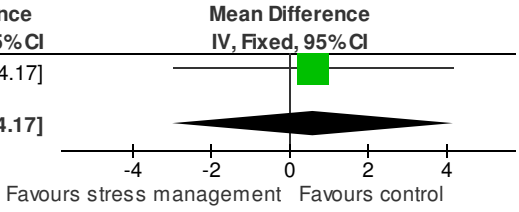


2 Stress management + exercise vs. routine care control (8 weeks)

2.1 Frequency of angina (average no. of daily attacks)

Study or Subgroup	stress management Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Bundy 1998	8	5.7	20	7.4	5.2	16	100.0%	0.60 [-2.97, 4.17]
Total (95% CI)			**20**			**16**	**100.0%**	**0.60 [-2.97, 4.17]**

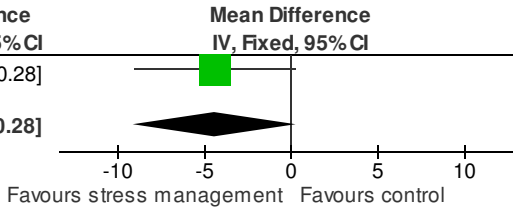
Heterogeneity: Not applicable
Test for overall effect: Z = 0.33 (P = 0.74)



2.2 Duration of angina (min)

Study or Subgroup	stress management Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Bundy 1998	7	6.6	20	11.4	7.5	16	100.0%	-4.40 [-9.08, 0.28]
Total (95% CI)			**20**			**16**	**100.0%**	**-4.40 [-9.08, 0.28]**

Heterogeneity: Not applicable
Test for overall effect: Z = 1.84 (P = 0.07)

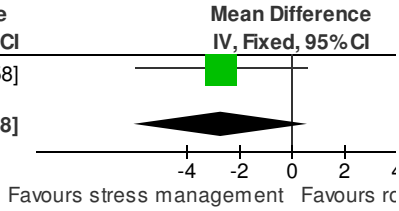


3 Stress management + exercise vs. routine care (8 weeks) (change scores)

3.1 Frequency of angina

Study or Subgroup	Stress management +exerci Mean	SD	Total	routine care Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Bundy 1994	4.3	3	14	7	5.7	15	100.0%	-2.70 [-5.98, 0.58]
Total (95% CI)			**14**			**15**	**100.0%**	**-2.70 [-5.98, 0.58]**

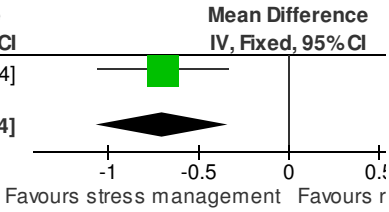
Heterogeneity: Not applicable
Test for overall effect: Z = 1.61 (P = 0.11)



3.2 Duration of angina

Study or Subgroup	Stress management +exerci Mean	SD	Total	routine care Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Bundy 1994	1.2	0.5	14	1.9	0.5	15	100.0%	-0.70 [-1.06, -0.34]
Total (95% CI)			**14**			**15**	**100.0%**	**-0.70 [-1.06, -0.34]**

Heterogeneity: Not applicable
Test for overall effect: Z = 3.77 (P = 0.0002)

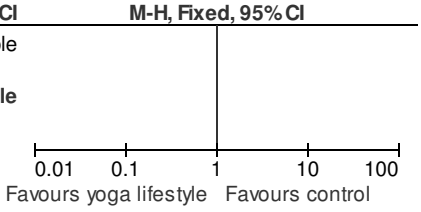


4 Yoga life style intervention programme vs. Control (1 year)

4.1 Mortality

Study or Subgroup	Yoga lifestyle Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Manchanda 2000	0	21	0	21		Not estimable
Total (95% CI)		**21**		**21**		**Not estimable**
Total events	0		0			

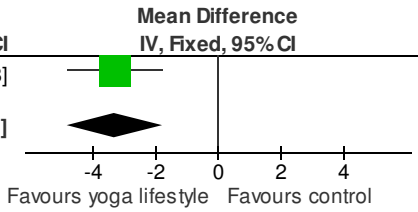
Heterogeneity: Not applicable
Test for overall effect: Not applicable



4.2 Angina episodes per week

Study or Subgroup	Yoga lifestyle Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Manchanda 2000	2.1	2.7	21	5.4	2.3	21	100.0%	-3.30 [-4.82, -1.78]
Total (95% CI)			**21**			**21**	**100.0%**	**-3.30 [-4.82, -1.78]**

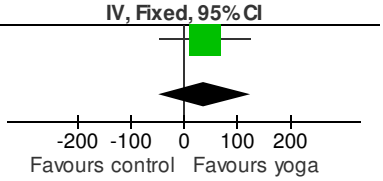
Heterogeneity: Not applicable
Test for overall effect: Z = 4.26 (P < 0.0001)



4.3 Exercise duration (sec)

Study or Subgroup	Yoga lifestyle Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Manchanda 2000	413	132	21	374	151	21	100.0%	39.00 [-46.78, 124.78]
Total (95% CI)			**21**			**21**	**100.0%**	**39.00 [-46.78, 124.78]**

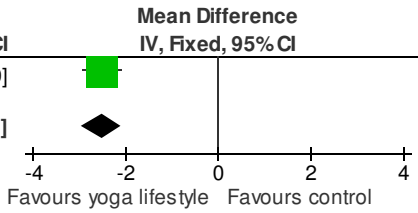
Heterogeneity: Not applicable
Test for overall effect: Z = 0.89 (P = 0.37)



4.4 ST segment depression (mm)

Study or Subgroup	Yoga lifestyle Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Manchanda 2000	0.18	0.8	21	2.7	0.6	21	100.0%	-2.52 [-2.95, -2.09]
Total (95% CI)			**21**			**21**	**100.0%**	**-2.52 [-2.95, -2.09]**

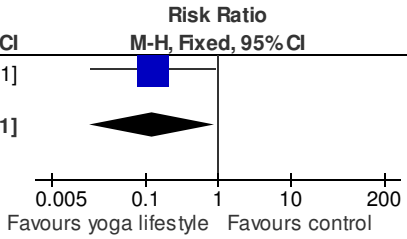
Heterogeneity: Not applicable
Test for overall effect: Z = 11.55 (P < 0.00001)



4.5 Revascularisation

Study or Subgroup	Yoga lifestyle Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Manchanda 2000	1	21	8	21	100.0%	0.13 [0.02, 0.91]
Total (95% CI)		**21**		**21**	**100.0%**	**0.13 [0.02, 0.91]**
Total events	1		8			

Heterogeneity: Not applicable
Test for overall effect: Z = 2.05 (P = 0.04)

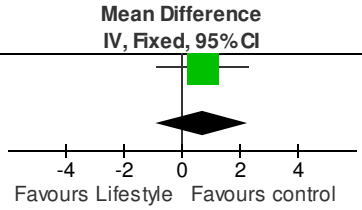


5 Intensive lifestyle programme vs. control (5 years)

5.1 Angina frequency (times per week)

Study or Subgroup	lifestyle programme Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Ornish 1998	1.6	2.7	18	0.9	1.9	14	100.0%	0.70 [-0.90, 2.30]
Total (95% CI)			**18**			**14**	**100.0%**	**0.70 [-0.90, 2.30]**

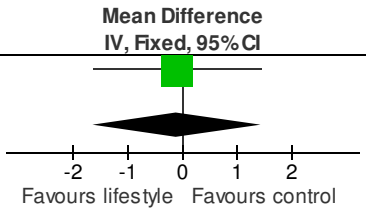
Heterogeneity: Not applicable
Test for overall effect: Z = 0.86 (P = 0.39)



5.2 chest pain duration (min)

Study or Subgroup	lifestyle programme Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Ornish 1998	0.9	1.3	18	1	2.7	14	100.0%	-0.10 [-1.64, 1.44]
Total (95% CI)			**18**			**14**	**100.0%**	**-0.10 [-1.64, 1.44]**

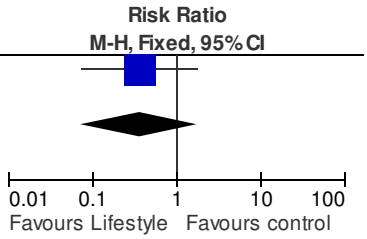
Heterogeneity: Not applicable
Test for overall effect: Z = 0.13 (P = 0.90)



5.3 MI

Study or Subgroup	lifestyle programme Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Ornish 1998	2	28	4	20	100.0%	0.36 [0.07, 1.76]
Total (95% CI)		**28**		**20**	**100.0%**	**0.36 [0.07, 1.76]**
Total events	2		4			

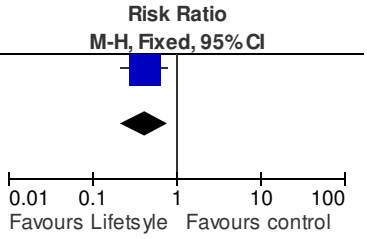
Heterogeneity: Not applicable
Test for overall effect: Z = 1.26 (P = 0.21)



5.4 PTCA

Study or Subgroup	lifestyle programme Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Ornish 1998	8	28	14	20	100.0%	0.41 [0.21, 0.78]
Total (95% CI)		**28**		**20**	**100.0%**	**0.41 [0.21, 0.78]**
Total events	8		14			

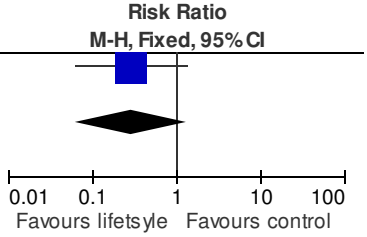
Heterogeneity: Not applicable
Test for overall effect: Z = 2.69 (P = 0.007)



5.5 CABG

Study or Subgroup	lifestyle programme Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Ornish 1998	2	28	5	20	100.0%	0.29 [0.06, 1.33]
Total (95% CI)		**28**		**20**	**100.0%**	**0.29 [0.06, 1.33]**
Total events	2		5			

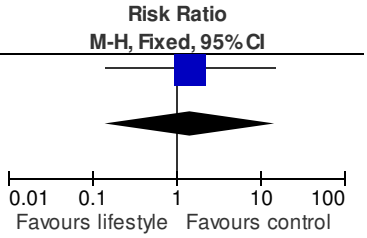
Heterogeneity: Not applicable
Test for overall effect: Z = 1.60 (P = 0.11)



5.6 Death

Study or Subgroup	lifestyle programme Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Ornish 1998	2	28	1	20	100.0%	1.43 [0.14, 14.70]
Total (95% CI)		**28**		**20**	**100.0%**	**1.43 [0.14, 14.70]**
Total events	2		1			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.30 (P = 0.76)

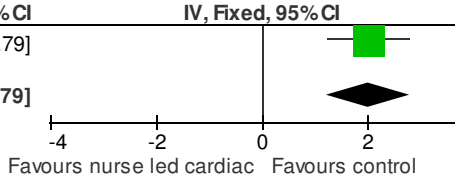


6 Nurse led cardiac rehab vs. routine care (6 months)

6.1 Walking performance (Jenkins activity checklist for walking)

Study or Subgroup	nurse led cardiac rehab Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Jiang 2007	10.63	2.13	83	8.62	2.98	84	100.0%	2.01 [1.23, 2.79]
Total (95% CI)			**83**			**84**	**100.0%**	**2.01 [1.23, 2.79]**

Heterogeneity: Not applicable
Test for overall effect: Z = 5.02 (P < 0.00001)

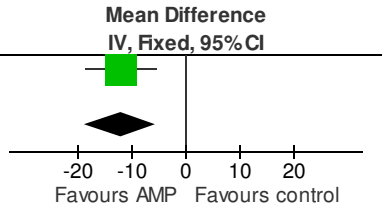


7 Angina management programme (AMP) vs. control (at the end of 8 week treatment period)

7.1 Mean no. of Episodes of angina per week

Study or Subgroup	AMP Mean	AMP SD	AMP Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Fixed, 95% CI
Lewin 1995 (AMP)	4.5	5.7	34	16.6	17.8	31	100.0%	-12.10 [-18.65, -5.55]
Total (95% CI)			**34**			**31**	**100.0%**	**-12.10 [-18.65, -5.55]**

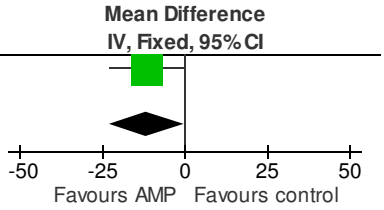
Heterogeneity: Not applicable
Test for overall effect: Z = 3.62 (P = 0.0003)



7.2 Severity of angina (self rated out of 100 with scores being worse)

Study or Subgroup	AMP Mean	AMP SD	AMP Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Fixed, 95% CI
Lewin 1995 (AMP)	21.2	21.8	34	32.9	24.6	31	100.0%	-11.70 [-23.04, -0.36]
Total (95% CI)			**34**			**31**	**100.0%**	**-11.70 [-23.04, -0.36]**

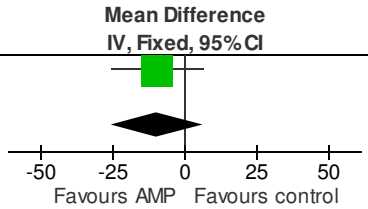
Heterogeneity: Not applicable
Test for overall effect: Z = 2.02 (P = 0.04)



7.3 Duration of angina (mins)

Study or Subgroup	AMP Mean	AMP SD	AMP Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Fixed, 95% CI
Lewin 1995 (AMP)	16.3	23.8	34	26	39.7	31	100.0%	-9.70 [-25.80, 6.40]
Total (95% CI)			**34**			**31**	**100.0%**	**-9.70 [-25.80, 6.40]**

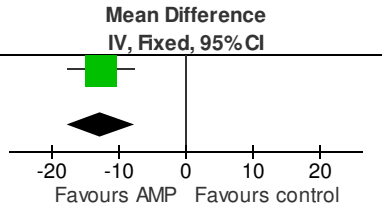
Heterogeneity: Not applicable
Test for overall effect: Z = 1.18 (P = 0.24)



7.4 Disability (Sickness Impact Profile) (100 being completely medically dependent and 0 indicating no measurable impairment)

Study or Subgroup	AMP Mean	AMP SD	AMP Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Fixed, 95% CI
Lewin 1995 (AMP)	6.8	6.3	34	19.5	12.9	31	100.0%	-12.70 [-17.71, -7.69]
Total (95% CI)			**34**			**31**	**100.0%**	**-12.70 [-17.71, -7.69]**

Heterogeneity: Not applicable
Test for overall effect: Z = 4.97 (P < 0.00001)

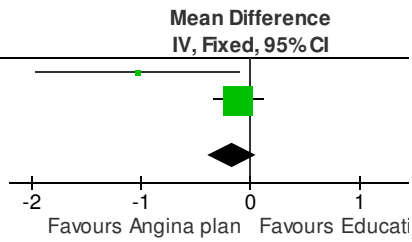


8 Angina Plan vs. Education session (6 months) (all of the outcomes below report change scores)

8.1 Anxiety (HAD scale) (scores between 8 and 10 indicate bordeline presence of anxiety)

Study or Subgroup	Angina Plan Mean	Angina Plan SD	Angina Plan Total	Education session Mean	Education session SD	Education session Total	Weight	Mean Difference IV, Fixed, 95% CI
Lewin 2002 (Angina plan)	-1.03	2.61	68	0	3.07	74	5.9%	-1.03 [-1.96, -0.10]
Zetta 2009 (Angina Plan)	-0.35	0.92	109	-0.24	0.84	109	94.1%	-0.11 [-0.34, 0.12]
Total (95% CI)			**177**			**183**	**100.0%**	**-0.16 [-0.39, 0.06]**

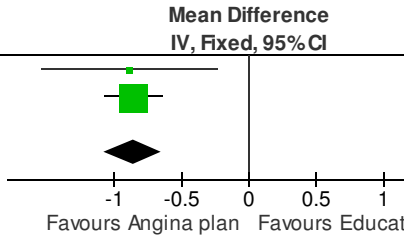
Heterogeneity: $Chi^2 = 3.50$, df = 1 (P = 0.06); $I^2 = 71\%$
Test for overall effect: Z = 1.42 (P = 0.16)



8.2 Depression (HAD scale) (scores between 8 and 10 indicate borderline presence of depression)

Study or Subgroup	Angina Plan Mean	SD	Total	Education session Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Lewin 2002 (Angina plan)	-0.48	1.89	68	0.41	2.1	74	9.9%	-0.89 [-1.55, -0.23]
Zetta 2009 (Angina Plan)	-0.07	0.87	109	0.79	0.77	109	90.1%	-0.86 [-1.08, -0.64]
Total (95% CI)			**177**			**183**	**100.0%**	**-0.86 [-1.07, -0.66]**

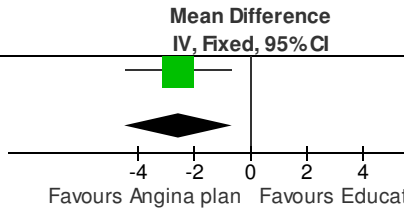
Heterogeneity: Chi² = 0.01, df = 1 (P = 0.93); I² = 0%
Test for overall effect: Z = 8.17 (P < 0.00001)



8.3 Angina attacks per week

Study or Subgroup	Angina Plan Mean	SD	Total	Education session Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Lewin 2002 (Angina plan)	-2.98	5.54	68	-0.41	5.97	74	100.0%	-2.57 [-4.46, -0.68]
Total (95% CI)			**68**			**74**	**100.0%**	**-2.57 [-4.46, -0.68]**

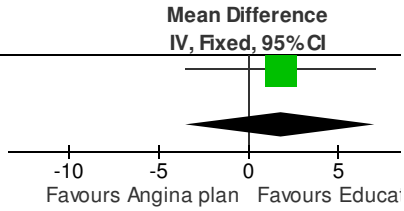
Heterogeneity: Not applicable
Test for overall effect: Z = 2.66 (P = 0.008)



8.4 Mean pain score

Study or Subgroup	Angina Plan Mean	SD	Total	Education session Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Lewin 2002 (Angina plan)	-1.69	14.78	68	-3.48	17.35	74	100.0%	1.79 [-3.50, 7.08]
Total (95% CI)			**68**			**74**	**100.0%**	**1.79 [-3.50, 7.08]**

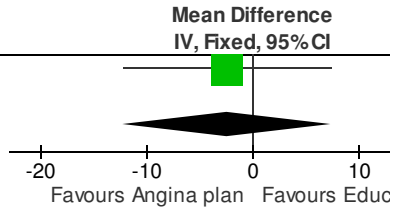
Heterogeneity: Not applicable
Test for overall effect: Z = 0.66 (P = 0.51)



8.5 Mean duration of pain

Study or Subgroup	Angina Plan Mean	SD	Total	Education session Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Lewin 2002 (Angina plan)	-9.21	34.87	68	-6.78	22.98	74	100.0%	-2.43 [-12.23, 7.37]
Total (95% CI)			**68**			**74**	**100.0%**	**-2.43 [-12.23, 7.37]**

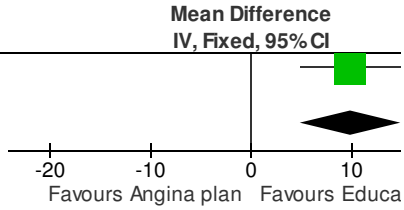
Heterogeneity: Not applicable
Test for overall effect: Z = 0.49 (P = 0.63)



8.6 Physical limitation (Seattle Angina questionnaire) (0 to 100 scale with higher scores indicating better functioning)

Study or Subgroup	Angina Plan Mean	SD	Total	Education session Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Lewin 2002 (Angina plan)	8.42	16.07	68	-1.43	14.24	74	100.0%	9.85 [4.84, 14.86]
Total (95% CI)			**68**			**74**	**100.0%**	**9.85 [4.84, 14.86]**

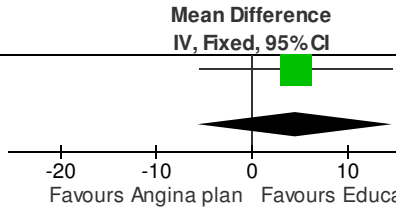
Heterogeneity: Not applicable
Test for overall effect: Z = 3.85 (P = 0.0001)



8.7 Angina stability (Seattle Angina questionnaire)(0 to 100 scale with higher scores indicating better functioning)

Study or Subgroup	Angina Plan Mean	SD	Total	Education session Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Lewin 2002 (Angina plan)	8.73	31.48	68	4.17	29.93	74	100.0%	4.56 [-5.56, 14.68]
Total (95% CI)			**68**			**74**	**100.0%**	**4.56 [-5.56, 14.68]**

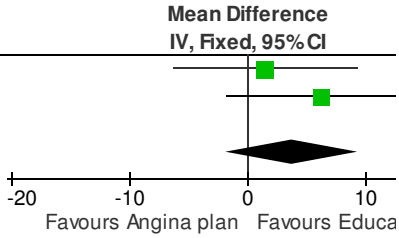
Heterogeneity: Not applicable
Test for overall effect: Z = 0.88 (P = 0.38)



8.8 Angina frequency (Seattle Angina questionnaire)(0 to 100 scale with higher scores indicating better functioning)

Study or Subgroup	Angina Plan Mean	SD	Total	Education session Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Lewin 2002 (Angina plan)	5.71	23.54	68	4.24	24.06	74	51.2%	1.47 [-6.36, 9.30]
Zetta 2009 (Angina Plan)	24.54	31.29	109	18.33	29.11	109	48.8%	6.21 [-1.81, 14.23]
Total (95% CI)			**177**			**183**	**100.0%**	**3.78 [-1.82, 9.39]**

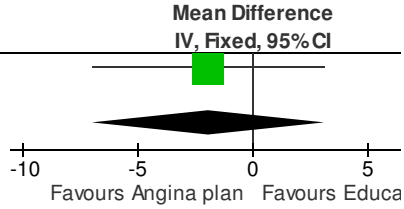
Heterogeneity: Chi² = 0.69, df = 1 (P = 0.41); I² = 0%
Test for overall effect: Z = 1.32 (P = 0.19)



8.9 Treatment satisfaction (Seattle Angina questionnaire)(0 to 100 scale with higher scores indicating better functioning)

Study or Subgroup	Angina Plan Mean	SD	Total	Education session Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Lewin 2002 (Angina plan)	0.81	16.82	68	2.75	13.52	74	100.0%	-1.94 [-6.99, 3.11]
Total (95% CI)			**68**			**74**	**100.0%**	**-1.94 [-6.99, 3.11]**

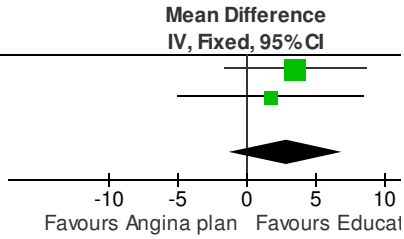
Heterogeneity: Not applicable
Test for overall effect: Z = 0.75 (P = 0.45)



8.10 Disease perception (Seattle Angina questionnaire)(0 to 100 scale with higher scores indicating better functioning)

Study or Subgroup	Angina Plan Mean	SD	Total	Education session Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Lewin 2002 (Angina plan)	7.8	14.35	68	4.29	16.94	74	63.4%	3.51 [-1.64, 8.66]
Zetta 2009 (Angina Plan)	21.16	28.2	109	19.43	22.51	109	36.6%	1.73 [-5.04, 8.50]
Total (95% CI)			**177**			**183**	**100.0%**	**2.86 [-1.24, 6.96]**

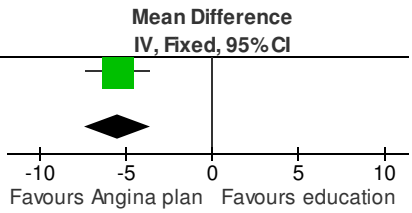
Heterogeneity: Chi² = 0.17, df = 1 (P = 0.68); I² = 0%
Test for overall effect: Z = 1.37 (P = 0.17)



8.11 Misconceptions/knowledge

Study or Subgroup	Angina Plan Mean	SD	Total	Education session Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Zetta 2009 (Angina Plan)	-7.51	7.76	109	-2.01	6.39	109	100.0%	-5.50 [-7.39, -3.61]
Total (95% CI)			**109**			**109**	**100.0%**	**-5.50 [-7.39, -3.61]**

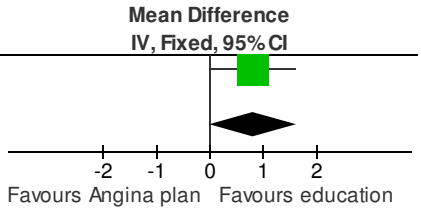
Heterogeneity: Not applicable
Test for overall effect: Z = 5.71 (P < 0.00001)



8.12 CLASP angina

Study or Subgroup	Angina Plan Mean	SD	Total	Education session Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Zetta 2009 (Angina Plan)	-1.64	2.87	109	-2.44	3.23	109	100.0%	0.80 [-0.01, 1.61]
Total (95% CI)			**109**			**109**	**100.0%**	**0.80 [-0.01, 1.61]**

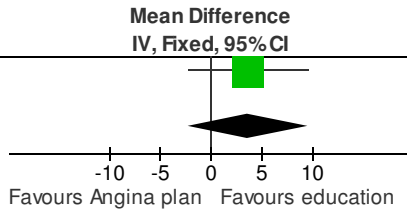
Heterogeneity: Not applicable
Test for overall effect: Z = 1.93 (P = 0.05)



8.13 Physical function (SF-36) (scores between 0 to 100 with higher scores representing better health status)

Study or Subgroup	Angina Plan Mean	SD	Total	Education session Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Zetta 2009 (Angina Plan)	3.69	21.77	109	0.02	23.22	109	100.0%	3.67 [-2.31, 9.65]
Total (95% CI)			**109**			**109**	**100.0%**	**3.67 [-2.31, 9.65]**

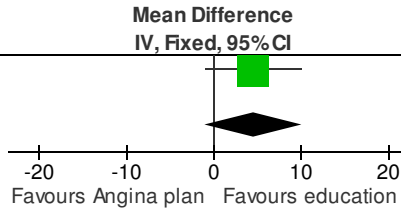
Heterogeneity: Not applicable
Test for overall effect: Z = 1.20 (P = 0.23)



8.14 Energy and and vitality (SF-36)(scores between 0 to 100 with higher scores representing better health status)

Study or Subgroup	Angina Plan Mean	SD	Total	Education session Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Zetta 2009 (Angina Plan)	5.82	20.35	109	1.3	21.34	109	100.0%	4.52 [-1.02, 10.06]
Total (95% CI)			**109**			**109**	**100.0%**	**4.52 [-1.02, 10.06]**

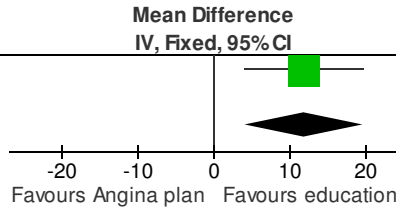
Heterogeneity: Not applicable
Test for overall effect: Z = 1.60 (P = 0.11)



8.15 Pain (SF-36)(scores between 0 to 100 with higher scores representing better health status)

Study or Subgroup	Angina Plan Mean	SD	Total	Education session Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Zetta 2009 (Angina Plan)	11.89	27.75	109	0.02	31.15	109	100.0%	11.87 [4.04, 19.70]
Total (95% CI)			**109**			**109**	**100.0%**	**11.87 [4.04, 19.70]**

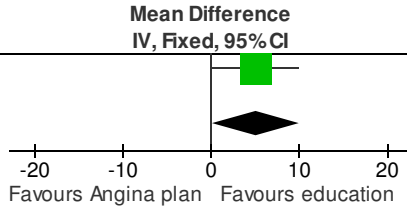
Heterogeneity: Not applicable
Test for overall effect: Z = 2.97 (P = 0.003)



8.16 GH perception (SF-36)(scores between 0 to 100 with higher scores representing better health status)

Study or Subgroup	Angina Plan Mean	SD	Total	Education session Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Zetta 2009 (Angina Plan)	6.37	16.74	109	1.34	20.1	109	100.0%	5.03 [0.12, 9.94]
Total (95% CI)			**109**			**109**	**100.0%**	**5.03 [0.12, 9.94]**

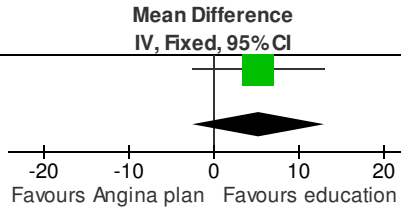
Heterogeneity: Not applicable
Test for overall effect: Z = 2.01 (P = 0.04)



8.17 Change in health (SF-36)(scores between 0 to 100 with higher scores representing better health status)

Study or Subgroup	Angina Plan Mean	SD	Total	Education session Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Zetta 2009 (Angina Plan)	15.24	27.19	109	9.99	31.2	109	100.0%	5.25 [-2.52, 13.02]
Total (95% CI)			**109**			**109**	**100.0%**	**5.25 [-2.52, 13.02]**

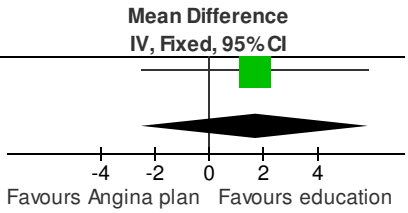
Heterogeneity: Not applicable
Test for overall effect: Z = 1.32 (P = 0.19)



8.18 SEI QOL- DW QOL score (overall score ranging from 0-100 with higher scores reflecting better quality of life)

Study or Subgroup	Angina Plan Mean	SD	Total	Education session Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Zetta 2009 (Angina Plan)	6.53	15.02	109	4.83	16.57	109	100.0%	1.70 [-2.50, 5.90]
Total (95% CI)			**109**			**109**	**100.0%**	**1.70 [-2.50, 5.90]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.79 (P = 0.43)

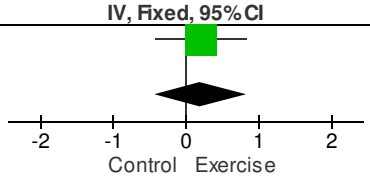


1 Exercise (1 year intensive) vs Control

1.1 Max ST depression (mm)

Study or Subgroup	Exercise Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Todd & Ballantyne 1990	1.6	1.2	20	1.4	0.8	20	100.0%	0.20 [-0.43, 0.83]
Total (95% CI)			**20**			**20**	**100.0%**	**0.20 [-0.43, 0.83]**

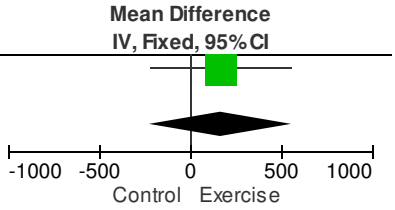
Heterogeneity: Not applicable
Test for overall effect: Z = 0.62 (P = 0.54)



1.2 Time to 1mm ST depression (sec)

Study or Subgroup	Exercise Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Todd & Ballantyne 1990	881	668	20	715	580	20	100.0%	166.00 [-221.71, 553.71]
Total (95% CI)			**20**			**20**	**100.0%**	**166.00 [-221.71, 553.71]**

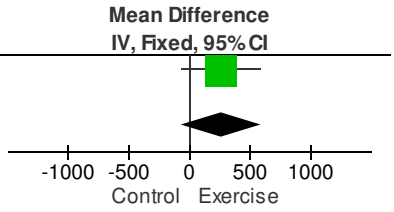
Heterogeneity: Not applicable
Test for overall effect: Z = 0.84 (P = 0.40)



1.3 Treadmill time (s)

Study or Subgroup	Exercise Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Todd & Ballantyne 1990	1,272	514	20	1,010	546	20	100.0%	262.00 [-66.64, 590.64]
Total (95% CI)			**20**			**20**	**100.0%**	**262.00 [-66.64, 590.64]**

Heterogeneity: Not applicable
Test for overall effect: Z = 1.56 (P = 0.12)

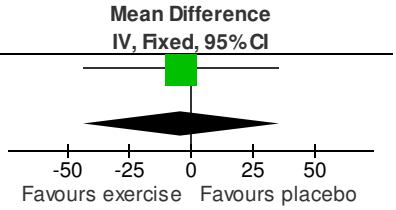


2 Exercise (and placebo) vs. Placebo

2.1 Maximal working capacity kpm/min

Study or Subgroup	Exercise (and placebo) Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Malmborg et al. 1974	15	21	8	19	53	8	100.0%	-4.00 [-43.50, 35.50]
Total (95% CI)			**8**			**8**	**100.0%**	**-4.00 [-43.50, 35.50]**

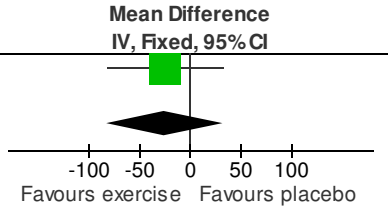
Heterogeneity: Not applicable
Test for overall effect: Z = 0.20 (P = 0.84)



2.2 Anginal attacks / week

Study or Subgroup	Exercise (and placebo) Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Malmborg et al. 1974	24	50	8	49	66	8	100.0%	-25.00 [-82.38, 32.38]
Total (95% CI)			**8**			**8**	**100.0%**	**-25.00 [-82.38, 32.38]**

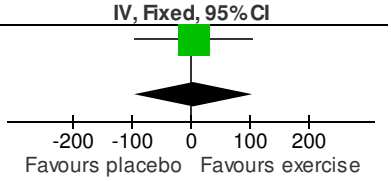
Heterogeneity: Not applicable
Test for overall effect: Z = 0.85 (P = 0.39)



2.3 Nitroglycerin tabl / week

Study or Subgroup	Exercise (and placebo) Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Malmborg et al. 1974	4	54	8	0	135	8	100.0%	4.00 [-96.75, 104.75]
Total (95% CI)			**8**			**8**	**100.0%**	**4.00 [-96.75, 104.75]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.08 (P = 0.94)

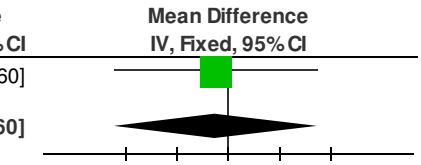


3 Exercise and beta blockers vs. Beta blocker

3.1 Maximal working capacity kpm/min

Study or Subgroup	Exercise + beta blocker Mean	SD	Total	Beta blocker Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Malmborg et al. 1974	42	49	6	48	41	7	100.0%	-6.00 [-55.60, 43.60]
Total (95% CI)			**6**			**7**	**100.0%**	**-6.00 [-55.60, 43.60]**

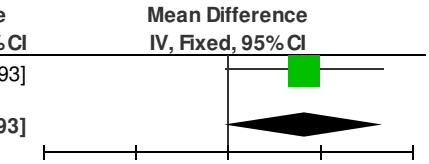
Heterogeneity: Not applicable
Test for overall effect: Z = 0.24 (P = 0.81)



3.2 Anginal attacks / week

Study or Subgroup	Exercise + beta blocker Mean	SD	Total	Beta blocker Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Malmborg et al. 1974	-44	50	6	-85	21	7	100.0%	41.00 [-1.93, 83.93]
Total (95% CI)			**6**			**7**	**100.0%**	**41.00 [-1.93, 83.93]**

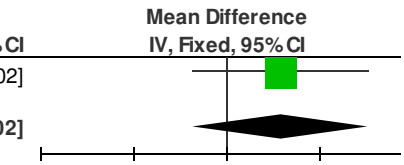
Heterogeneity: Not applicable
Test for overall effect: Z = 1.87 (P = 0.06)



3.3 Nitroglycerin tabl / week

Study or Subgroup	Exercise + beta blocker Mean	SD	Total	Beta blocker Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Malmborg et al. 1974	-15	115	6	-73	32	7	100.0%	58.00 [-37.02, 153.02]
Total (95% CI)			**6**			**7**	**100.0%**	**58.00 [-37.02, 153.02]**

Heterogeneity: Not applicable
Test for overall effect: Z = 1.20 (P = 0.23)

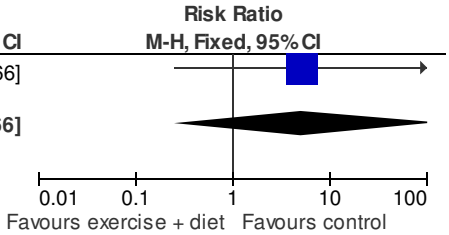


4 Exercise + low fat diet vs. Control

4.1 Cardiac mortality

Study or Subgroup	Exercise + low fat diet Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Schuler et al. 1992	2	56	0	57	100.0%	5.09 [0.25, 103.66]
Total (95% CI)		**56**		**57**	**100.0%**	**5.09 [0.25, 103.66]**
Total events	2		0			

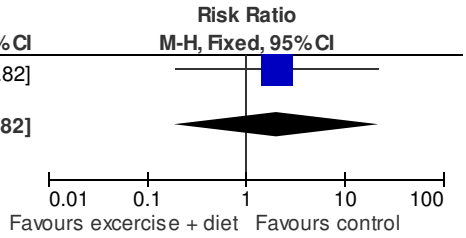
Heterogeneity: Not applicable
Test for overall effect: Z = 1.06 (P = 0.29)



4.2 Mortality (all)

Study or Subgroup	Exercise + low fat diet Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Schuler et al. 1992	2	56	1	57	100.0%	2.04 [0.19, 21.82]
Total (95% CI)		**56**		**57**	**100.0%**	**2.04 [0.19, 21.82]**
Total events	2		1			

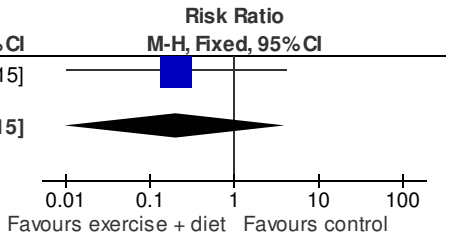
Heterogeneity: Not applicable
Test for overall effect: Z = 0.59 (P = 0.56)



4.3 Non-fatal MI

Study or Subgroup	Exercise + low fat diet Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Schuler et al. 1992	0	56	2	57	100.0%	0.20 [0.01, 4.15]
Total (95% CI)		**56**		**57**	**100.0%**	**0.20 [0.01, 4.15]**
Total events	0		2			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.04 (P = 0.30)

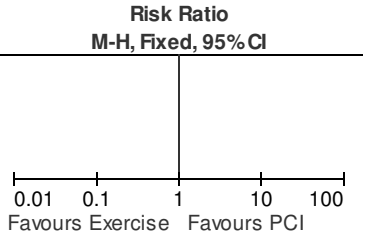


5 Exercise vs. PCI

5.1 Death of cardiac causes

Study or Subgroup	Exercise Events	Total	PCI Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Hambrecht 2004	0	51	0	50		Not estimable
Total (95% CI)		**51**		**50**		**Not estimable**
Total events	0		0			

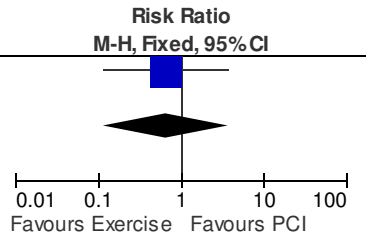
Heterogeneity: Not applicable
Test for overall effect: Not applicable



5.2 Cerebrovascular accident

Study or Subgroup	Exercise Events	Total	PCI Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Hambrecht 2004	2	51	3	50	100.0%	0.65 [0.11, 3.75]
Total (95% CI)		**51**		**50**	**100.0%**	**0.65 [0.11, 3.75]**
Total events	2		3			

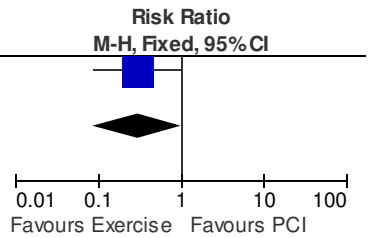
Heterogeneity: Not applicable
Test for overall effect: Z = 0.48 (P = 0.63)



5.3 Revascularisation

Study or Subgroup	Exercise Events	Total	PCI Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Hambrecht 2004	3	51	10	50	100.0%	0.29 [0.09, 1.01]
Total (95% CI)		**51**		**50**	**100.0%**	**0.29 [0.09, 1.01]**
Total events	3		10			

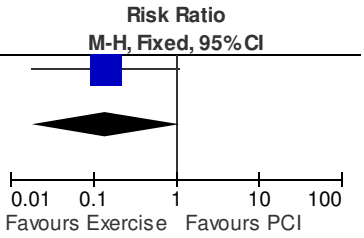
Heterogeneity: Not applicable
Test for overall effect: Z = 1.95 (P = 0.05)



5.4 Hospitalisation and coronary angiography owing to worsening angina

Study or Subgroup	Exercise Events	Exercise Total	PCI Events	PCI Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Hambrecht 2004	1	51	7	50	100.0%	0.14 [0.02, 1.10]
Total (95% CI)		**51**		**50**	**100.0%**	**0.14 [0.02, 1.10]**
Total events	1		7			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.87 (P = 0.06)

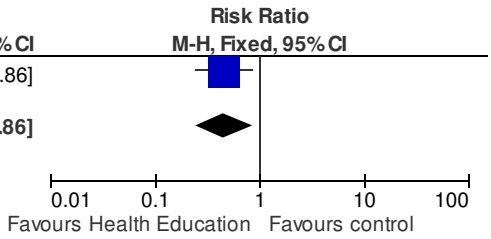


6 Health Education vs Control

6.1 Mortality

Study or Subgroup	Health Education Events	Health Education Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Cupples & McKnight, 1994	13	342	29	346	100.0%	0.45 [0.24, 0.86]
Total (95% CI)		**342**		**346**	**100.0%**	**0.45 [0.24, 0.86]**
Total events	13		29			

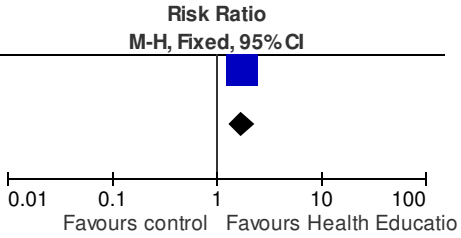
Heterogeneity: Not applicable
Test for overall effect: Z = 2.43 (P = 0.01)



6.2 Increase in frequency of exercise

Study or Subgroup	Health Education Events	Health Education Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Cupples & McKnight, 1994	108	342	63	346	100.0%	1.73 [1.32, 2.28]
Total (95% CI)		**342**		**346**	**100.0%**	**1.73 [1.32, 2.28]**
Total events	108		63			

Heterogeneity: Not applicable
Test for overall effect: Z = 3.96 (P < 0.0001)

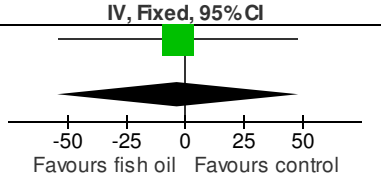


1 Fish oil capsules vs. Placebo (Follow-up at end of treatment period)

1.1 Anginal episodes per week

Study or Subgroup	Fish oil Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Salachas 1994	8.36	103.6	20	11.36	51.7	19	100.0%	-3.00 [-54.01, 48.01]
Total (95% CI)			**20**			**19**	**100.0%**	**-3.00 [-54.01, 48.01]**

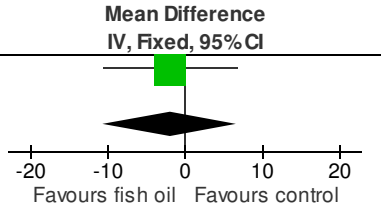
Heterogeneity: Not applicable
Test for overall effect: Z = 0.12 (P = 0.91)



1.2 GTN consumption per week

Study or Subgroup	Fish oil Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Salachas 1994	10.43	15.07	20	12.42	12.61	19	100.0%	-1.99 [-10.69, 6.71]
Total (95% CI)			**20**			**19**	**100.0%**	**-1.99 [-10.69, 6.71]**

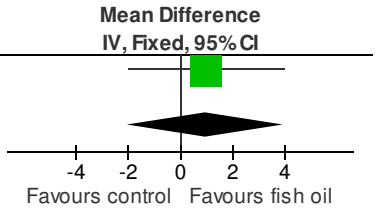
Heterogeneity: Not applicable
Test for overall effect: Z = 0.45 (P = 0.65)



1.3 Exercise test duration (min)

Study or Subgroup	Fish oil Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Salachas 1994	10.09	5.16	20	9.1	4.38	19	100.0%	0.99 [-2.01, 3.99]
Total (95% CI)			**20**			**19**	**100.0%**	**0.99 [-2.01, 3.99]**

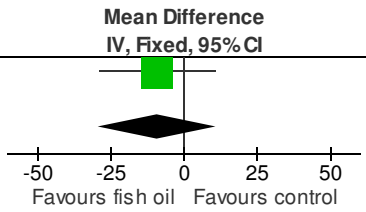
Heterogeneity: Not applicable
Test for overall effect: Z = 0.65 (P = 0.52)



1.4 Number of anginal attacks per 30 days

Study or Subgroup	Fish oil Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Aucamp 1993	12.9	13.7	12	22.1	31.1	11	100.0%	-9.20 [-29.15, 10.75]
Total (95% CI)			**12**			**11**	**100.0%**	**-9.20 [-29.15, 10.75]**

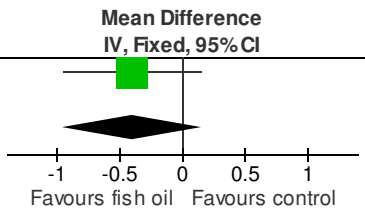
Heterogeneity: Not applicable
Test for overall effect: Z = 0.90 (P = 0.37)



1.5 Duration of angina attacks per minute

Study or Subgroup	Fish oil Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Aucamp 1993	1.8	0.5	12	2.2	0.8	11	100.0%	-0.40 [-0.95, 0.15]
Total (95% CI)			**12**			**11**	**100.0%**	**-0.40 [-0.95, 0.15]**

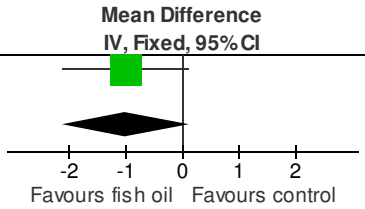
Heterogeneity: Not applicable
Test for overall effect: Z = 1.42 (P = 0.15)



1.6 Intensity of pain per attack per patient (on a 10 cm visual analogue scale)

Study or Subgroup	Fish oil Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Aucamp 1993	2.5	1.2	12	3.5	1.5	11	100.0%	-1.00 [-2.12, 0.12]
Total (95% CI)			**12**			**11**	**100.0%**	**-1.00 [-2.12, 0.12]**

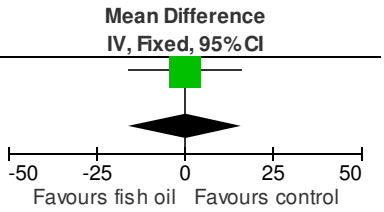
Heterogeneity: Not applicable
Test for overall effect: Z = 1.76 (P = 0.08)



1.7 No. of sublingual isosorbide dinitrate tablets taken per 30 days

Study or Subgroup	Fish oil Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Aucamp 1993	17	22.5	12	17	16.8	11	100.0%	0.00 [-16.14, 16.14]
Total (95% CI)			**12**			**11**	**100.0%**	**0.00 [-16.14, 16.14]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.00 (P = 1.00)

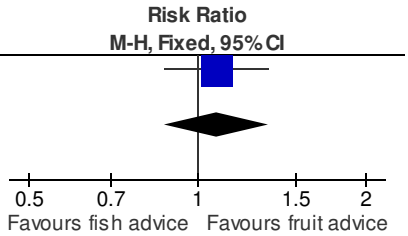


2 Fish advice (dietary fish advice + fish oil capsule) vs. Fruit advice (Mortality ascertained after 3 to 9 yrs)

2.1 All death

Study or Subgroup	Fish oil advice Events	Total	Fruit advice Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Burr 2003	141	764	133	779	100.0%	1.08 [0.87, 1.34]
Total (95% CI)		**764**		**779**	**100.0%**	**1.08 [0.87, 1.34]**
Total events	141		133			

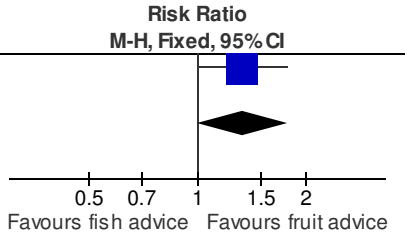
Heterogeneity: Not applicable
Test for overall effect: Z = 0.71 (P = 0.48)



2.2 Cardiac death

Study or Subgroup	Fish oil advice Events	Total	Fruit advice Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Burr 2003	94	764	72	779	100.0%	1.33 [1.00, 1.78]
Total (95% CI)		**764**		**779**	**100.0%**	**1.33 [1.00, 1.78]**
Total events	94		72			

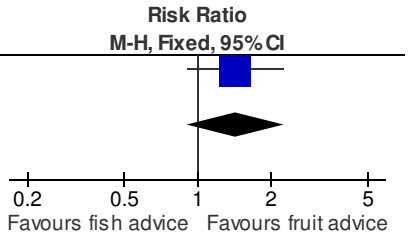
Heterogeneity: Not applicable
Test for overall effect: Z = 1.93 (P = 0.05)



2.3 Sudden death

Study or Subgroup	Fish oil advice Events	Total	Fruit advice Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Burr 2003	42	764	30	779	100.0%	1.43 [0.90, 2.26]
Total (95% CI)		**764**		**779**	**100.0%**	**1.43 [0.90, 2.26]**
Total events	42		30			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.52 (P = 0.13)

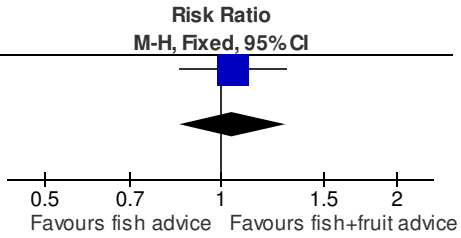


3 Fish advice (dietary fish advice+ fish oil capsule) vs. Fish +Fruit advice (Mortality ascertained after 3 to 9 yrs)

3.1 All death

Study or Subgroup	Fish advice Events	Total	.Fish+fruit Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Burr 2003	141	764	142	807	100.0%	1.05 [0.85, 1.30]
Total (95% CI)		**764**		**807**	**100.0%**	**1.05 [0.85, 1.30]**
Total events	141		142			

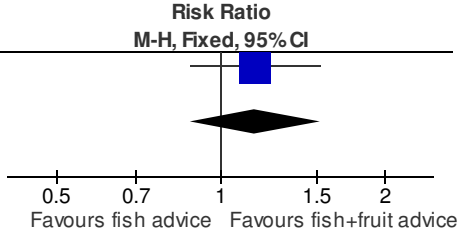
Heterogeneity: Not applicable
Test for overall effect: Z = 0.44 (P = 0.66)



3.2 Cardiac death

Study or Subgroup	Fish advice Events	Total	.Fish+fruit Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Burr 2003	94	764	86	807	100.0%	1.15 [0.88, 1.52]
Total (95% CI)		**764**		**807**	**100.0%**	**1.15 [0.88, 1.52]**
Total events	94		86			

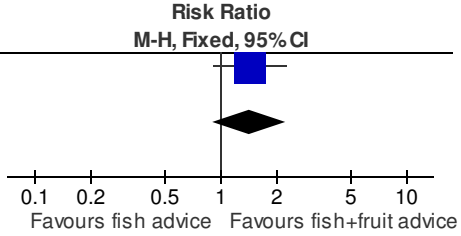
Heterogeneity: Not applicable
Test for overall effect: Z = 1.02 (P = 0.31)



3.3 Sudden death

Study or Subgroup	Fish advice Events	Total	.Fish+fruit Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Burr 2003	42	764	31	807	100.0%	1.43 [0.91, 2.25]
Total (95% CI)		**764**		**807**	**100.0%**	**1.43 [0.91, 2.25]**
Total events	42		31			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.55 (P = 0.12)

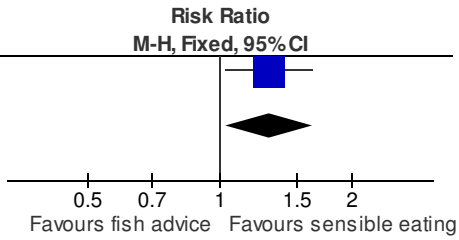


4 Fish advice (dietary fish advice + fish oil capsule) vs. Sensible eating (non -specific advice) (Mortality ascertained after 3 to 9 yrs)

4.1 All deaths

Study or Subgroup	Fish oil advice Events	Total	Sensible eating Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Burr 2003	141	764	109	764	100.0%	1.29 [1.03, 1.63]
Total (95% CI)		**764**		**764**	**100.0%**	**1.29 [1.03, 1.63]**
Total events	141		109			

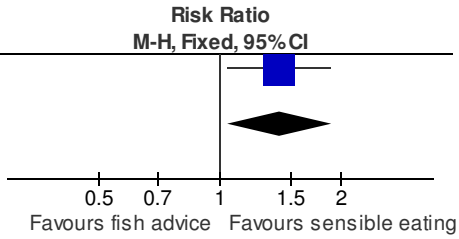
Heterogeneity: Not applicable
Test for overall effect: Z = 2.20 (P = 0.03)



4.2 Cardiac death

Study or Subgroup	Fish oil advice Events	Total	Sensible eating Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Burr 2003	94	764	67	764	100.0%	1.40 [1.04, 1.89]
Total (95% CI)		**764**		**764**	**100.0%**	**1.40 [1.04, 1.89]**
Total events	94		67			

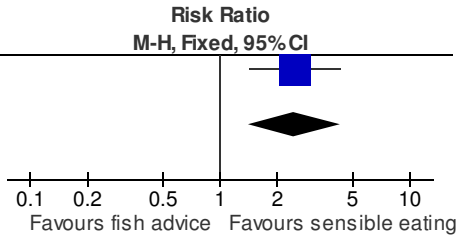
Heterogeneity: Not applicable
Test for overall effect: Z = 2.24 (P = 0.03)



4.3 Sudden death

Study or Subgroup	Fish oil advice Events	Total	Sensible eating Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Burr 2003	42	764	17	764	100.0%	2.47 [1.42, 4.30]
Total (95% CI)		**764**		**764**	**100.0%**	**2.47 [1.42, 4.30]**
Total events	42		17			

Heterogeneity: Not applicable
Test for overall effect: Z = 3.20 (P = 0.001)

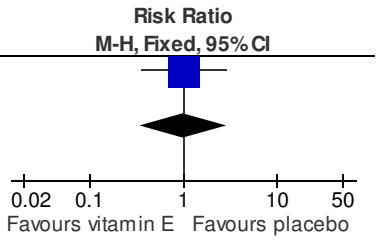


6 Vitamin E vs. Placebo ((Follow-up at the end of treatment period))

6.1 Improved anginal symptoms

Study or Subgroup	Vitamin E Events	Total	control Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Anderson 1974	5	18	5	18	100.0%	1.00 [0.35, 2.87]
Total (95% CI)		**18**		**18**	**100.0%**	**1.00 [0.35, 2.87]**
Total events	5		5			

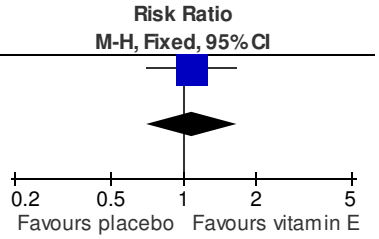
Heterogeneity: Not applicable
Test for overall effect: Z = 0.00 (P = 1.00)



6.2 No change in anginal symptoms

Study or Subgroup	Vitamin E Events	Total	control Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Anderson 1974	13	18	12	18	100.0%	1.08 [0.70, 1.67]
Total (95% CI)		**18**		**18**	**100.0%**	**1.08 [0.70, 1.67]**
Total events	13		12			

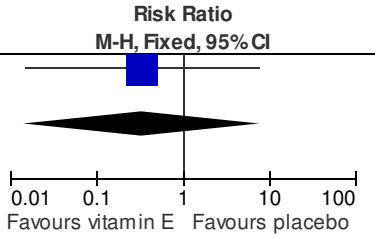
Heterogeneity: Not applicable
Test for overall effect: Z = 0.36 (P = 0.72)



6.3 Slightly worse anginal symptoms

Study or Subgroup	Vitamin E Events	Total	control Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Anderson 1974	0	18	1	18	100.0%	0.33 [0.01, 7.68]
Total (95% CI)		**18**		**18**	**100.0%**	**0.33 [0.01, 7.68]**
Total events	0		1			

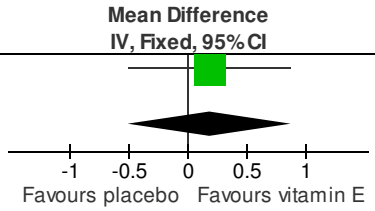
Heterogeneity: Not applicable
Test for overall effect: Z = 0.69 (P = 0.49)



6.4 Duration treadmill (min)

Study or Subgroup	Vitamin E Mean	SD	Total	control Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Gillian 1977	5.48	1.69	48	5.3	1.6	40	100.0%	0.18 [-0.51, 0.87]
Total (95% CI)			**48**			**40**	**100.0%**	**0.18 [-0.51, 0.87]**

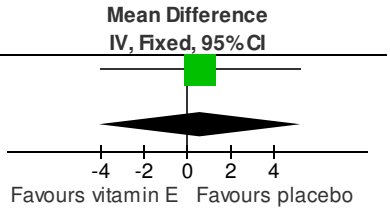
Heterogeneity: Not applicable
Test for overall effect: Z = 0.51 (P = 0.61)



6.5 Angina attacks per week

Study or Subgroup	Vitamin E Mean	SD	Total	control Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Gillian 1977	7.3	12.6	48	6.7	10.5	48	100.0%	0.60 [-4.04, 5.24]
Total (95% CI)			**48**			**48**	**100.0%**	**0.60 [-4.04, 5.24]**

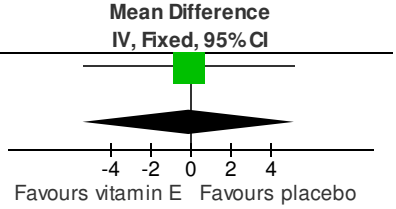
Heterogeneity: Not applicable
Test for overall effect: Z = 0.25 (P = 0.80)



6.6 Nitroglycerin consumption per week

Study or Subgroup	Vitamin E Mean	SD	Total	control Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Gillian 1977	7.6	12.1	48	7.7	14.2	48	100.0%	-0.10 [-5.38, 5.18]
Total (95% CI)			**48**			**48**	**100.0%**	**-0.10 [-5.38, 5.18]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.04 (P = 0.97)

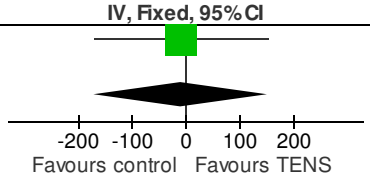


1 TENS vs.control (no TENS) (Follow-up 2 weeks after treatment)

1.1 Exercise tolerance (W.min)

Study or Subgroup	TENS Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Mannheimer 1985	523	231	11	532	139	10	100.0%	-9.00 [-170.42, 152.42]
Total (95% CI)			**11**			**10**	**100.0%**	**-9.00 [-170.42, 152.42]**

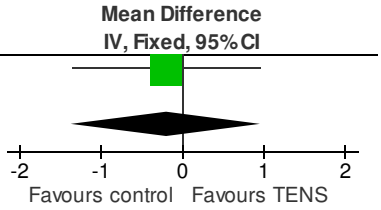
Heterogeneity: Not applicable
Test for overall effect: Z = 0.11 (P = 0.91)



1.2 ST segment depression (mm) during exercise

Study or Subgroup	TENS Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Mannheimer 1985	2.8	1.3	11	3	1.4	10	100.0%	-0.20 [-1.36, 0.96]
Total (95% CI)			**11**			**10**	**100.0%**	**-0.20 [-1.36, 0.96]**

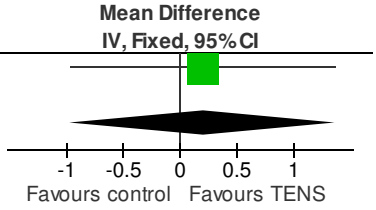
Heterogeneity: Not applicable
Test for overall effect: Z = 0.34 (P = 0.74)



1.3 ST segment depression (mm) after exercise

Study or Subgroup	TENS Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Mannheimer 1985	3	1.2	11	2.8	1.5	10	100.0%	0.20 [-0.97, 1.37]
Total (95% CI)			**11**			**10**	**100.0%**	**0.20 [-0.97, 1.37]**

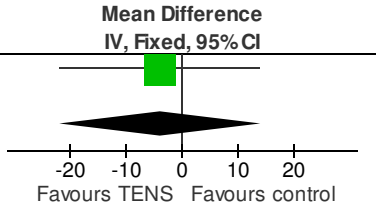
Heterogeneity: Not applicable
Test for overall effect: Z = 0.34 (P = 0.74)



1.4 Frequency of angina attacks per week

Study or Subgroup	TENS Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Mannheimer 1985	19	23	11	23	19	10	100.0%	-4.00 [-21.98, 13.98]
Total (95% CI)			**11**			**10**	**100.0%**	**-4.00 [-21.98, 13.98]**

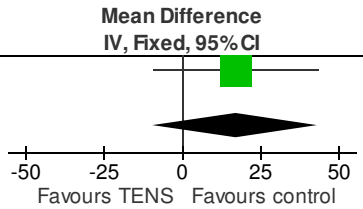
Heterogeneity: Not applicable
Test for overall effect: Z = 0.44 (P = 0.66)



1.5 Nitroglycerin consumption per week

Study or Subgroup	Favours TENS Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Mannheimer 1985	31	43	11	14	11	10	100.0%	17.00 [-9.31, 43.31]
Total (95% CI)			**11**			**10**	**100.0%**	**17.00 [-9.31, 43.31]**

Heterogeneity: Not applicable
Test for overall effect: Z = 1.27 (P = 0.21)

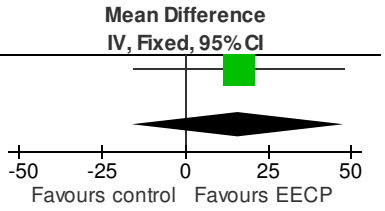


2 EECP vs. inactive CP (Follow-up 3 days after treatment for angina pain counts, one week after treatment for exercise duration)

2.1 Exercise duration (sec) (change scores) (follow-up after 1 week)

Study or Subgroup	EECP Mean	EECP SD	EECP Total	Inactive CP Mean	Inactive CP SD	Inactive CP Total	Weight	Mean Difference IV, Fixed, 95% CI
Arora 2010	42	82.9	57	26	91.3	58	100.0%	16.00 [-15.86, 47.86]
Total (95% CI)			**57**			**58**	**100.0%**	**16.00 [-15.86, 47.86]**

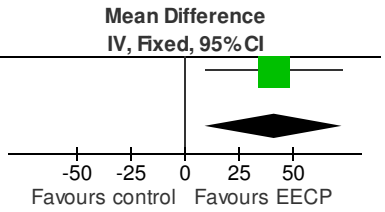
Heterogeneity: Not applicable
Test for overall effect: Z = 0.98 (P = 0.33)



2.2 Time to >1mm ST segment depression (Sec) (change scores) (follow-up after 1 week)

Study or Subgroup	EECP Mean	EECP SD	EECP Total	Inactive CP Mean	Inactive CP SD	Inactive CP Total	Weight	Mean Difference IV, Fixed, 95% CI
Arora 2010	37	82.2	56	-4	89.7	56	100.0%	41.00 [9.13, 72.87]
Total (95% CI)			**56**			**56**	**100.0%**	**41.00 [9.13, 72.87]**

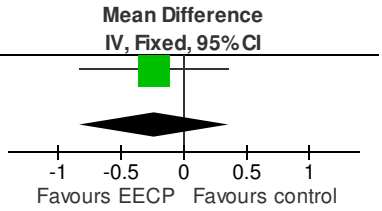
Heterogeneity: Not applicable
Test for overall effect: Z = 2.52 (P = 0.01)



2.3 Angina episodes/day (change scores) (follow-up after 3 days)

Study or Subgroup	EECP Mean	EECP SD	EECP Total	Inactive CP Mean	Inactive CP SD	Inactive CP Total	Weight	Mean Difference IV, Fixed, 95% CI
Arora 2010	-0.11	1.76	71	0.13	1.78	66	100.0%	-0.24 [-0.83, 0.35]
Total (95% CI)			**71**			**66**	**100.0%**	**-0.24 [-0.83, 0.35]**

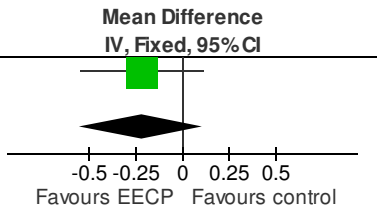
Heterogeneity: Not applicable
Test for overall effect: Z = 0.79 (P = 0.43)



2.4 NTG use/day (change scores) (follow-up after 3 days)

Study or Subgroup	EECP Mean	EECP SD	EECP Total	Inactive CP Mean	Inactive CP SD	Inactive CP Total	Weight	Mean Difference IV, Fixed, 95% CI
Arora 2010	-0.32	1	71	-0.1	0.97	66	100.0%	-0.22 [-0.55, 0.11]
Total (95% CI)			**71**			**66**	**100.0%**	**-0.22 [-0.55, 0.11]**

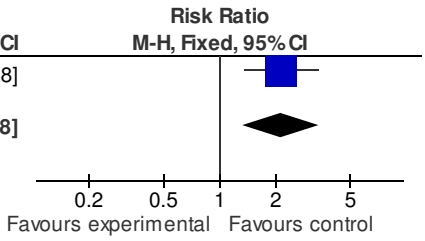
Heterogeneity: Not applicable
Test for overall effect: Z = 1.31 (P = 0.19)



2.5 Adverse events (no. of patients) (up to the end of treatment)

Study or Subgroup	EECP Events	EECP Total	Inactive CP Events	Inactive CP Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Arora 2010	39	71	17	66	100.0%	2.13 [1.35, 3.38]
Total (95% CI)		**71**		**66**	**100.0%**	**2.13 [1.35, 3.38]**
Total events	39		17			

Heterogeneity: Not applicable
Test for overall effect: Z = 3.22 (P = 0.001)

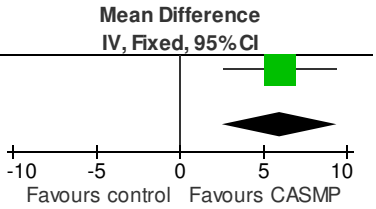


3 Chronic angina self management Program (CASMP) vs. control (Follow-up 3 months from start of treatment)

3.1 Physical functioning (SF-36) (range 0-100 -higher score better functioning) (change scores)

Study or Subgroup	CASMP Mean	CASMP SD	CASMP Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Fixed, 95% CI
McGillion 2008	5.3	9.4	57	-0.68	9.3	60	100.0%	5.98 [2.59, 9.37]
Total (95% CI)			**57**			**60**	**100.0%**	**5.98 [2.59, 9.37]**

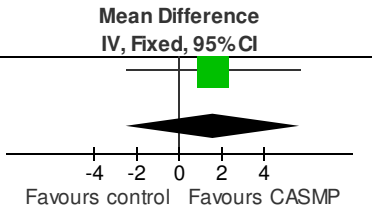
Heterogeneity: Not applicable
Test for overall effect: Z = 3.46 (P = 0.0005)



3.2 Role physical functioning (SF-36) (change scores) (range 0-100)

Study or Subgroup	CASMP Mean	CASMP SD	CASMP Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Fixed, 95% CI
McGillion 2008	4.8	12.7	57	3.2	9.6	60	100.0%	1.60 [-2.50, 5.70]
Total (95% CI)			**57**			**60**	**100.0%**	**1.60 [-2.50, 5.70]**

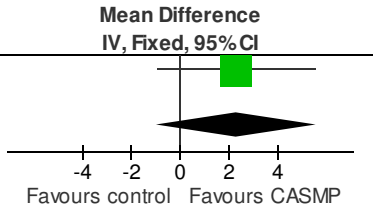
Heterogeneity: Not applicable
Test for overall effect: Z = 0.77 (P = 0.44)



3.3 Bodily pain (SF-36) (change scores) (range 0-100)

Study or Subgroup	CASMP Mean	CASMP SD	CASMP Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Fixed, 95% CI
McGillion 2008	4.4	8.7	57	2.1	9.2	60	100.0%	2.30 [-0.94, 5.54]
Total (95% CI)			**57**			**60**	**100.0%**	**2.30 [-0.94, 5.54]**

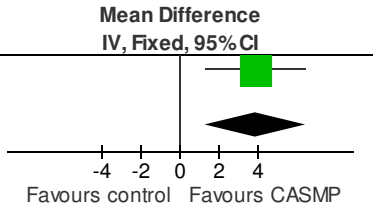
Heterogeneity: Not applicable
Test for overall effect: Z = 1.39 (P = 0.16)



3.4 General Health (SF-36) (change scores) (0-100)

Study or Subgroup	CASMP Mean	CASMP SD	CASMP Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Fixed, 95% CI
McGillion 2008	2.27	7.7	57	-1.6	6.4	60	100.0%	3.87 [1.30, 6.44]
Total (95% CI)			**57**			**60**	**100.0%**	**3.87 [1.30, 6.44]**

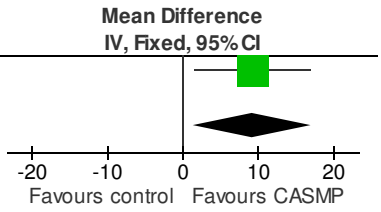
Heterogeneity: Not applicable
Test for overall effect: Z = 2.95 (P = 0.003)



3.5 Angina frequency (SAQ) (range 0-100- higher scores better functioning) (change scores)

Study or Subgroup	CASMP Mean	CASMP SD	CASMP Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Fixed, 95% CI
McGillion 2008	11.4	23.7	57	2.2	18.4	60	100.0%	9.20 [1.48, 16.92]
Total (95% CI)			**57**			**60**	**100.0%**	**9.20 [1.48, 16.92]**

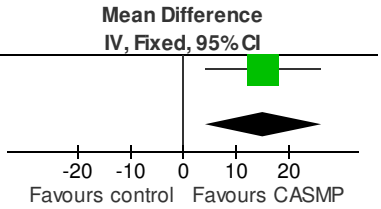
Heterogeneity: Not applicable
Test for overall effect: Z = 2.34 (P = 0.02)



3.6 Angina stability (SAQ) (range 0-100) (change scores)

Study or Subgroup	CASMP Mean	CASMP SD	CASMP Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Fixed, 95% CI
McGillion 2008	18	35	57	2.9	24.4	60	100.0%	15.10 [4.11, 26.09]
Total (95% CI)			**57**			**60**	**100.0%**	**15.10 [4.11, 26.09]**

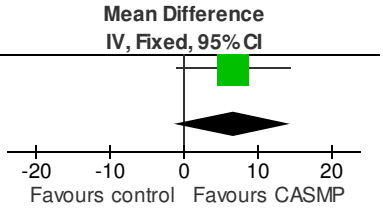
Heterogeneity: Not applicable
Test for overall effect: Z = 2.69 (P = 0.007)



3.7 Disease perception (SAQ) (range 0-100) (change scores)

Study or Subgroup	CASMP Mean	CASMP SD	CASMP Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Fixed, 95% CI
McGillion 2008	9.9	23.5	57	3.3	19.1	60	100.0%	6.60 [-1.18, 14.38]
Total (95% CI)			**57**			**60**	**100.0%**	**6.60 [-1.18, 14.38]**

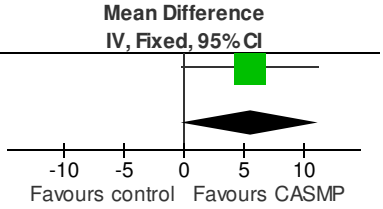
Heterogeneity: Not applicable
Test for overall effect: Z = 1.66 (P = 0.10)



3.8 Physical limitation (SAQ) (range 0-100) (change scores)

Study or Subgroup	CASMP Mean	CASMP SD	CASMP Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Fixed, 95% CI
McGillion 2008	7.1	16.5	57	1.6	15.1	60	100.0%	5.50 [-0.24, 11.24]
Total (95% CI)			**57**			**60**	**100.0%**	**5.50 [-0.24, 11.24]**

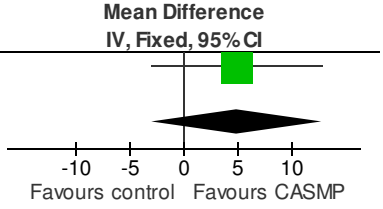
Heterogeneity: Not applicable
Test for overall effect: Z = 1.88 (P = 0.06)



3.9 Treatment satisfaction (SAQ) (range 0-100) (change scores)

Study or Subgroup	CASMP Mean	CASMP SD	CASMP Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Fixed, 95% CI
McGillion 2008	9.7	24.6	57	4.8	18.7	60	100.0%	4.90 [-3.05, 12.85]
Total (95% CI)			**57**			**60**	**100.0%**	**4.90 [-3.05, 12.85]**

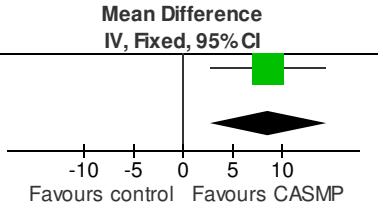
Heterogeneity: Not applicable
Test for overall effect: Z = 1.21 (P = 0.23)



3.10 Self-Efficay Scale (range scores 10- 100 -higher scores better) (change scores)

Study or Subgroup	CASMP Mean	CASMP SD	CASMP Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Fixed, 95% CI
McGillion 2008	8.4	17.6	57	-0.2	14.4	60	100.0%	8.60 [2.76, 14.44]
Total (95% CI)			**57**			**60**	**100.0%**	**8.60 [2.76, 14.44]**

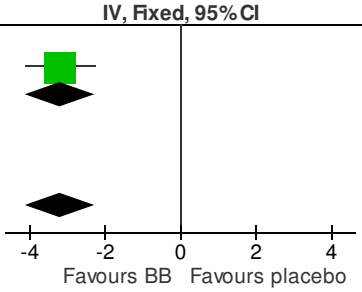
Heterogeneity: Not applicable
Test for overall effect: Z = 2.88 (P = 0.004)



1 beta blocker vs placebo

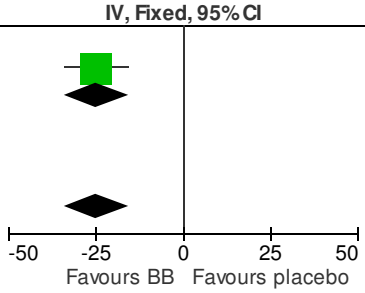
1.1 ischemic episodes

Study or Subgroup	beta blocker Mean	SD	Total	placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
1.1.1 propanolol vs placebo								
Bugiardini 1989	0.7	0.6	16	3.9	1.8	16	100.0%	-3.20 [-4.13, -2.27]
Subtotal (95% CI)			**16**			**16**	**100.0%**	**-3.20 [-4.13, -2.27]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 6.75 (P < 0.00001)								
Total (95% CI)			**16**			**16**	**100.0%**	**-3.20 [-4.13, -2.27]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 6.75 (P < 0.00001)								
Test for subgroup differences: Not applicable								



1.2 ischemic duration (min)

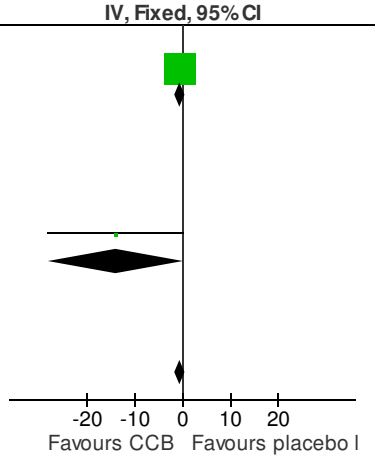
Study or Subgroup	beta blocker Mean	SD	Total	placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
1.2.1 propanolol vs placebo								
Bugiardini 1989	4	5	16	29	18	16	100.0%	-25.00 [-34.15, -15.85]
Subtotal (95% CI)			**16**			**16**	**100.0%**	**-25.00 [-34.15, -15.85]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 5.35 (P < 0.00001)								
Total (95% CI)			**16**			**16**	**100.0%**	**-25.00 [-34.15, -15.85]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 5.35 (P < 0.00001)								
Test for subgroup differences: Not applicable								



2 calcium channel blockers vs placebo

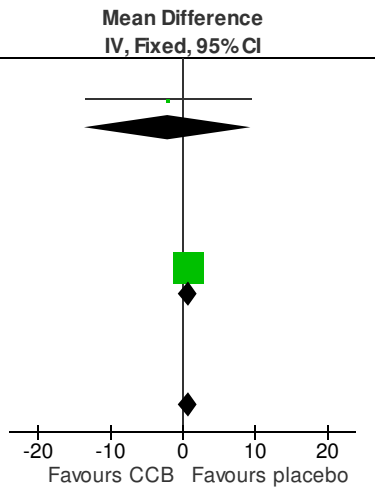
2.1 ischemic episodes

Study or Subgroup	calcium channel blockers Mean	SD	Total	placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
2.1.1 verapamil vs placebo								
Bugiardini 1989	3.4	1.7	16	3.9	1.8	16	99.3%	-0.50 [-1.71, 0.71]
Subtotal (95% CI)			**16**			**16**	**99.3%**	**-0.50 [-1.71, 0.71]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.81 (P = 0.42)								
2.1.2 verapamil or nifedipine vs placebo								
Cannon 1985	21	21	22	35	27	22	0.7%	-14.00 [-28.29, 0.29]
Subtotal (95% CI)			**22**			**22**	**0.7%**	**-14.00 [-28.29, 0.29]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.92 (P = 0.05)								
Total (95% CI)			**38**			**38**	**100.0%**	**-0.60 [-1.81, 0.61]**
Heterogeneity: Chi² = 3.40, df = 1 (P = 0.07); I² = 71%								
Test for overall effect: Z = 0.97 (P = 0.33)								
Test for subgroup differences: Chi² = 3.40, df = 1 (P = 0.07), I² = 70.6%								



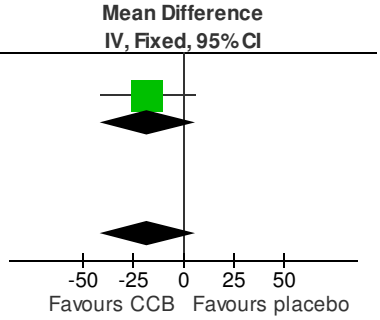
2.2 ischemia duration (min)

Study or Subgroup	calcium channel blockers Mean	SD	Total	placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
2.2.1 verapamil vs placebo								
Bugiardini 1989	27	15	16	29	18	16	1.3%	-2.00 [-13.48, 9.48]
Subtotal (95% CI)			**16**			**16**	**1.3%**	**-2.00 [-13.48, 9.48]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.34 (P = 0.73)								
2.2.2 verapamil or nifedipine vs placebo								
Cannon 1985	4.63	2.15	22	3.85	2.27	22	98.7%	0.78 [-0.53, 2.09]
Subtotal (95% CI)			**22**			**22**	**98.7%**	**0.78 [-0.53, 2.09]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.17 (P = 0.24)								
Total (95% CI)			**38**			**38**	**100.0%**	**0.74 [-0.55, 2.04]**
Heterogeneity: Chi² = 0.22, df = 1 (P = 0.64); I² = 0%								
Test for overall effect: Z = 1.12 (P = 0.26)								
Test for subgroup differences: Chi² = 0.22, df = 1 (P = 0.64), I² = 0%								



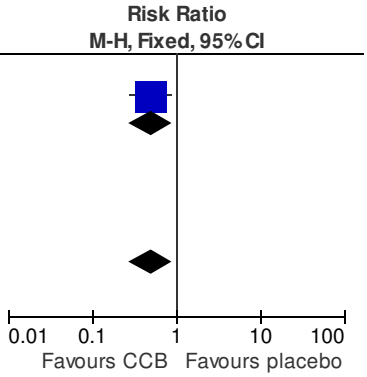
2.3 Nitroglycerin tablets consumption

Study or Subgroup	calcium channel blockers Mean	SD	Total	placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
2.3.1 verapamil or nifedipine vs placebo								
Cannon 1985	23	27	22	41	50	22	100.0%	-18.00 [-41.74, 5.74]
Subtotal (95% CI)			**22**			**22**	**100.0%**	**-18.00 [-41.74, 5.74]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.49 (P = 0.14)								
Total (95% CI)			**22**			**22**	**100.0%**	**-18.00 [-41.74, 5.74]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.49 (P = 0.14)								
Test for subgroup differences: Not applicable								



2.4 presence of chest pain during exercise

Study or Subgroup	calcium channel blockers Events	Total	placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
2.4.1 verapamil or nifedipine vs placebo						
Cannon 1985	9	25	16	22	100.0%	0.49 [0.28, 0.89]
Subtotal (95% CI)		**25**		**22**	**100.0%**	**0.49 [0.28, 0.89]**
Total events	9		16			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.37 (P = 0.02)						
Total (95% CI)		**25**		**22**	**100.0%**	**0.49 [0.28, 0.89]**
Total events	9		16			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.37 (P = 0.02)						
Test for subgroup differences: Not applicable						

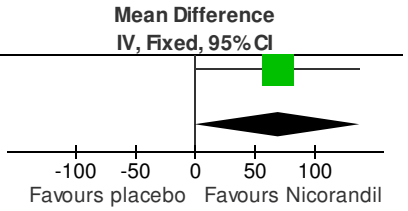


3 Nicorandil vs placebo

3.3 Time to 1mm ST-segment depression (sec)

Study or Subgroup	nicorandil Mean	SD	Total	placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Chen 1997	342	104	13	273	72	13	100.0%	69.00 [0.24, 137.76]
Total (95% CI)			**13**			**13**	**100.0%**	**69.00 [0.24, 137.76]**

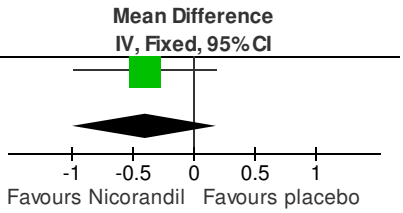
Heterogeneity: Not applicable
Test for overall effect: Z = 1.97 (P = 0.05)



3.4 maximum ST-segment depression (mm)

Study or Subgroup	nicorandil Mean	SD	Total	placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Chen 1997	1.5	0.6	13	1.9	0.9	13	100.0%	-0.40 [-0.99, 0.19]
Total (95% CI)			**13**			**13**	**100.0%**	**-0.40 [-0.99, 0.19]**

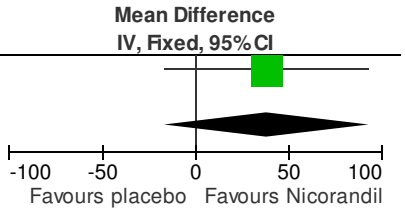
Heterogeneity: Not applicable
Test for overall effect: Z = 1.33 (P = 0.18)



3.5 Total exercise duration (sec)

Study or Subgroup	nicorandil Mean	SD	Total	placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Chen 1997	443	78	13	405	64	13	100.0%	38.00 [-16.85, 92.85]
Total (95% CI)			**13**			**13**	**100.0%**	**38.00 [-16.85, 92.85]**

Heterogeneity: Not applicable
Test for overall effect: Z = 1.36 (P = 0.17)



4 beta blockers vs calcium channel blockers in patients with pressure-rate product variation <1050

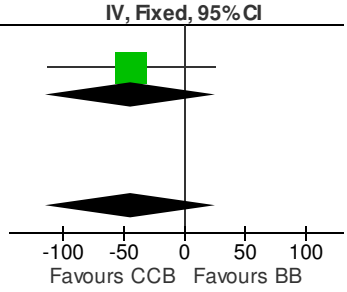
4.1 exercise duration (sec)

Study or Subgroup	beta blockers Mean	SD	Total	calcium channel blockers Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
4.1.1 acebutolol vs verapamil in patients with pressure-rate product variation >1050								
Romeo 1988	318	101	15	362	93	15	100.0%	-44.00 [-113.48, 25.48]
Subtotal (95% CI)			**15**			**15**	**100.0%**	**-44.00 [-113.48, 25.48]**

Heterogeneity: Not applicable
Test for overall effect: Z = 1.24 (P = 0.21)

Total (95% CI)			**15**			**15**	**100.0%**	**-44.00 [-113.48, 25.48]**

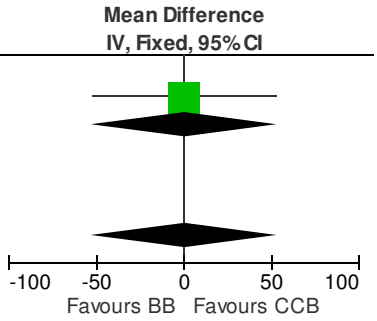
Heterogeneity: Not applicable
Test for overall effect: Z = 1.24 (P = 0.21)
Test for subgroup differences: Not applicable



5 beta blockers vs calcium channel blockers in patients with pressure-rate product variation >1050

5.1 exercise duration (sec)

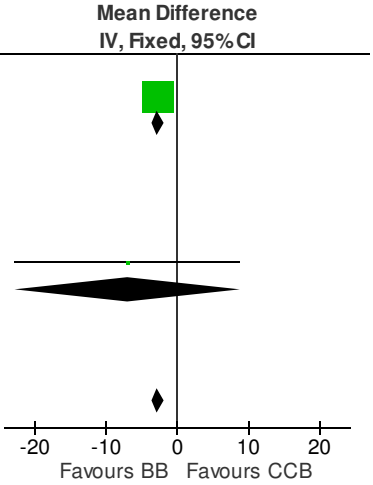
Study or Subgroup	beta blockers Mean	SD	Total	calcium channel blockers Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
5.1.1 acebutolol vs verapamil in patients with pressure-rate product variation <1050								
Romeo 1988	288	66	15	288	80	15	100.0%	0.00 [-52.48, 52.48]
Subtotal (95% CI)			**15**			**15**	**100.0%**	**0.00 [-52.48, 52.48]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.00 (P = 1.00)								
Total (95% CI)			**15**			**15**	**100.0%**	**0.00 [-52.48, 52.48]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.00 (P = 1.00)								
Test for subgroup differences: Not applicable								



6 Beta blockers vs calcium channel blockers

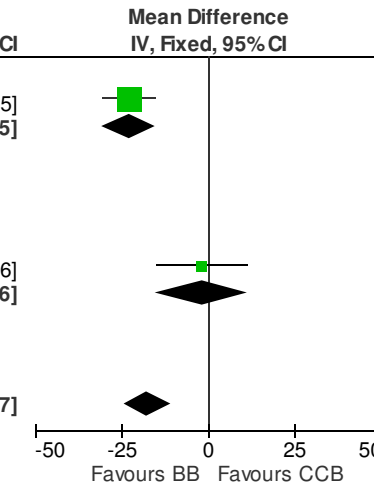
6.1 Number of anginal episodes (per 4 weeks per patient)

Study or Subgroup	beta blockers Mean	SD	Total	calcium channel blockers Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
6.1.1 propanolol vs verapamil								
Bugiardini 1989	0.7	0.6	16	3.4	1.7	16	99.7%	-2.70 [-3.58, -1.82]
Subtotal (95% CI)			**16**			**16**	**99.7%**	**-2.70 [-3.58, -1.82]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 5.99 (P < 0.00001)								
6.1.2 atenolol vs amlodipine								
Lanza 1999	15	13	10	22	22	10	0.3%	-7.00 [-22.84, 8.84]
Subtotal (95% CI)			**10**			**10**	**0.3%**	**-7.00 [-22.84, 8.84]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.87 (P = 0.39)								
Total (95% CI)			**26**			**26**	**100.0%**	**-2.71 [-3.60, -1.83]**
Heterogeneity: Chi² = 0.28, df = 1 (P = 0.60); I² = 0%								
Test for overall effect: Z = 6.03 (P < 0.00001)								
Test for subgroup differences: Chi² = 0.28, df = 1 (P = 0.60), I² = 0%								



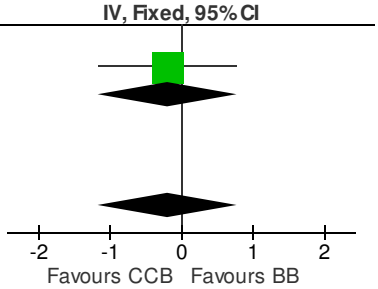
6.2 Chest pain episodes duration (min)

Study or Subgroup	beta blockers Mean	SD	Total	calcium channel blockers Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
6.2.1 propanolol vs verapamil								
Bugiardini 1989	4	5	16	27	15	16	74.6%	-23.00 [-30.75, -15.25]
Subtotal (95% CI)			**16**			**16**	**74.6%**	**-23.00 [-30.75, -15.25]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 5.82 (P < 0.00001)								
6.2.2 atenolol vs amlodipine								
Lanza 1999	14	13	10	16	17	10	25.4%	-2.00 [-15.26, 11.26]
Subtotal (95% CI)			**10**			**10**	**25.4%**	**-2.00 [-15.26, 11.26]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.30 (P = 0.77)								
Total (95% CI)			**26**			**26**	**100.0%**	**-17.66 [-24.35, -10.97]**
Heterogeneity: Chi² = 7.18, df = 1 (P = 0.007); I² = 86%								
Test for overall effect: Z = 5.17 (P < 0.00001)								
Test for subgroup differences: Chi² = 7.18, df = 1 (P = 0.007), I² = 86.1%								



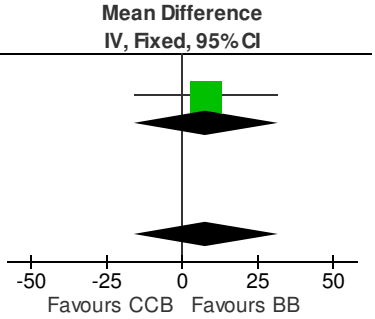
6.3 severity of chest pain (scale 1-5)

Study or Subgroup	beta blockers Mean	SD	Total	calcium channel blockers Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
6.3.1 atenolol vs amlodipine								
Lanza 1999	2.5	1.2	10	2.7	1	10	100.0%	-0.20 [-1.17, 0.77]
Subtotal (95% CI)			**10**			**10**	**100.0%**	**-0.20 [-1.17, 0.77]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.40 (P = 0.69)								
Total (95% CI)			**10**			**10**	**100.0%**	**-0.20 [-1.17, 0.77]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.40 (P = 0.69)								
Test for subgroup differences: Not applicable								



6.4 quality of life (scale 0-100 mm)

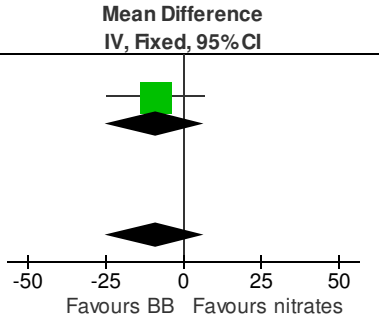
Study or Subgroup	beta blockers Mean	SD	Total	calcium channel blockers Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
6.4.1 atenolol vs amlodipine								
Lanza 1999	59	29	10	51	25	10	100.0%	8.00 [-15.73, 31.73]
Subtotal (95% CI)			**10**			**10**	**100.0%**	**8.00 [-15.73, 31.73]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.66 (P = 0.51)								
Total (95% CI)			**10**			**10**	**100.0%**	**8.00 [-15.73, 31.73]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.66 (P = 0.51)								
Test for subgroup differences: Not applicable								



7 beta blockers vs nitrates

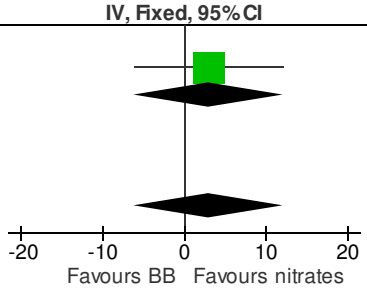
7.1 Number of anginal episodes (per 4 weeks per patient)

Study or Subgroup	beta blockers Mean	SD	Total	nitrates Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
7.1.1 atenolol vs ISMN								
Lanza 1999	15	13	10	24	22	10	100.0%	-9.00 [-24.84, 6.84]
Subtotal (95% CI)			**10**			**10**	**100.0%**	**-9.00 [-24.84, 6.84]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.11 (P = 0.27)								
Total (95% CI)			**10**			**10**	**100.0%**	**-9.00 [-24.84, 6.84]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.11 (P = 0.27)								
Test for subgroup differences: Not applicable								



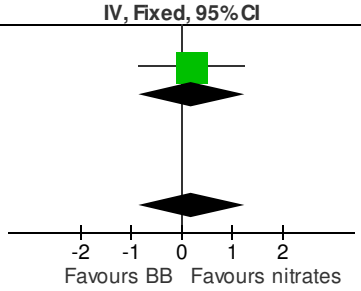
7.2 Chest pain episodes duration (min)

Study or Subgroup	beta blockers Mean	SD	Total	nitrates Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
7.2.1 atenolol vs ISMN								
Lanza 1999	14	13	10	11	7	10	100.0%	3.00 [-6.15, 12.15]
Subtotal (95% CI)			**10**			**10**	**100.0%**	**3.00 [-6.15, 12.15]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.64 (P = 0.52)								
Total (95% CI)			**10**			**10**	**100.0%**	**3.00 [-6.15, 12.15]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.64 (P = 0.52)								
Test for subgroup differences: Not applicable								



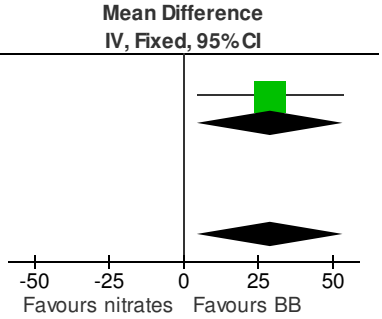
7.3 severity of chest pain (scale 1-5)

Study or Subgroup	beta blockers Mean	SD	Total	nitrates Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
7.3.1 atenolol vs ISMN								
Lanza 1999	2.5	1.2	10	2.3	1.2	10	100.0%	0.20 [-0.85, 1.25]
Subtotal (95% CI)			**10**			**10**	**100.0%**	**0.20 [-0.85, 1.25]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.37 (P = 0.71)								
Total (95% CI)			**10**			**10**	**100.0%**	**0.20 [-0.85, 1.25]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.37 (P = 0.71)								
Test for subgroup differences: Not applicable								



7.4 quality of life (scale 0-100 mm)

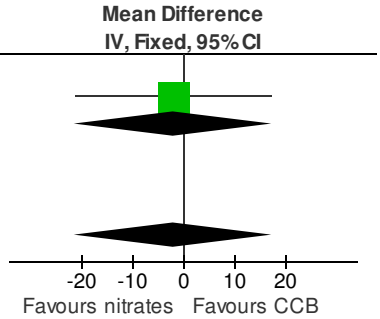
Study or Subgroup	beta blockers Mean	SD	Total	nitrates Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
7.4.1 atenolol vs ISMN								
Lanza 1999	59	29	10	30	27	10	100.0%	29.00 [4.44, 53.56]
Subtotal (95% CI)			**10**			**10**	**100.0%**	**29.00 [4.44, 53.56]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 2.31 (P = 0.02)								
Total (95% CI)			**10**			**10**	**100.0%**	**29.00 [4.44, 53.56]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 2.31 (P = 0.02)								
Test for subgroup differences: Not applicable								



8 Calcium channel blockers vs nitrates

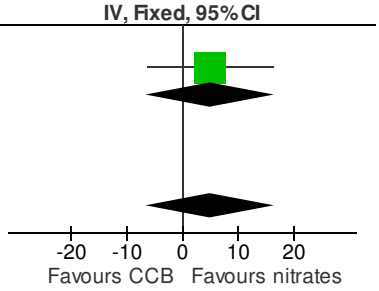
8.1 Number of anginal episodes (per 4 weeks per patient)

Study or Subgroup	calcium channel blockers Mean	SD	Total	nitrates Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
8.1.1 amlodipine vs ISMN								
Lanza 1999	22	22	10	24	22	10	100.0%	-2.00 [-21.28, 17.28]
Subtotal (95% CI)			**10**			**10**	**100.0%**	**-2.00 [-21.28, 17.28]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.20 (P = 0.84)								
Total (95% CI)			**10**			**10**	**100.0%**	**-2.00 [-21.28, 17.28]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.20 (P = 0.84)								
Test for subgroup differences: Not applicable								



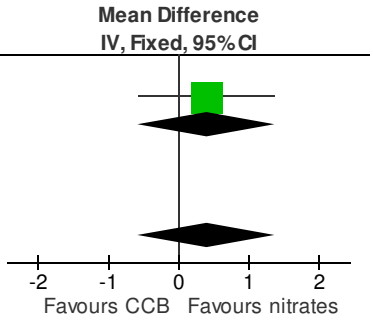
8.2 Chest pain episodes duration (min)

Study or Subgroup	calcium channel blockers Mean	SD	Total	nitrates Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
8.2.1 amlodipine vs ISMN								
Lanza 1999	16	17	10	11	7	10	100.0%	5.00 [-6.39, 16.39]
Subtotal (95% CI)			**10**			**10**	**100.0%**	**5.00 [-6.39, 16.39]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.86 (P = 0.39)								
Total (95% CI)			**10**			**10**	**100.0%**	**5.00 [-6.39, 16.39]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.86 (P = 0.39)								
Test for subgroup differences: Not applicable								



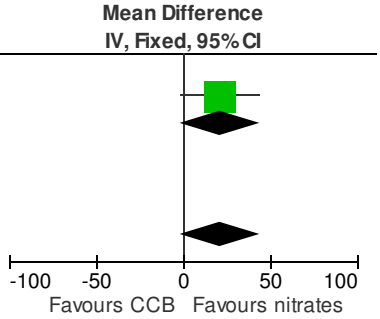
8.3 severity of chest pain (scale 1-5)

Study or Subgroup	calcium channel blockers Mean	SD	Total	nitrates Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
8.3.1 amlodipine vs ISMN								
Lanza 1999	2.7	1	10	2.3	1.2	10	100.0%	0.40 [-0.57, 1.37]
Subtotal (95% CI)			**10**			**10**	**100.0%**	**0.40 [-0.57, 1.37]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.81 (P = 0.42)								
Total (95% CI)			**10**			**10**	**100.0%**	**0.40 [-0.57, 1.37]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.81 (P = 0.42)								
Test for subgroup differences: Not applicable								



8.4 quality of life (scale 0-100 mm)

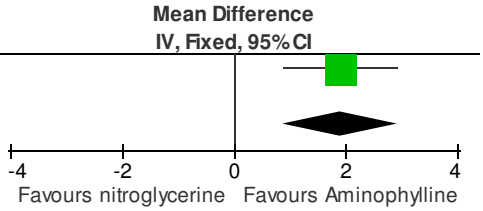
Study or Subgroup	calcium channel blockers Mean	SD	Total	nitrates Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
8.4.1 amlodipine vs ISMN								
Lanza 1999	51	25	10	30	27	10	100.0%	21.00 [-1.81, 43.81]
Subtotal (95% CI)			**10**			**10**	**100.0%**	**21.00 [-1.81, 43.81]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.80 (P = 0.07)								
Total (95% CI)			**10**			**10**	**100.0%**	**21.00 [-1.81, 43.81]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.80 (P = 0.07)								
Test for subgroup differences: Not applicable								



9 Aminophylline vs Nitroglycerine

9.1 Time to 1mm ST depression

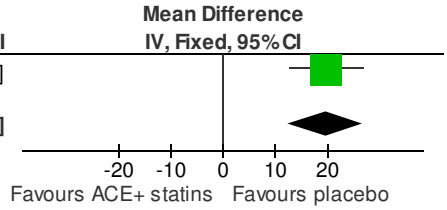
Study or Subgroup	Aminophylline Mean	SD	Total	Nitroglycerine Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Radice 1996	5.5	1.6	20	3.6	1.7	20	100.0%	1.90 [0.88, 2.92]
Total (95% CI)			**20**			**20**	**100.0%**	**1.90 [0.88, 2.92]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 3.64 (P = 0.0003)								



10 Angiotensin-Converting Enzyme Inhibitors and statins vs placebo

10.1 Seattle Angina Questionnaire angina frequency score

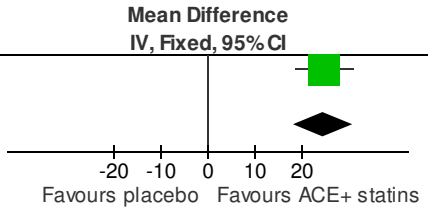
Study or Subgroup	ACE + statins Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Pizzi 2004	82.1	13.8	22	62.4	10.5	23	100.0%	19.70 [12.51, 26.89]
Total (95% CI)			**22**			**23**	**100.0%**	**19.70 [12.51, 26.89]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 5.37 (P < 0.00001)								



10.2 Seattle Angina Questionnaire Quality of life score

	ACE + statins			Placebo				Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI
Pizzi 2004	86.5	11.7	22	61.9	9.4	23	100.0%	24.60 [18.38, 30.82]
Total (95% CI)			**22**			**23**	**100.0%**	**24.60 [18.38, 30.82]**

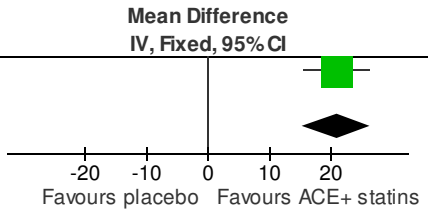
Heterogeneity: Not applicable
Test for overall effect: Z = 7.75 (P < 0.00001)



10.3 Seattle Angina Questionnaire summary score

	ACE + statins			Placebo				Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI
Pizzi 2004	84.2	9.8	22	63.3	8.6	23	100.0%	20.90 [15.50, 26.30]
Total (95% CI)			**22**			**23**	**100.0%**	**20.90 [15.50, 26.30]**

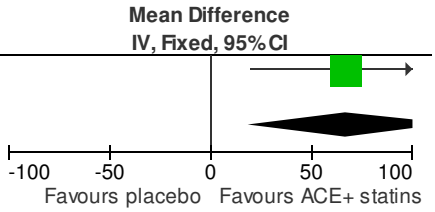
Heterogeneity: Not applicable
Test for overall effect: Z = 7.59 (P < 0.00001)



10.4 Peak exercise time (s)

	ACE + statins			Placebo				Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI
Pizzi 2004	555.6	84.6	22	488.4	79.2	23	100.0%	67.20 [19.27, 115.13]
Total (95% CI)			**22**			**23**	**100.0%**	**67.20 [19.27, 115.13]**

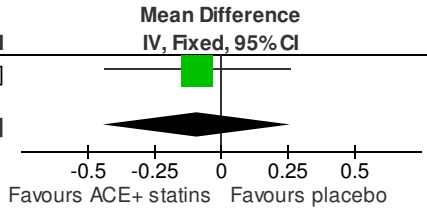
Heterogeneity: Not applicable
Test for overall effect: Z = 2.75 (P = 0.006)



10.5 ST depression (mV)

	ACE + statins			Placebo				Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI
Pizzi 2004	0.12	0.3	22	0.21	0.8	23	100.0%	-0.09 [-0.44, 0.26]
Total (95% CI)			**22**			**23**	**100.0%**	**-0.09 [-0.44, 0.26]**

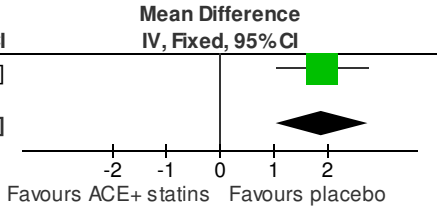
Heterogeneity: Not applicable
Test for overall effect: Z = 0.50 (P = 0.61)



10.6 Flow-mediated Dilation of brachial artery (%)

	ACE + statins			Placebo				Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI
Pizzi 2004	4.2	1.7	22	2.3	1.2	23	100.0%	1.90 [1.04, 2.76]
Total (95% CI)			**22**			**23**	**100.0%**	**1.90 [1.04, 2.76]**

Heterogeneity: Not applicable
Test for overall effect: Z = 4.31 (P < 0.0001)

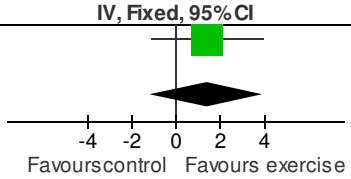


1 Exercise programme + symptom monitoring versus symptoms monitoring only

1.1 HADS total (8 week follow up)

Study or Subgroup	Exercise + monitoring Mean	SD	Total	Monitoring only Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Asbury 2008	11.5	5.7	32	10.1	4.6	32	100.0%	1.40 [-1.14, 3.94]
Total (95% CI)			**32**			**32**	**100.0%**	**1.40 [-1.14, 3.94]**

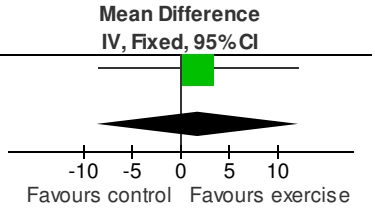
Heterogeneity: Not applicable
Test for overall effect: Z = 1.08 (P = 0.28)



1.2 SF-36 physical functioning (8 week follow up)

Study or Subgroup	Exercise + monitoring Mean	SD	Total	Monitoring only Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Asbury 2008	62.1	19.7	32	60.3	22.2	32	100.0%	1.80 [-8.48, 12.08]
Total (95% CI)			**32**			**32**	**100.0%**	**1.80 [-8.48, 12.08]**

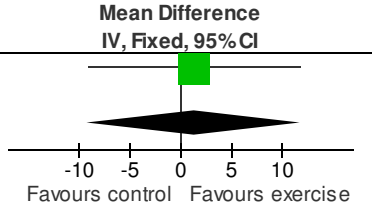
Heterogeneity: Not applicable
Test for overall effect: Z = 0.34 (P = 0.73)



1.3 SF-36 pain (8 week follow up)

Study or Subgroup	Exercise + monitoring Mean	SD	Total	Monitoring only Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Asbury 2008	58.7	22.3	32	57.4	20.3	32	100.0%	1.30 [-9.15, 11.75]
Total (95% CI)			**32**			**32**	**100.0%**	**1.30 [-9.15, 11.75]**

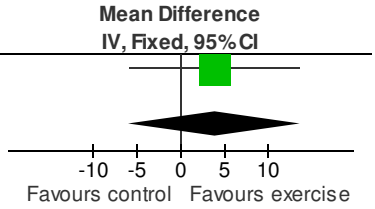
Heterogeneity: Not applicable
Test for overall effect: Z = 0.24 (P = 0.81)



1.4 SF-36 general health (8 week follow up)

Study or Subgroup	Exercise + monitoring Mean	SD	Total	Monitoring only Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Asbury 2008	58.2	16.4	32	54.3	22.9	32	100.0%	3.90 [-5.86, 13.66]
Total (95% CI)			**32**			**32**	**100.0%**	**3.90 [-5.86, 13.66]**

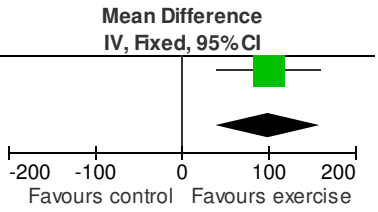
Heterogeneity: Not applicable
Test for overall effect: Z = 0.78 (P = 0.43)



1.5 Shuttle walk test (m) (8 week follow up)

Study or Subgroup	Exercise + monitoring Mean	SD	Total	Monitoring only Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Asbury 2008	426.6	133	32	326.8	111	32	100.0%	99.80 [39.78, 159.82]
Total (95% CI)			**32**			**32**	**100.0%**	**99.80 [39.78, 159.82]**

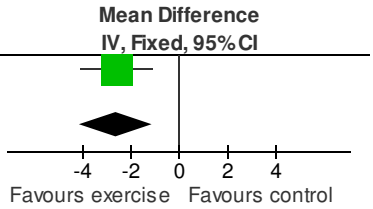
Heterogeneity: Not applicable
Test for overall effect: Z = 3.26 (P = 0.001)



1.6 Symptom frequency (8 week follow up)

Study or Subgroup	Exercise + monitoring Mean	SD	Total	Monitoring only Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Asbury 2008	2	2.1	32	4.6	3.8	32	100.0%	-2.60 [-4.10, -1.10]
Total (95% CI)			**32**			**32**	**100.0%**	**-2.60 [-4.10, -1.10]**

Heterogeneity: Not applicable
Test for overall effect: Z = 3.39 (P = 0.0007)

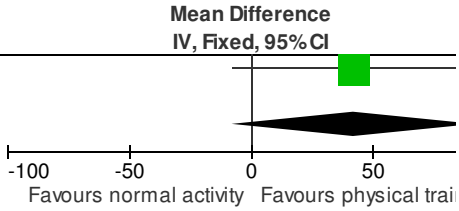


2 Physical training versus normal activity

2.1 Distance walked (m) (8 week follow up)

Study or Subgroup	Physical training Mean	SD	Total	Normal activity Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Tyni-Lenne 2002	587	49	7	545	46	7	100.0%	42.00 [-7.79, 91.79]
Total (95% CI)			**7**			**7**	**100.0%**	**42.00 [-7.79, 91.79]**

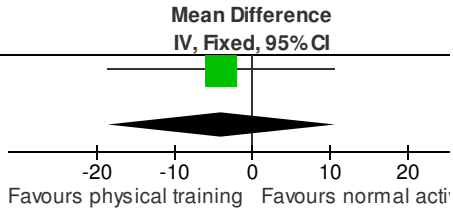
Heterogeneity: Not applicable
Test for overall effect: Z = 1.65 (P = 0.10)



2.2 Peak heart rate (bpm) (8 week follow up)

Study or Subgroup	Physical training Mean	SD	Total	Normal activity Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Tyni-Lenne 2002	102	17	7	106	10	7	100.0%	-4.00 [-18.61, 10.61]
Total (95% CI)			**7**			**7**	**100.0%**	**-4.00 [-18.61, 10.61]**

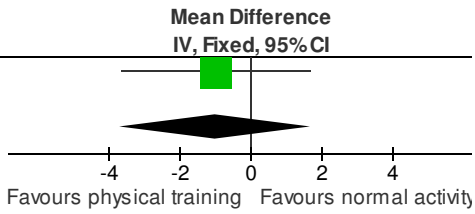
Heterogeneity: Not applicable
Test for overall effect: Z = 0.54 (P = 0.59)



2.3 Exertion (Borg RPE) (8 week follow up)

Study or Subgroup	Physical training Mean	SD	Total	Normal activity Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Tyni-Lenne 2002	13	3	7	14	2	7	100.0%	-1.00 [-3.67, 1.67]
Total (95% CI)			**7**			**7**	**100.0%**	**-1.00 [-3.67, 1.67]**

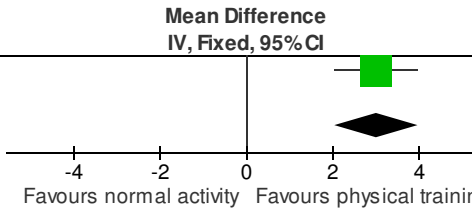
Heterogeneity: Not applicable
Test for overall effect: Z = 0.73 (P = 0.46)



2.4 Pain onset (min) after exercise (8 week follow up)

Study or Subgroup	Physical training Mean	SD	Total	Normal activity Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Eriksson 2000	6	1	7	3	1	10	100.0%	3.00 [2.03, 3.97]
Total (95% CI)			**7**			**10**	**100.0%**	**3.00 [2.03, 3.97]**

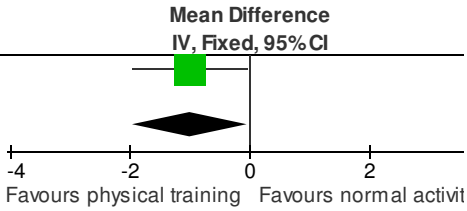
Heterogeneity: Not applicable
Test for overall effect: Z = 6.09 (P < 0.00001)



2.5 Max pain (Borg CR-10) (8 week follow up)

Study or Subgroup	Physical training Mean	SD	Total	Normal activity Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Eriksson 2000	3	1	7	4	1	10	100.0%	-1.00 [-1.97, -0.03]
Total (95% CI)			**7**			**10**	**100.0%**	**-1.00 [-1.97, -0.03]**

Heterogeneity: Not applicable
Test for overall effect: Z = 2.03 (P = 0.04)

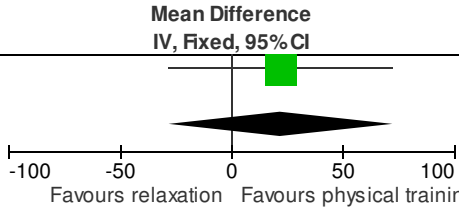


3 Physical training versus relaxation

3.1 Distance walked (m) (8 week follow up)

Study or Subgroup	Physical training Mean	SD	Total	Relaxation Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Tyni-Lenne 2002	587	49	7	565	47	7	100.0%	22.00 [-28.30, 72.30]
Total (95% CI)			**7**			**7**	**100.0%**	**22.00 [-28.30, 72.30]**

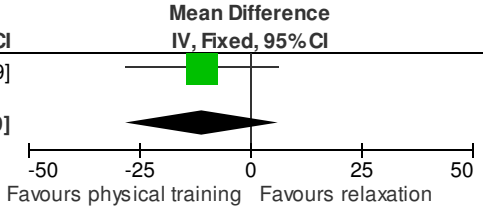
Heterogeneity: Not applicable
Test for overall effect: Z = 0.86 (P = 0.39)



3.2 Peak heart rate (bpm) (8 week follow up)

Study or Subgroup	Physical training Mean	SD	Total	Relaxation Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Tyni-Lenne 2002	102	17	7	113	16	7	100.0%	-11.00 [-28.29, 6.29]
Total (95% CI)			**7**			**7**	**100.0%**	**-11.00 [-28.29, 6.29]**

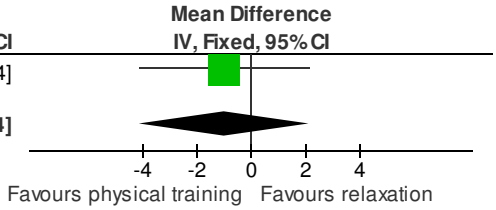
Heterogeneity: Not applicable
Test for overall effect: Z = 1.25 (P = 0.21)



3.3 Exertion (Borg RPE) (8 week follow up)

Study or Subgroup	Physical training Mean	SD	Total	Relaxation Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Tyni-Lenne 2002	13	3	7	14	3	7	100.0%	-1.00 [-4.14, 2.14]
Total (95% CI)			**7**			**7**	**100.0%**	**-1.00 [-4.14, 2.14]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.62 (P = 0.53)

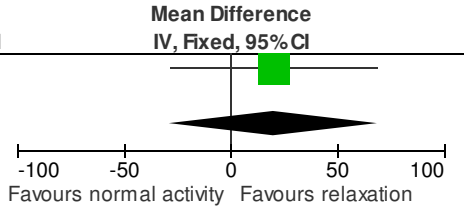


4 Relaxation versus normal activity

4.1 Distance walked (m) (8 week follow up)

Study or Subgroup	Relaxation Mean	SD	Total	Normal activity Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Tyni-Lenne 2002	565	47	7	545	46	7	100.0%	20.00 [-28.72, 68.72]
Total (95% CI)			**7**			**7**	**100.0%**	**20.00 [-28.72, 68.72]**

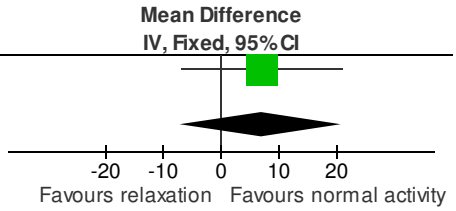
Heterogeneity: Not applicable
Test for overall effect: Z = 0.80 (P = 0.42)



4.2 Peak heart rate (bpm) (8 week follow up)

Study or Subgroup	Relaxation Mean	SD	Total	Normal activity Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Tyni-Lenne 2002	113	16	7	106	10	7	100.0%	7.00 [-6.98, 20.98]
Total (95% CI)			**7**			**7**	**100.0%**	**7.00 [-6.98, 20.98]**

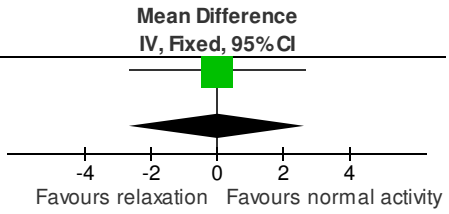
Heterogeneity: Not applicable
Test for overall effect: Z = 0.98 (P = 0.33)



4.3 Exertion (Borg RPE) (8 week follow up)

Study or Subgroup	Relaxation Mean	SD	Total	Normal activity Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Tyni-Lenne 2002	14	3	7	14	2	7	100.0%	0.00 [-2.67, 2.67]
Total (95% CI)			**7**			**7**	**100.0%**	**0.00 [-2.67, 2.67]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.00 (P = 1.00)

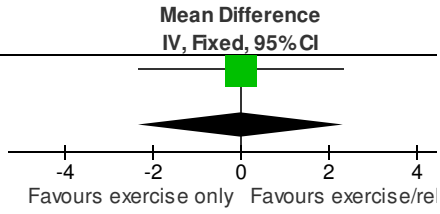


5 Exercise plus relaxation training versus exercise training

5.4 Pain onset (min) after exercise (8 week follow up)

Study or Subgroup	Exercise + relaxation Mean	SD	Total	Exercise only Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Eriksson 2000	6	3	7	6	1	7	100.0%	0.00 [-2.34, 2.34]
Total (95% CI)			**7**			**7**	**100.0%**	**0.00 [-2.34, 2.34]**

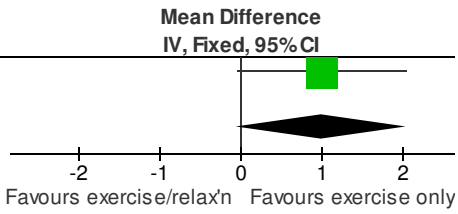
Heterogeneity: Not applicable
Test for overall effect: Z = 0.00 (P = 1.00)



5.5 Max pain (Borg CR-10) (8 week follow up)

Study or Subgroup	Exercise/relaxation Mean	SD	Total	Exercise only Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Eriksson 2000	4	1	7	3	1	7	100.0%	1.00 [-0.05, 2.05]
Total (95% CI)			**7**			**7**	**100.0%**	**1.00 [-0.05, 2.05]**

Heterogeneity: Not applicable
Test for overall effect: Z = 1.87 (P = 0.06)

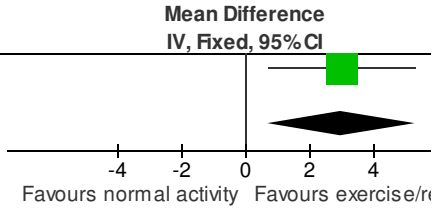


6 Exercise plus relaxation training versus normal activity

6.4 Pain onset (min) after exercise (8 week follow up)

Study or Subgroup	Exercise + relaxation Mean	SD	Total	Normal activity Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Eriksson 2000	6	3	7	3	1	10	100.0%	3.00 [0.69, 5.31]
Total (95% CI)			**7**			**10**	**100.0%**	**3.00 [0.69, 5.31]**

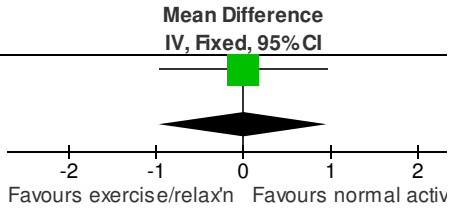
Heterogeneity: Not applicable
Test for overall effect: Z = 2.55 (P = 0.01)



6.5 Max pain (Borg CR-10) (8 week follow up)

Study or Subgroup	Exercise/relaxation Mean	SD	Total	Normal activity Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Eriksson 2000	4	1	7	4	1	10	100.0%	0.00 [-0.97, 0.97]
Total (95% CI)			**7**			**10**	**100.0%**	**0.00 [-0.97, 0.97]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.00 (P = 1.00)



Appendix G. Evidence tables: Economic studies

Abbreviations

CABG	Coronary artery bypass graft
CCS	Canadian cardiovascular society
CI	Confidence interval
CVD	Cardiovascular disease
EECP	Enhanced external counterpulsation
EVPI	Expected value of perfect information
HRQoL	Health-related quality of life
ICER	Incremental cost-effectiveness ratio
ICU	Intensive care unit
ITT	Intention to treat analysis
Int	Intervention
LOS	Length of stay
MACCE	Major adverse cardiac and cerebrovascular event
M/F	Male/female
MI	Myocardial infarction
N	Total number of patients randomised
NA	Not applicable
NR	Not reported
PCI	Percutaneous coronary intervention
PTCA	Percutaneous transluminal coronary angioplasty
QALY	Quality-Adjusted Life Years
RCT	Randomised controlled trial
SA	Sensitivity analysis
SAQ	Seattle Angina Questionnaire
SD	Standard deviation
SE	Standard error
Sig	Statistically significant at 5%

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Abizaid 2001[1] USA **Economic analysis:** Cost consequences analysis **Study design** RCT* **Duration of follow-up:** 1 year **Perspective:** Healthcare provider **Discount rates:** Costs: NA Effects: NA	**Patient group:** Patients with diabetes and multi-vessel coronary artery disease from the ARTS trial. **<u>All patients</u>** **N:** 208 **Age (mean):** NR **M/F:** 149/59 **Unstable angina:** 82 **Drop outs:** 0 **<u>Group 1</u>** **N:** 112 **Age (mean):** 62.4 **M/F:** 82/30 **Unstable angina:** 44 **Drop outs:** 0 **<u>Group 2</u>** **N:** 96 **Age (mean):** 62.6 **M/F:** 67/29 **Unstable angina:** 38 **Drop outs:** 0	**Group 1:** PCI Stent **Group 2:** CABG	Number of patients dead at 1 year	**Group 1:** 7 (6.3%) **Group 2:** 3 (3.1%) **p value:** 0.294	**Funding/conflict of interest:** NR **Limitations:** Short time-horizon. Cost of further medications not included (only hospital costs). Costs of resources from one hospital only. No sensitivity analysis. **Overall quality and applicability** Potentially serious limitations; partial applicability. **Data sources:** Unit costs from Dijkzigt Hospital. **Notes:** * based on a subgroup from the ARTS trial **calculated by NCGC
			Number of patients experiencing cerebrovascular events at 1 year	**Group 1:** 2 (1.8%) **Group 2:** 6 (6.3%) **p value:** 0.096	
			Number of patients experiencing myocardial infarction at 1 year	**Group 1:** 7 (6.3%) **Group 2:** 3 (3.1%) **p value:** 0.294	
			Number of patients having repeated vascularisation (CABG and PTCA) at 1 year	**Group 1:** 25 (22.3%) **Group 2:** 3 (3.1%) **p value:** <0.001	
			Number of event-free patients alive at 1 year	**Group 1:** 71 (63.4%) **Group 2:** 81 (84.4%) **p value:** <0.001	
			Mean cost per patient 1998 USD, cost of procedure and follow-up	**Group 1:** $12,855 (£8,291) **Group 2:** $16,585 (£10,052) **p value:** <0.001	
			Cost-effectiveness** Incremental cost per additional event-free patient	Group 2 vs Group 1: $8,386 (£5,409)	
			Sensitivity analysis	NR	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Borghi 2000[2] UK **Economic analysis:** Cost analysis **Study design** Cross-sectional study **Duration of follow-up:** One year **Perspective:** UK NHS **Discount rates:** Costs: NA Effects: NA	**Patient group:** New, switched and existing stable angina patients. **<u>All patients</u>** **N:** 1825 **N with comorbidities:** 640 (35%) **<u>Group 1</u>** **N:** 1253 **N with comorbidities:** 473 (38%) **<u>Group 2</u>** **N:** 572 **N with comorbidities:** 167 (29%)	**Group 1:** Beta-blocker (Tenormin) **Group 2:** Calcium-channel blocker (Tildiem)	**Mean cost per patient without comorbidities over one year** **a) new patient** **b) after switching** **c) existing patient** 1997/98 GBP. Cost of anti-anginal drugs, additional medication, GP-initiated tests, GP and practice nurse visits, outpatient visits, elective and emergency admissions.	**Group 1:** a) £656 b) £871 c) £320 **Group 2:** a) £1,014 b) £774 c) £336 **p value:** NR	**Funding/conflict of interest:** NR **Limitations:** Based on a cross-sectional study. No measure of effectiveness was assessed. **Overall quality and applicability** Potentially serious limitations; partial applicability. **Data sources:** Resource use data obtained from the IMS Health Database, UK Mediplus ® Resource costs obtained from NHS databases and UK cost studies.
			Cost-effectiveness	NR	
			Sensitivity analysis One-way SA	The costs in patients with comorbidities had the same trend in the year after switching and for existing patients. Only for new patients with comorbidities treatment with beta-blocker was associated with higher costs. The overall results do not change when: - frequency of GP visits is varied - incidence of hospitalisation is varied (from 0 to double) - the cost of generic drugs is used.	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
De Feyter 2002[3] Netherlands **Economic analysis:** Cost-effectiveness analysis **Study design** RCT* **Duration of follow-up:** 12 months **Perspective:** Healthcare provider **Discount rates:** Costs: NA Effects: NA	**Patient group:** patients with stable angina from the ARTS trial **<u>All patients</u>**** **N:** 755 **Age (mean):** NR **M/F:** 574/181 **Drop outs:** 0 **<u>Group 1</u>** **N:** 381 **Mean age (range):** 62 (32-81) **M/F:** 293/88 **Drop outs:** 0 **<u>Group 2</u>** **N:** 374 **Mean age (range):** 61 (35-83) **M/F:** 281/93 **Drop outs:** 0	**Group 1:** Stented angioplasty **Group 2:** CABG	Number of patients dead at 1 year	**Group 1:** 9 (2.4%) **Group 2:** 12 (3.2%) **p value:** Not sig	**Funding/conflict of interest:** NR **Limitations:** No sensitivity analysis was performed. No HRQoL outcomes were considered. Some costs (e.g. GP visits) might have been missed. **Overall quality and applicability** Potentially serious limitations; partial applicability. **Data sources:** Unit cost from the Netherlands. **Notes:** *ARTS trial **Only subset of stable angina patients is included in our review.
			Number of patients experiencing cerebrovascular accidents at 1 year	**Group 1:** 9 (2.1%) **Group 2:** 5 (1.3%) **p value:** Not sig	
			Number of patients experiencing myocardial infarction at 1 year	**Group 1:** 19 (5.1%) **Group 2:** 11 (2.9%) **p value:** Not sig	
			Number of patients having repeat revascularisation at 1 year	**Group 1:** 63 (16.8%) **Group 2:** 13 (3.5%) **p value:** <0.01	
			Number of angina and medication free patients at 1 year	**Group 1:** 67 (18%) **Group 2:** 160 (42%) **p value:** <0.003	
			Number of MACCE-free patients at 1 year	**Group 1:** 275 (73.5%) **Group 2:** 340 (89.2%) **p value:** <0.0001	
			Mean cost per patient 1998 USD, cost of procedure, hospitalisation, follow-up, rehospitalisation, medication.	**Group 1:** $10,368 (£6,687) **Group 2:** $12,960 (£8,359) **p value:** Not sig	
			Cost-effectiveness Incremental cost per additional MACCE-free patient.	Group 2 vs Group 1: $16,510 (£10,649)	
			Sensitivity analysis	NR	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Eefting 2003[4] The Netherlands **Economic analysis:** Cost-utility analysis **Study design** RCT **Duration of follow-up:** 1 year **Perspective:** NHS **Discount rates:** Costs: NA Effects: NA	**Patient group:** Patients with stable or unstable angina and/or documented ischemia. **<u>All patients</u>** **N:** 280 **Age (mean):** NR **Stable angina CCS I or II:** 60 **Stable angina CCS III or IV:** 128 **M/F:** 199/81 **Drop outs:** 0 [a] **<u>Group 1</u>** **N:** 138 **Age (mean):** 60.3 **Stable angina CCS I or II:** 22 [b] **Stable angina CCS III or IV:** 73 [b] **M/F:** 97/41 **Drop outs:** 0 [a] **<u>Group 2</u>** **N:** 142 **Age (mean):** 58.9 **Stable angina CCS I or II:** 38 [b] **Stable angina CCS III or IV:** 55 [b] **M/F:** 102/40 **Drop outs:** 0 [a]	**Group 1:** Stenting performed by use of standard techniques. **Group 2:** Off-pump bypass surgery by use of the Octopus tissue stabilizer.	Number of patients dead at 1 year	**Group 1:** 0 (0.0%) **Group 2:** 4 (2.8%) **p value:** NR	**Funding/conflict of interest:** Netherlands National Health Insurance Council. **Limitations:** Short follow-up. Lack of blinding. At baseline patients in Group 1 had more severe angina symptoms. **Overall quality and applicability** Potentially serious limitations; partial applicability. **Notes:** [a] 7 in Group 1 and 6 in Group 2 did not undergo the assigned treatment [b] significantly more patients in Group 1 were in CCS III or IV. [c] costs were estimated in Dutch florins and converted to US dollars ($1 = 2.5 DFL). [d] The main cost drivers were operating room, intensive care, ward, additional investigations and outpatient rehab.
			Number of patients experiencing myocardial infarction at 1 year	**Group 1:** 6 (4.4%) **Group 2:** 7 (4.9%) **p value:** Not Sig	
			Number of patients with repeated revascularisation at 1 year	**Group 1:** 21 (15.2%) **Group 2:** 6 (4.2%) **p value:** Sig	
			Number of event-free patients still alive at 1 year	**Group 1:** 118 (85.5%) **Group 2:** 130 (91.5%) **p value:** Not Sig	
			QALYs	**Group 1:** 0.82 **Group 2:** 0.79 **p value:** 0.09	
			Mean cost per patient at 1 year 1999 USD [c], direct cost of procedure, hospitalisation, follow-up including reoperation, rehabilitation, medications and tests [d].	**Group 1:** $7,043 (£4,599) **Group 2:** $9,518 (£6,215) **p value:** <0.01	
			Cost-effectiveness Incremental cost per QALY gained	Stenting is dominant	
			Sensitivity analysis Bootstrap simulation	Stenting is dominant in 95% of the 500 simulations.	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Griffin 2007[5] UK **Economic analysis:** Cost-utility analysis **Study design** Cohort study **Duration of follow-up:** 6 years **Perspective:** NHS **Discount rates:** Costs: 3.5% Effects: 3.5%	**Patient group:** Consecutive patients who had coronary angiography between 15 April 1996 and 14 April 1997 at three hospitals of one NHS trust in London and who were suitable for both CABG and PCI. Their suitability to have revascularisation was assessed using the RAND appropriateness method. **<u>All patients</u>** **N:** 520 **Age (mean):** 59 **M/F:** 403/117 **Drop outs:** NR **<u>Group 1</u>** **N:** 173 **Age (mean):** NR **M/F:**NR **Drop outs:** NR **<u>Group 2</u>** **N:** 149 **Age (mean):** NR **M/F:** NR **Drop outs:** NR **<u>Group 3</u>** **N:** 198 **Age (mean):** NR **M/F:** NR **Drop outs:** NR	**Group 1:** PCI **Group 2:** CABG **Group 3:** Medical management	Number of patients who died at 6 years	**Group 1:** 28 (16%) **Group 2:** 18 (12%) **Group 3:** 34 (17%) **p value:** Adjusted HR sig for Group 2 vs Group 1	**Funding/conflict of interest:** British Heart Foundation. The authors declared no competing interests. **Limitations:** Not a randomised study. PCI procedure could have been without stents. EQ-5D data were not collected at baseline and at one year; scores were only predicted at these time points from other variables. Criteria for assessment of the suitability for revascularisation could have changed since time of study. **Overall quality and applicability** Potentially serious limitations; partial applicability. **Data sources:** Occurrence of admissions and LOS from the NHS-wide clearing service; data on drugs from hospital case notes, GP and patients' questionnaires; unit costs from published studies and pricing lists for the UK **Notes:** * based on the adjusted mean difference of QALYs (0.24 vs Group 1 and 0.39 vs Group 3) and costs (£3,820 vs Group 1 and £7,255 vs group 3).
			Number of patients with angina at 6 years	**Group 1:** 61/102 (60%) **Group 2:** 52/89 (58%) **Group 3:** 82/119 (69%) **p value:** Adjusted odd ratio not sig	
			Number of patients experiencing non-fatal myocardial infarction at 6 years	**Group 1:** 19 (11%) **Group 2:** 15 (10%) **Group 3:** 16 (8%) **p value:** NR	
			Number of patients having further revascularisation at 6 years	**Group 1:** 47 (27%) **Group 2:** 9 (6%) **Group 3:** 83 (42%) **p value:** NR	
			Number of patients admitted for chest pain at 6 years	**Group 1:** 73 (42%) **Group 2:** 58 (39%) **Group 3:** 82 (41%) **p value:** NR	
			Discounted mean QALYs (SD) over 6 years	**Group 1:** 2.93 (1.65) (n=127) **Group 2:** 3.13 (1.37) (n=114) **Group 3:** 2.83 (1.39) (n=164) **p value:** NR	
			Discounted mean cost per patient over 6 years 2004 GBP, cost of intervention, angiography, hospital stay, drugs, admissions for chest pain, GP and outpatient visits, visits to the emergency department.	**Group 1:** 14,007 (SD 10,453) **Group 2:** 17,859 (SD 6,940) **Group 3:** 10,690 (SD 7,888) **p value:** Sig	
			Cost-effectiveness incremental cost per QALY gained	Group 1 vs 3: £22,900/QALY* Group 2 vs 1: £15,917/QALY* Group 2 vs 3: £18,603/QALY*	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
			Sensitivity analysis	For patients deemed appropriate for CABG only, the ICERs become: Group 1 vs 3 £10,560/QALY Group 2 vs 1 £21,533/QALY Group 2 vs 3 £14,675/QALY For patients deemed appropriate for PCI only, CABG is dominated and the ICER of Group 1 vs 3 is £47,450. At a threshold of £20,000/QALY all the strategies have a similar probability of being cost-effective.	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Hambrecht 2004[6] Germany **Economic analysis:** cost-consequences analysis **Study design** RCT **Duration of follow-up:** 1 year **Perspective:** Health care provider **Discount rates:** Costs: NA Effects: NA	**Patient group: male** patients aged 70 years or less with stable CAD and one native coronary artery stenosis of at least 75% by visual assessment amenable to PCI; class I to II of angina with documented myocardial ischemia. Patients who had CABG or PCI within the last 12 months were excluded. **<u>All patients</u>** **N:** 101 **Age (mean):** **M/F:** 101/0 **Drop outs:** 4 **<u>Group 1</u>** **N:** 50 **Age (mean):** 60±1 **M/F:** 50/0 **Drop outs:** 2 **<u>Group 2</u>** **N:** 51 **Age (mean):** 62±1 **M/F:** 50/0 **Drop outs:** 2	**Group 1:** Stent angioplasty **Group 2:** Exercise training. During the first two weeks patients exercised in the hospital 6 times per day for 10 minutes on a bicycle ergometer at 70% of the symptom-limited maximal heart rate. At discharge, patients were asked to exercise for 20 minutes per day and to participate in one 60-minute group training session of aerobic exercise per week.	Number of deaths of cardiac causes	**Group 1:** 0 **Group 2:** 0 **p value:** NA	**Funding/conflict of interest:** Unconditional scientific grant from Aventis, Germany. **Limitations:** A breakdown of costs was not provided. An overall summary of cost-effectiveness was provided only in the text. **Overall quality and applicability** Potentially serious limitations; partial applicability. **Additional outcomes:** To gain 1CCS class, the cost was $6956 (£4,396) in the angioplasty group and $3429 (£2,167) in the exercise group.
			Number of cerebrovascular accidents (%)	**Group 1:** 3 (6%) **Group 2:** 2 (3.9%) **p value:** Not sig	
			Number of revascularisation (%), including CABG, PTCA of target lesion as event and PTCA of other coronary segments as event	**Group 1:** 10 (20%) **Group 2:** 3 (5.9%) **p value:** Not sig	
			Hospitalisation and coronary angiography	**Group 1:** 7 (14%) **Group 2:** 1 (2%) **p value:** Not sig	
			Mean cost per patient (±SE) 2003 USD, cost of interventions including hospital charges, expenses for supervised training sessions, bicycle ergometer, coronary angiographies, and rehospitalisation.	**Group 1:** $6,086 (±370) (£3,846) **Group 2:** $3,708 (±156) (£2,344) **p value:** <0.001	
			Cost-effectiveness	NR	
			Sensitivity analysis	NR	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Henderson 1998[7] UK **Economic analysis:** Cost consequences analysis **Study design** RCT* **Duration of follow-up:** 6.5 years (median) **Perspective:** NHS **Discount rates:** Costs: 6% Effects: NR	**Patient group:** Patients with angina, with single- or multi-vessel disease, in whom equivalent revascularisation could be achieved by either CABG or PTCA. **<u>All patients</u>** **N:** 1011 **Age (mean):** NR (the majority was in the range 50-59) **M/F:** 815/196 **Drop outs:** 28 **<u>Group 1</u>**** **N:** 510 **Age (mean):** NR **M/F**: NR **Drop outs:** 17 **<u>Group 2</u>**** **N:** 501 **Age (mean):** NR **M/F**: NR **Drop outs:** 11	**Group 1:** PTCA without stents. Stents were used in only 14 PTCAs. **Group 2:** CABG	Number of patients dead at follow-up	**Group 1:** 39 (7.6%) **Group 2:** 45 (9.0%) **p value:** 0.51	**Funding/conflict of interest:** UK Department of Health; British Heart Foundation and the British Cardiac Society. **Limitations:** Not an incremental analysis. HRQoL was not assessed. **Overall quality and applicability** Potentially serious limitations; partial applicability. **Data sources:** Unit costs taken from one London centre and one centre from elsewhere. **Notes:** * based on the RITA-1 trial ** An intention-to-treat analysis was performed.
			Number of patients experiencing non-fatal myocardial infarction	**Group 1:** 55 (10.8%) **Group 2:** 37 (7.4%) **p value:** 0.08	
			Number of patients having repeated revascularisation (either PTCA or CABG) at follow-up	**Group 1:** 226 (44.3%) **Group 2:** 54 (10.8%) **p value:** NR	
			Patients with improved or no angina between 1-year and 5-year follow-up visits	**Group 1:** 312/461 (67.8%) **Group 2:** 334/446 (74.9%) **p value:** NR	
			Discounted mean cost per patient at 5 years 1997 GBP, cost of initial procedure, subsequent procedures, other inpatient care, medications.	**Group 1:** £8,842 (SD £7,516) **Group 2:** £9,268 (SD £5,384) **p value:** Not sig	
			Cost-effectiveness	NR	
			Sensitivity analysis One-way SA	When a 3% discount rate was used the costs of PTCA were 96% of the costs of CABG; if no discount rate is used the ratio is 98% (cost difference not statistically significant at any of these rates)	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Hlatky 2009[8] USA **Economic analysis:** Cost-utility analysis **Study design** Multi-centre RCT* **Duration of follow-up:** 4 years **Perspective:** Healthcare provider **Discount rates:** Costs: 3% Effects: NR	**Patient group:** patients with type 2 diabetes mellitus and stable, angiographically documented coronary disease. **<u>All patients</u>** **N:** 2005 **Drop outs:** 1323** **<u>Group 1</u>** **N:** 988 **<u>Group 2</u>** **N:** 1017	**Group 1:** Early revascularisation with a) CABG b) PCI as decided by the physician **Group 2:** Medical therapy	Life years***	**a) CABG stratum** **Group 1:** 3.56 **Group 2:** 3.59 **p value:** NR **b) PCI stratum** **Group 1:** 3.58 **Group 2:** 3.65 **p value:** NR	**Funding/conflict of interest:** National Heart, Lung and Blood Institute, GlaxoSmithKline, Lantheus Medical Imaging, Astellas Pharma, Merck & Co, Abbott Laboratories, Pfizer, MediSense Products, Bayer Diagnostics, Becton, Dickinson and Co, J.R. Carlson Labs, Centocor Inc, Eli Lilly, lipoScience, Merck Sante, Novartis, Novo Nordisk. **Limitations:** Not clear how utilities were used to calculate results in the study. In the clinical paper the probability of cardiovascular events was lower in the CABG stratum (inconsistent with the QALYs calculation). QALYs were not adjusted by baseline values. **Overall quality and applicability** Potentially serious limitations; partial applicability. **Additional outcomes:** A regression analysis showed the baseline factors that affected cumulative costs at 2 years (intervention assigned, use of insulin, baseline HbA level, gender, body mass index). None of these factors had a significant interaction with treatment assignment. **Notes:** *Based on the BARI 2D trial.
			QALY ***	**a) CABG stratum** **Group 1:** 3.267 **Group 2:** 3.274 **p value:** NR **b) PCI stratum** **Group 1:** 3.221 **Group 2:** 3.248 **p value:** NR	
			Mean 4 year cost per patient # 2007 USD, hospitalisation, outpatient visits, nursing home/rehab, medications, test and procedure. Hospital costs calculated using a ratio of cost to charges.	**a) CABG stratum** **Group 1:** $124,400 (£69,115) **Group 2:** $103,600 (£57,560) **p value:** NR **b) PCI stratum** **Group 1:** $106,300 (£59,060) **Group 2:** $96,400 (£53,560) **p value:** NR	
			Cost-effectiveness incremental cost per QALY gained	Medical therapy is dominant.	
			Sensitivity analysis	Medical therapy was not dominant but still cost-effective when: - results were extrapolated to lifetime assuming costs after 4 years are the same in the 2 groups - QALYs were adjusted by baseline values	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
				- a reduced survival after MI (2 and 3 years) and after non-fatal stroke (3 years) was assumed When cost differences persist indefinitely medical treatment is reported to be less cost-effective (counterintuitive).	** At the end of follow-up economic outcomes were available for 34% of the participants. *** PCI stratum results only (n=667 Group1, n=680 Group 2) # 2008 GBP obtained by using the purchasing power parities and GDP deflator indexes (http://eppi.ioe.ac.uk/costconversion/default.aspx)

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Legrand 2004[9] The Netherlands **Economic analysis:** Cost-effectiveness analysis **Study design** RCT* **Duration of follow-up:** 3 years **Perspective:** Healthcare provider **Discount rates:** Costs: NR Effects: NR	**Patient group:** Patients with multivessel disease** **<u>All patients</u>** **N:** 1205 **Age (mean):** 61 **M/F:** 922/283 **Drop outs:** 6*** **<u>Group 1</u>** **N:** 600 **Age (mean):** 61 **M/F:** 462/138 **Drop outs:** NR **<u>Group 2</u>** **N:** 605 **Age (mean):** 61 **M/F:** 460/145 **Drop outs:** NR	**Group 1:** Stent **Group 2:** CABG	Number of patients dead at 3 years	**Group 1:** 22 (3.7%) **Group 2:** 28 (4.6%) **p value:** Not Sig	**Funding/conflict of interest:** NR **Limitations:** Baseline quality of life was not reported. Number of patients and percentages reported do not match. Unclear if discounting was applied to costs and effects. **Overall quality and applicability** Potentially serious limitations; partial applicability. **Additional outcomes:** At 3 years patients in Group 2 had significantly less angina (12.8% vs 18.4%, P=0.011) and lower rate of use of antianginal medications (65.4% vs 78.4%, P<0.001). **Notes:** * based on the ARTS trial. ** both stable and unstable angina patients ***1 lost to follow-up, 3 withdrew consent, 2 never treated by either modality.
			Number of patients experiencing cardiovascular accident at 3 years	**Group 1:** 20 (3.3%) **Group 2:** 20 (3.3%) **p value:** Not sig	
			Number of patients experiencing myocardial infarction at 3 years	**Group 1:** 44 (7.3%) **Group 2:** 34 (5.7%) **p value:** Not sig	
			Number of patients having repeated procedure (either PCI or CABG) at 3 years	**Group 1:** 175 (29.2%) **Group 2:** 44 (7.3%) **p value:** Sig	
			Number of event-free patients still alive at 1 year	**Group 1:** 395 (65.8%) **Group 2:** 504 (83.3%) **p value:** <0.0001	
			Summary of EQ-5D score at 3 years (mean ± SD)	**Group 1:** 85 ± 17 **Group 2:** 86 ± 17 **p value:** 0.74	
			Mean cost per patient over 3 years 1998 Euro, diagnostic tests, devices and material, procedures, hospital stay, medications, rehabilitation.	**Group 1:** €14,302 (£10,183) **Group 2:** €16,100 (£11,463) **p value:** 0.0001	
			Cost-effectiveness Incremental cost for additional event-free patient	Group 2 vs Group 1: €10, 492 (£7,470) 95%CI €3,722 – €20,772 (£2,650–£14,790)	
			Sensitivity analysis One-way SA	The ICER is less favourable to CAGB when repeated procedure is excluded as an efficacy end point or when a shorter follow-up (1 year) is considered.	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
McKenna 2009[10] UK **Economic analysis:** CUA **Study design** Decision analysis based on the MUST-EECP RCT. **Time horizon:** lifetime **Perspective:** UK NHS and Personal Social Services **Discount rates:** Costs:3.5% Effects: 3.5%	**Patient group:** patients with angina with an average age of 64 years.	**Intervention 1:** No treatment **Intervention 2:** EECP	QALY	**Int 1:** 7.237 **Int 2:** 7.492 **p value:** NR	**Funding/conflict of interest:** HTA programme **Limitations:** The analysis was based on limited data (one small RCT). Utilities were obtained from an algorithm converting SF-36 to EQ-5D. Durability of benefits obtained from expert opinion. The model does not consider: the effect of intervention on mortality or MI, the cost of escalating medical treatment over time, costs associated with no intervention. Only 20% of the patients in the EUROPA trial had angina and they could have a different mortality compared to refractory angina patients. **Overall quality and applicability** Potentially serious limitations; direct applicability. **Additional outcomes:** At a threshold £20k/QALY individual patient EVPI is £971 and population EVPI is £107,556,668. **Data sources:** Based on the MUST-EECP (Arora 1999 and 2002). QoL improvement calculated as EQ-5D scores using an algorithm to convert the SF-36 scores into EQ-5D. QoL after one year was estimated with expert elicitation techniques (frequency chart). Mortality data from CVD causes obtained from the EUROPA trial. General mortality based on standard UK rates adjusted to exclude CVD deaths. Cost data from personal communication and price list of supplier.
			Mean cost per patient 2008 GBP, capital cost of EECP machine, equipment replacement costs, consumables, staffing costs, overheads, repeat operations.	**Int 1:** 0 **Int 2:** 4,750 **p value:** NR	
			Cost-effectiveness Cost per QALY gained	Int 2 vs Int 1: £18,643/QALY	
			Sensitivity analysis One-way SA:	Ranges of ICER calculated varying the following: Probability of sustaining QoL benefits over time from separate expert opinion: £10,664 - £28,158. Cost of EECP per patient increased/decreased by £1000: £14,353 - £22,932. Results not sensitive to the rate of repeat EECP within two years (varied from 10% to 30%), subgroup analysis of women/men and different ages; discount rates 6% for costs and 1.5% for outcomes.	
			Worst-case/best-case scenario	When QoL benefits from EECP are only sustained in the first year, the ICER =£63,000. When QoL benefits are sustained over a lifetime, the ICER = £5,830	
			Monte Carlo simulation	Probability of being cost-effective at £20k/QALY threshold: 44.4% EECP.	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
O'Neill 1996[11] UK **Economic analysis:** cost-consequences analysis **Study design** RCT[12,13] **Duration of follow-up:** 2 years **Perspective:** NHS **Discount rates:** Costs: NR Effects: NR	**Patient group:** patients in the Belfast area aged less than 75 years and known to have angina for at least 6 months **<u>All patients</u>** **N:** 688 **Drop outs:** 29 **<u>Group 1</u>** **N:** 342 **Age (mean):** 62.7 (SD 7.1) **M/F:** 203/139 **Drop outs:** 12 **<u>Group 2</u>** **N:** 346 **Age (mean):** 63.6 (SD 6.8) **M/F:** 205/141 **Drop outs:** 17	**Group 1:** Three visits per year from a health visitor whose brief was discuss ways of living more easily with their disease and in which risks of further events might be reduced. **Group 2:** control	**Number of deaths**	**Group 1:** 13 (3.8%) **Group 2:** 29 (8.4%) **p value:** Not sig	**Funding/conflict of interest:** Medical Research Council. **Limitations:** Unclear whether the costs are per patient over two years. Old study, medical treatment might have not been optimal at that time. Unclear what intervention the control group received. Not all the important outcomes were evaluated (e.g. angina symptoms, MI). **Overall quality and applicability** Potentially serious limitations; partial applicability.
			Mean cost per patient 1996 GBP, Cost of intervention (staff time and travel related costs), drugs, GP visits, hospital visits (inpatient and outpatient), tests and other treatments.. Community care costs were excluded.	**Group 1:** £1,851 **Group 2:** £1,812 **p value:** Not sig	
			Cost-effectiveness	NR	
			Sensitivity analysis	NR	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Sculpher 1994[14] UK **Economic analysis:** cost consequences analysis **Study design** RCT [a] **Duration of follow-up:** 2 years **Perspective:** **Discount rates:** Costs: 6% Effects: NA	**Patient group:** patients with arteriographically proven coronary artery disease requiring revascularisation. Patients with previous PTCA or CABG were excluded. **<u>All patients</u>** **N:** 1011 **<u>Group 1</u>** **N:** 510 [b, c] **<u>Group 2</u>** **N:** 501 [b, c]	**Group 1:** Percutaneous transluminal coronary angioplasty (PTCA) **Group 2:** Coronary artery bypass grafting (CABG)	Number of patients dead at 2 years	**Group 1:** 13 (2.5%) **Group 2:** 9 (1.8%) **p value:** Not sig	**Funding/conflict of interest:** British Heart Foundation, British Cardiac Society, and Department of Health; ACS UK (Basingstoke, Nats), Medtronic Ltd (Watford, Herts), Schneider (Staines, Middx). **Limitations:** Not an incremental analysis. HRQoL was not assessed. **Overall quality and applicability** Potentially serious limitations; partial applicability. **Data sources:** Hospital unit costs from two hospitals (one in London, one outside). Drugs cost from BNF. **Notes:** [a] based on the RITA trial [b] cost data were missing for 6 patients. [c] ITT analysis: in the CABG group 5 patients had PCTA and 6 no intervention; in the PTCA group 7 patients had CABG, 29 PTCA and CABG in the same admission, and 10 no intervention. [c] Data from non-London centre
			Number of patients experiencing non-fatal myocardial infarction at 2 years	**Group 1:** 32 (6.3%) **Group 2:** 25 (4.9%) **p value:** Not sig	
			Number of patients with no angina at 1 year	**Group 1:** 343 (69.1%) **Group 2:** 398 (82.9%) **p value:** <0.0001	
			Number of patients with no angina at 2 years	**Group 1:** 328 (64.3%) **Group 2:** 373 (79.1%) **p value:** 0.0023	
			Mean cost per patient over 2 years [d] 1994 GBP, cost of procedures, admissions, reoperations, coronary arteriograms, hospital stay for reasons not related to revascularisation, antianginal medications.	**Group 1:** £5,448 (SE £173) **Group 2:** £6,498 (SE £134) **p value:** Sig	
			Cost-effectiveness	NR	
			Sensitivity analysis	The difference in cost was £1823 (sig) when data from the London hospital were used; £1145 in the single vessel disease subgroup; £970 in the multiple vessel disease subgroup.	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Sculpher 2002[15] UK **Economic analysis:** Cost consequences analysis. **Study design** RCT* **Duration of follow-up:** 3 years **Perspective:** NHS **Discount rates:** Costs: 6% Effects: NA	**Patient group:** patients with arteriographically proven coronary artery disease recruited from 20 centres in the UK and Ireland and suitable for both continued medical therapy and PTCA. **<u>All patients</u>** **N:** 1018 **Age (mean):** **M/F:** **Drop outs:** **<u>Group 1</u>**** **N:** 514 **Age (mean):** **M/F:** **Drop outs:** **<u>Group 2</u>**** **N:** 504 **Age (mean):** **M/F:** **Drop outs:**	**Group 1:** Medical management with possible discontinuation if a patient no longer had angina symptoms. **Group 2:** PTCA. Stents and other coronary interventional techniques were only used if initial revascularisation with balloon angioplasty was unsatisfactory.	Number of deaths at 3 years	**Group 1:** 9 (1.8%) **Group 2:** 14 (2.8%) **p value:** 0.3***	**Funding/conflict of interest:** British Heart Foundation; Medical Research Council; Advanced Cardiovascular Systems Inc. (USA), Interventions (UK), Cordis Ltd, Schneider (UK) and Nycomed Ltd. **Limitations:** Utility values were not estimated. No incremental analysis was conducted. Stents were not used in the primary intervention. **Overall quality and applicability** Minor limitations; partial applicability. **Data sources:** Unit costs from five UK hospitals in different locations and national sources. Cost of drugs from the Prescription Pricing Authority. **Notes:** * based on RITA-2[16] ** ITT analysis: 471 of group 2 underwent the randomised PTCA. *** calculated by NCGC using a two-tailed Fisher's exact test
			Number of deaths and MI at 3 years	**Group 1:** 21 (4.1%) **Group 2:** 37 (7.3%) **p value:** 0.025	
			Patients with grade 2 or worse angina at 1 year	**Group 1:** 139 (27.4%) **Group 2:** 83 (17.0%) **p value:** 0.001	
			Patients with grade 2 or worse angina at 3 years	**Group 1:** 106 (21.5%) **Group 2:** 93 (19.5%) **p value:** 0.43	
			Number of subsequent revascularisation (CABG or PTCA) at 3 years	**Group 1:** 155 **Group 2:** 111 **p value:** NR	
			Mean cost per patient 1999 GBP, cardiac procedures, in-hospital stay, subsequent procedures, GP and outpatient visits, antianginal and cardiac drugs	**Group 1:** £3,613 **Group 2:** £6,299 **p value:** Sig	
			Cost-effectiveness	NR	
			Sensitivity analysis Subgroup analysis One-way SA	Similar results when patients were stratified by CCS score, breathlessness, exercise time, and overall score. Similar results when no discount rate is applied, the cost of visits for non-cardiac reasons is excluded, or when unit costs from the 5 hospitals are used separately.	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Walker 2006[17] UK **Economic analysis:** Cost-effectiveness analysis **Study design** RCT **Duration of follow-up:** 1.6 years **Perspective:** UK NHS **Discount rates:** Costs: 0% Effects: 0%	**Patient group:** high risk angina patients participating in the IONA trial[18]. **<u>All patients</u>** **N:** 5126 **<u>Group 1</u>** **N:** 2561 **<u>Group 2</u>** **N:** 2565	**Group 1:** Placebo + usual care **Group 2:** Nicorandil + usual care Usual care was 57% beta-blockers, 56% calcium channel blockers, 87% nitrates, 88% aspirin.	Primary end points averted (coronary heart disease death, non-fatal myocardial infarction, hospital admission for cardiac chest pain)*	**Group 2 - Group 1:** 2.4% **p value:** NR	**Funding/conflict of interest:** Merck KGaA **Limitations:** Effectiveness data were reported only in the incremental analysis. SA was made only on the primary analysis (cost of care after discharge excluded). HRQoL was not assessed. **Overall quality and applicability** Potentially serious limitations; partial applicability. **Data sources:** Resources used from RCT[18]. Cost of units from national sources. **Notes:** * calculated by NCGC from the incremental analysis
			Cases of definite acute coronary syndromes (coronary heart disease death, non-fatal myocardial infarction or unstable angina)*	**Group 2 - Group 1:** 1.5% **p value:** NR	
			Number of people free from any major cardiovascular event (coronary heart disease death, non-fatal myocardial infarction, unstable angina, definite or probable angina, stroke or hospital admission for transient ischaemic attack).	**Group 1:** 2069 (80.8%) **Group 2:** 2136 (83.3%) **p value:** NR	
			Mean cost per patient 2002 GBP, cost of nicorandil (including 10% dispensing fee and two additional physician visits), adverse events related to nicorandil, hospital admissions, surgical procedures	**Group 1:** 243.7 **Group 2:** 243.6 **p value:** NR	
			Cost-effectiveness Cost per additional unit of effectiveness	Nicorandil+usual care was dominant for all the three outcomes considered	
			Sensitivity analysis One-way SA	Nicorandil is more costly than usual care when: - cost of care after discharge is included - either cost of cardiology, cardiac surgery or ICU is reduced by 20%	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Weintraub 1995[19] USA **Economic analysis:** Cost consequences analysis **Study design** RCT* **Duration of follow-up:** 3 years **Perspective:** Health care provider **Discount rates:** Costs: NR Effects: NR	**Patient group:** patients with multivessel coronary artery disease (60% two-vessel disease and 40% three-vessel disease) **<u>All patients</u>**** **N:** 392 **M/F:** 289/103 **Diabetes:** 90 **Prior MI:** 160 **Drop outs:** 8 **<u>Group 1</u>** **N:** 198 **Age (mean±CI):** 62±10 **M/F:** 148/50 **Diabetes:** 49 **Prior MI:** 81 **Drop outs:** 2 **<u>Group 2</u>** **N:** 194 **Age (mean±CI):** 61±10 **M/F:** 141/53 **Diabetes:** 41 **Prior MI:** 79 **Drop outs:** 6	**Group 1:** PTCA **Group 2:** CABG	Number of in-hospital deaths	**Group 1:** 2 (1%) **Group 2:** 2 (1%) **p value:** Not sig	**Funding/conflict of interest:** Grant from the National Heart, Lung and Blood Institute. **Limitations:** Other direct medical costs (e.g. medications) were not included. Costs were calculated based on charges. The authors note that costs and outcomes of procedures could vary over time. Costs from one US hospital only. HRQoL was not assessed. **Overall quality and applicability** Potentially serious limitations; partial applicability. **Additional outcomes:** Proportions of patients with overall good health, complete recovery, same economic status than before, returned to work, retired after procedure were not statistically different in the two groups. **Data sources:** Costs were calculated from hospital charges applying the cost-to-charge ratios. **Notes:** * Based on the EAST trial ** Intention-to-treat analysis
			Number of in-hospital MI	**Group 1:** 6 (3%) **Group 2:** 20 (10.3%) **p value:** 0.005	
			Number of deaths during 3-year follow-up	**Group 1:** 14 (7.1%) **Group 2:** 12 (6.2%) **p value:** Not sig	
			Number of MI during 3-year follow-up	**Group 1:** 29/173 (14.6%) **Group 2:** 38/172 (19.6%) **p value:** Not sig	
			Patients requiring additional procedures during follow-up	**Group 1:** 89 (45%) **Group 2:** 25 (13%) **p value:** <0.0001	
			Proportion of patients in angina class 0 – 1 – 2 – 3 – 4 at 3 years.	**Group 1:** 76% - 4% - 7% - 5% - 7% **Group 2:** 86% - 2% - 5% - 1% - 6% **p value:** 0.056	
			Proportion of patients on 0 – 1 – 2 – 3 antianginal medication	**Group 1:** 34% - 47% - 17% - 2% **Group 2:** 49% - 39% - 10% - 2% **p value:** 0.029	
			Mean cost per 3-year procedure 1987 USD, hospital costs and physician charges.	**Group 1:** $23,735 (£13,078) **Group 2:** $25,310 (£13,946) **p value:** <0.0001	
			Cost-effectiveness	NR	
			Sensitivity analysis	When costs were inflated to 1993 USD or when charges were used instead of costs, the overall results did not change. The two interventions had similar costs (difference not sig) in patients with triple vessel disease with ≥50% diameter luminal narrowing in more than one site in at least one affected vessel. Multiple regression analysis: the surgical group was strongly correlated with initial hospital costs but it was not correlated with 3-year cumulative costs.	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Weintraub 2000[20] USA **Economic analysis:** Cost consequences analysis **Study design** RCT* **Duration of follow-up:** 8 years **Perspective:** Health care provider **Discount rates:** Costs: 3% Effects: NR	**Patient group:** patients with multivessel coronary artery disease (60% two-vessel disease and 40% three-vessel disease) **<u>All patients</u>**** **N:** 392 **M/F:** 289/103 **Diabetes:** 90 **Prior MI:** 160 **Drop outs:** 8 **<u>Group 1</u>** **N:** 198 **Age (mean±CI):** 62±10 **M/F:** 148/50 **Diabetes:** 49 **Prior MI:** 81 **Drop outs:** 2 **<u>Group 2</u>** **N:** 194 **Age (mean±CI):** 61±10 **M/F:** 141/53 **Diabetes:** 41 **Prior MI:** 79 **Drop outs:** 6	**Group 1:** PTCA **Group 2:** CABG	Number of deaths during 8-year follow-up	**Group 1:** 41 (20.7%) **Group 2:** 34 (17.3%) **p value:** 0.40	**Funding/conflict of interest:** NR **Limitations:** Other direct medical costs (e.g. medications) were not included. Costs were calculated based on charges. The authors note that costs and outcomes of procedures could vary over time. Costs from one US hospital only. HRQoL was not assessed. **Overall quality and applicability** Potentially serious limitations; partial applicability. **Data sources:** Costs were calculated from hospital charges applying the cost-to-charge ratios. **Notes:** * Based on the EAST trial ** Intention-to-treat analysis *** cost data available for 197 patients in Group 1 and 189 in Group 2.
			Discounted mean cost per 8-year procedure*** 1997 USD, hospital costs and physician charges.	**Group 1:** $43,758 (£27,786) **Group 2:** $46,225 (£29,353) **p value:** 0.29	
			Cost-effectiveness	NR	
			Sensitivity analysis	NR	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Weintraub 2004[21] UK **Economic analysis:** Cost-utility analysis **Study design** RCT** **Duration of follow-up:** One year **Perspective:** UK NHS **Discount rates:** Costs: NA Effects: NA	**Patient group:** patients with multivessel disease **<u>All patients</u>** **N:** 988 **<u>Group 1</u>** **N:** 488 **<u>Group 2</u>** **N:** 500	**Group 1:** Stent assisted PCI **Group 2:** CABG	Mortality rate	**Group 1:** 2.5% **Group 2:** 0.8% **p value:** 0.05	**Funding/conflict of interest:** consortium of stent manufacturers: Medtronic, Switzerland; Guidant, USA; Boston Scientific, Germany **Limitations:** Very short follow-up. Utility data were missing at one or more time points for 30% of the overall sample. No sensitivity analysis was conducted. **Overall quality and applicability** Potentially serious limitations; partial applicability. **Data sources:** Resources used calculated for all the patients in the trial. Costs per unit were obtained from BNF and NHS reference costs. Utilities were estimated from participants using EQ-5D scores. **Notes:** * based on the SoS trial **utility was imputed when missing at one or more of the three time points for 30% of the overall sample. ***calculated by NCGC
			Repeat revascularisation	**Group 1:** 17.2% **Group 2:** 4.2% **p value:** <0.001	
			QALY at one year**	**Group 1:** 0.6938 **Group 2:** 0.6954 **p value:** not sig	
			Mean cost per patient 2004 GBP, cost of hospitalisation, procedure, ward, complications, follow-up, readmission, rehabilitation, medications.	**Group 1:** 6,296 **Group 2:** 8,905 **p value:** sig	
			Cost-effectiveness*** incremental cost per QALY gained	Group 2 vs Group 1: £1,630,525	
			Sensitivity analysis	NR	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Weintraub 2008[22] USA **Economic analysis:** Cost-utility analysis **Study design** RCT* **Duration of follow-up:** 4.6 years 3 years for costs **Perspective:** Healthcare provider **Discount rates:** Costs: 3% Effects: 3%	**Patient group:** patients with stable coronary artery disease with >70% stenosis in at least one major epicardial coronary artery with objective evidence of myocardial ischemia or at least one coronary stenosis >80% and classic angina without provocative testing. **<u>All patients</u>** **N:** 2287 **Age (mean):** 62 **M/F:** 1947/340 **Previous MI:** 876 **Angina**: 88% **Multivessel disease**: 69% **Drop outs:** 0 **<u>Group 1</u>** **N:** 1149 **Age (mean):** 62 **M/F**: 979/170 **Previous MI:** 437 **Utility**: 0.90 (95% CI ±0.20) (n=775) **Drop outs:** 0 **<u>Group 2</u>** **N:** 1138 **Age (mean):** 62 **M/F**: 968/170 **Previous MI:** 439 **Utility**: 0.87 (95% CI ±0.22) (n=748) **Drop outs:** 0	**Group 1:** PCI – Stents and angioplasty **Group 2:** Medical therapy	Utility estimated by Standard Gamble at 1 month – mean ± 95%CI	**Group 1:** 0.92±0.19 (n=665) **Group 2:** 0.91±0.20 (n=699) **p value:** 0.66	**Funding/conflict of interest:** Dept of Veterans Affairs, Canadian Institutes for Health research; Merck&Co; Pfizer; Bristol-Myers Squibb Medical Imaging; Kos Pharmaceuticals; Data Scope; Astra Zeneca; Key Pharmaceutical, Sanofi-Aventis; First Horizon; Nycomed Amersham. **Limitations:** Valuation of utilities not obtained from public but from patients. Patients in the study were low risk. Effectiveness was estimated for the total duration of the trial (4.6 years) while costs only for 3 years. These results were combined. PCI group included angioplasty too. **Overall quality and applicability** Minor limitations; partial applicability. **Notes:** * based on the COURAGE trial[23] ** 2008 GBP obtained by using the purchasing power parities and GDP deflator indexes (http://eppi.ioe.ac.uk/costconversion/default.aspx)
			Utility estimated by Standard Gamble at 3 months – mean ± 95%CI	**Group 1:** 0.93±0.17 (n=669) **Group 2:** 0.92±0.19 (n=678) **p value:** 0.008	
			Utility estimated by Standard Gamble at 6 months – mean ± 95%CI	**Group 1:** 0.93±0.17 (n=701) **Group 2:** 0.93±0.15 (n=665) **p value:** 0.20	
			Utility estimated by Standard Gamble at 1 year – mean ± 95%CI	**Group 1:** 0.93±0.17 (n=648) **Group 2:** 0.93±0.15 (n=636) **p value:** 0.53	
			Utility estimated by Standard Gamble at 2 years – mean ± 95%CI	**Group 1:** 0.93±0.17 (n=550) **Group 2:** 0.92±0.17 (n=532) **p value:** 0.59	
			Utility estimated by Standard Gamble at 3 years – mean ± 95%CI	**Group 1:** 0.92±0.20 (n=385) **Group 2:** 0.90±0.21 (n=379) **p value:** 0.004	
			Discounted in-trial life years – mean ± 95%CI	**Group 1:** 4.15±1.50 **Group 2:** 4.12±1.51 **p value:** 0.03	
			Discounted in-trial QALYs – mean ± 95%CI	**Group 1:** 3.56±1.34 **Group 2:** 3.51±1.36 **p value:** 0.05	
			Mean cost per patient over 3 years** 2004 USD, hospitalisation, PCI, medication, outpatient services.	**Group 1:** $34,843 (£21,247) **Group 2:** $24,718 (£15,073) **p value:** Sig (95% CI of difference is always positive)	
			Cost-effectiveness** Incremental cost per QALY gained	PCI vs Medical Treatment: $206,229 (£125,759)	
			Sensitivity analysis Structural SA	Extrapolating beyond RCT follow-up: PCI is still significantly more	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
				costly and more effective (not sig); If drug-eluting stents are used, they assumed no revascularisation after PCI, added cost of $600 in the initial PCI and clopidogrel for one year, PCI would not be cost-effective (ICER=$197,465).	
			One-way SA	Life-years gained with PCI was varied from -40% to +40% → PCI still not cost-effective.	
			Threshold analysis	To achieve an ICER<$50,000/QALY, PCI would need to improve QALYs by 0.60.	
			PSA	Ranges of incremental QALY with PCI -0.5 to 0.5; incremental costs $4,000 to $16,000. At a $50k/QALY threshold PCI has a 25% probability of being cost-effective.	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Zhang 2006[24] UK **Economic analysis:** cost-consequences analysis **Study design** RCT* **Duration of follow-up:** 1 year **Perspective:** Hospital **Discount rates:** Costs: NA Effects: NA	**Patient group:** symptomatic patients with typical angina and multivessel disease eligible for both CABG and PCI. **<u>All patients</u>** **N:** 395 **Age (range):** NR **M/F:** 296/99 **Drop outs:** 0 **<u>Group 1</u>** **N:** 190 **Age (mean):** 70.4 **M/F:** 136/54 **Drop outs:** 0 **<u>Group 2</u>** **N:** 205 **Age (mean):** 70.6 **M/F:** 150/55 **Drop outs:** 0	**Group 1:** Stent-assisted PCI **Group 2:** CABG	Number patients dead at 1 year (%)	**Group 1:** 4 (2.1%) **Group 2:** 1 (0.5%) **p value:** 0.168	**Funding/conflict of interest:** NR **Limitations:** Source of costs not clear. No incremental analysis was conducted. Short follow-up. **Overall quality and applicability** Potentially serious limitations; partial applicability. **Additional outcomes:** In-hospital death, myocardial infarction, bleeding and cerebrovascular accident were not significantly different in the two groups. Average LOS was 13.2 days in group 2 vs 5.4 days in group 1 (Sig). **Data sources:** UK unit costs were applied to resource use recorded in the trial **Notes:** * based on the SoS trial ** scores of the Seattle Angina Questionnaire (SAQ) range from 0 to 100. A clinically important change is between 5 and 8 points. *** The difference was £2,948 (95% CI £1,432 – £4,198)
			Number of patients experiencing Q-wave myocardial infarction at 1 year (%)	**Group 1:** 13 (6.8%) **Group 2:** 17 (8.3%) **p value:** 0.998	
			Number of patients experiencing bleeding at 1 year (%)	**Group 1:** 3 (1.6%) **Group 2:** 5 (2.4%) **p value:** 0.219	
			Number of patients experiencing cerebrovascular accidents at 1 year (%)	**Group 1:** 5 (2.6%) **Group 2:** 5 (2.4%) **p value:** 0.388	
			Number of patients having a repeat revascularisation (%)	**Group 1:** 37 (19.5%) **Group 2:** 7 (3.4%) **p value:** <0.0001	
			Adjusted improvement in SAQ Quality of Life score at 6 months**	**Group 1:** 25.5 **Group 2:** 30.5 **p value:** 0.0335	
			Adjusted SAQ Quality of Life score at 1 year**	**Group 1:** 30.7 **Group 2:** 32.1 **p value:** 0.5601	
			Mean cost per patient 2000 GBP, cost of hospitalisation and follow-up	**Group 1:** £6,611 **Group 2:** £9,559 **p value:** Sig***	
			Cost-effectiveness	NR	
			Sensitivity analysis	Results were similar for younger patients (≤65 years).	

All non-UK costs converted into GBP using the Purchasing Power Parities[25].

Reference List

1 Abizaid A, Costa MA, Centemero M, et al. Clinical and economic impact of diabetes mellitus on percutaneous and surgical treatment of multivessel coronary disease patients: insights from the Arterial Revascularization Therapy Study (ARTS) trial. Circulation 2001 Jul 31;104:533-8.

2 Borghi J, Guest JF. Economic impact of Elantan LA compared to Isordil, Tenormin and Tildiem LA in the treatment of stable angina in the UK. Journal of Drug Assessment 2000;3:1-20.

3 de Feyter PJ, Serruys PW, Unger F, et al. Bypass surgery versus stenting for the treatment of multivessel disease in patients with unstable angina compared with stable angina. Circulation 2002;105:2367-72.

4 Eefting F, Nathoe H, van Dijk D, et al. Randomized comparison between stenting and off-pump bypass surgery in patients referred for angioplasty. Circulation 2003 Dec 9;108:2870-6.

5 Griffin SC, Barber JA, Manca A, et al. Cost effectiveness of clinically appropriate decisions on alternative treatments for angina pectoris: prospective observational study. Br Med J 2007;334:624-8.

6 Hambrecht R, Walther C, Mobius-Winkler S, et al. Percutaneous coronary angioplasty compared with exercise training in patients with stable coronary artery disease: a randomized trial. Circulation 2004 Mar 23;109:1371-8.

7 Henderson RA, Pocock SJ, Sharp SJ, et al. Long-term results of RITA-1 trial: clinical and cost comparisons of coronary angioplasty and coronary-artery bypass grafting. Lancet 1998 Oct 31;352:1419-25.

8 Hlatky MA, Boothroyd DB, Melsop KA, et al. Economic outcomes of treatment strategies for type 2 diabetes mellitus and coronary artery disease in the Bypass Angioplasty Revascularization Investigation 2 Diabetes trial. Circulation 2009 Dec 22;120:2550-8.

9 Legrand VM, Serruys PW, Unger F, et al. Three-year outcome after coronary stenting versus bypass surgery for the treatment of multivessel disease. Circulation 2004 Mar 9;109:1114-20.

10 McKenna C, McDaid C, Suekarran S, et al. Enhanced external counterpulsation for the treatment of stable angina and heart failure: A systematic review and economic analysis. Health Technol Assess 2009 Apr;13:1-90.

11 O'Neill C, Normand C, Cupples M, et al. Cost effectiveness of personal health education in primary care for people with angina in the greater Belfast area of Northern Ireland. J Epidemiol Community Health 1996 Oct;50:538-40.

12 O'Neill C, Normand C, Cupples M, et al. A comparison of three measures of perceived distress: results from a study of angina patients in general practice in Northern Ireland. J Epidemiol Community Health 1996 Apr;50:202-6.

13 Cupples ME, McKnight A. Randomised controlled trial of health promotion in general practice for patients at high cardiovascular risk. Br Med J 1994 Oct 15;309:993-6.

14 Sculpher MJ, Seed P, Henderson RA, et al. Health service costs of coronary angioplasty and coronary artery bypass surgery: the Randomised Intervention Treatment of Angina (RITA) trial. Lancet 1994;344:927-33.

15 Sculpher MJ, Smith DH, Clayton T, et al. Coronary angioplasty versus medical therapy for angina: health service costs based on the second Randomised Intervention Treatment of Angina (RITA-2) trial. Eur Heart J 2002;23:1291-300.

16 Chamberlain DA, Fox K.A., Henderson RA, et al. Coronary angioplasty versus medical therapy for angina: The second randomised intervention treatment of angina (RITA-2) trial. Lancet 1997;350:461-8.

17 Walker A, McMurray J, Stewart S, et al. Economic evaluation of the impact of nicorandil in angina (IONA) trial. Heart 2006 May 1;92:619-24.

18 Dargie HJ. Effect of nicorandil on coronary events in patients with stable angina: The Impact Of Nicorandil in Angina (IONA) randomised trial. Lancet 2002;359:1269-75.

19 Weintraub WS, Mauldin PD, Becker E, et al. A comparison of the costs of and quality of life after coronary angioplasty or coronary surgery for multivessel coronary artery disease. Results from the Emory Angioplasty Versus Surgery Trial (EAST). Circulation 1995 Nov 15;92:2831-40.

20 Weintraub WS, Becker ER, Mauldin PD, et al. Costs of revascularization over eight years in the randomized and eligible patients in the Emory Angioplasty versus Surgery Trial (EAST). Am J Cardiol 2000 Oct 1;86:747-52.

21 Weintraub WS, Mahoney EM, Zhang Z, et al. One year comparison of costs of coronary surgery versus percutaneous coronary intervention in the stent or surgery trial. Heart 2004 Jul;90:782-8.

22 Weintraub WS, Boden WE, Zhang Z, et al. Cost-effectiveness of percutaneous coronary intervention in optimally treated stable coronary patients. Circulation Cardiovascular Quality and Outcomes 2008 Sep;1:12-20.

23 Boden WE, O'Rourke RA, Teo KK, et al. Optimal medical therapy with or without PCI for stable coronary disease. N Engl J Med 2007 Apr 12;356:1503-16.

24 Zhang Z, Mahoney EM, Spertus JA, et al. The impact of age on outcomes after coronary artery bypass surgery versus stent-assisted percutaneous coronary intervention: one-year results from the Stent or Surgery (SoS) trial. Am Heart J 2006 Dec;152:1153-60.

25 Organisation for Economic Cooperation and Development. OECD Prices and Purchasing Power Parities (PPP). OECD; 2010.

Appendix H. Cost-effectiveness analysis

1 Introduction

An economic model was developed to compare the cost-effectiveness of CABG and PCI for patients considered suitable for either revascularisation method (Chapter 12). In our economic literature review we found several studies (Chapter 12) but none of them met the quality and applicability criteria in full. Some[1-6] were not UK based and therefore only partially applicable. UK-based studies were either cost-consequences analyses[7-9] or cost-utility analysis based on cohort studies[10] with high risk of bias, or had a limited follow-up time[11].

The GDG considered it was necessary to build a model to formally evaluate the uncertain trade-offs between clinical outcomes and costs of the two revascularisation strategies.

2 Methods

2.1 Model overview

A cost-utility analysis was undertaken where costs and quality-adjusted life-years (QALYs) were considered from a UK NHS and personal social services perspective. Both costs and QALYs were discounted at a rate of 3.5% per annum in line with NICE methodological guidance[12].

The following general principles were adhered to:

- The GDG was consulted during the construction and interpretation of the model.
- When published data was not available we used expert opinion to populate the model.
- Model assumptions were reported fully and transparently.
- The results were subject to sensitivity analysis and limitations were discussed.
- The model employed a cost-effectiveness threshold of £20,000 per QALY gained.
- The model was peer-reviewed by another health economist at the NCGC.

2.1.1 Comparators

The interventions compared are CABG and PCI (with either drug-eluting stents [DES] or bare-metal stents [BMS] or both). In the original meta-analysis (see review protocol in Appendix C) PCI included coronary balloon angioplasty but we decided to focus the economic analysis on PCI with stents as this is the widely used intervention and it is believed to be more effective than coronary balloon angioplasty. Costs and effectiveness in the model are therefore applicable to CABG and PCI with stents.

2.1.2 Population

We looked for data on patients with single vessel disease and multi-vessel disease separately as interventions might yield different outcomes (e.g. different probability of repeating intervention). We found only scarce data on the single vessel group (small sample sizes) and therefore focused solely on patients with multi-vessel disease.

2.1.3 Time horizon

In the base case analysis we adopted a ten-year time horizon, which was the longest follow-up available from the RCTs. In a sensitivity analysis we extrapolated results up to a life-time horizon assuming the annual probabilities of clinical events are constant from year ten.

2.2 Approach to modelling

2.2.1 Model structure

Given the recurrences of events over time, we decided to build a Markov model with a six-month cycle length as this was deemed the minimum clinically meaningful time interval to detect differences between interventions. All the probabilities, costs and health utilities were converted to reflect the six-month cycle length.

Clinical outcomes considered in the model were mortality, myocardial infarction (MI), further revascularisation procedures, and presence or absence of angina symptoms. Stroke was included in the clinical review; we did not include this outcome in the base case of the model as we observed only a non-significant trend for stroke to be more frequent in the CABG arm and the definition and severity of stroke was not reported in each study.

Both arms of the model have the same structure. In the first cycle (
Figure 1), patients undergo the intervention and in the following six months can experience one of the transitional events considered: MI, revascularisation, or death. In the first two events, a HRQoL decrement is applied to MI and the cost of treating MI or the cost of further revascularisation is added. In case of death, the patient ends up in the dead health state which is associated with no cost and a HRQoL equal to 0. If the patient is still alive at the end of the cycle, they can either still have or not have angina symptoms. The presence of angina symptoms defines the health state of the following cycle ('No angina' or 'Angina').

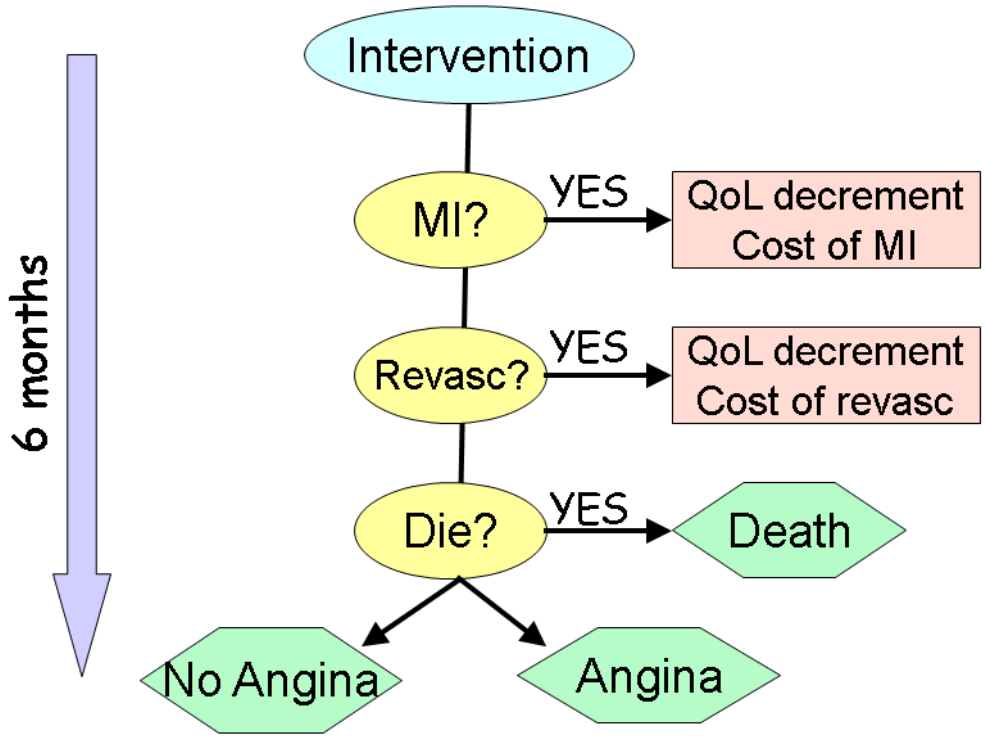


Figure 1 - First cycle of the model

In the following cycles patients re-enter the model and the same transitional events are evaluated with different time-dependent probabilities (see paragraph 2.3.2).
When a patient undergoes a further revascularisation in the base case we have assumed that this is a PCI. We have varied this assumption in a sensitivity analysis using different proportion of CABG and PCI for additional revascularisation.

For each strategy the expected healthcare costs and expected QALYs were calculated by estimating the costs and QALYs for each state and then multiplying them by the proportion of patients who would be in that state as determined by the strategy taken (see 2.4).

2.2.2 Uncertainty

In the **probabilistic analysis** a probability distribution is defined for each model input parameter. When the model is run a value for each input is randomly selected from its respective probability distribution and mean costs and mean QALYs are calculated using these values. The model is run repeatedly – in this case 10,000 times – and results are summarised. Probability distributions in the analysis were based on error estimates from data sources, for example confidence intervals around relative risk estimates.

The way in which distributions are defined reflects the nature of the data, so for example probabilities were given a beta distribution, which is bounded by zero and one – see Table 1. All of the variables that were probabilistic in the model and their distributional parameters are detailed in Table 2.

Table 1: Description of the type and properties of distributions used in the probabilistic sensitivity analysis

Parameter	Type of distribution	Properties of distribution	Parameters for the distribution
Probabilities	Beta	Bounded on 0 – 1 interval. Derived from sample size, number of patients experiencing events.	α = events β = sample size – α
Cost	Gamma	Bounded at 0. Derived from mean and standard error.	$\alpha = (\text{mean}/\text{SEM})^2$ $\lambda = \text{mean}/\text{SEM}^2$
Number of resources used (number of stents)	Triangular	Derived from expert opinion.	Min = minimum value Likeliest = mean Max = maximum value
Utility decrements	Gamma	Bounded at 0. Derived from mean and standard error.	$\alpha = (\text{mean}/\text{SEM})^2$ $\lambda = \text{mean}/\text{SEM}^2$
Relative risk	Lognormal	Bounded at 0. Derived from log (of the RR) and standard error.	$\mu = \ln(RR)$ $SD(\mu) = (\ln[\text{UpperCI}] - \ln[\text{lowerCI}])/1.96*2$

SEM=standard error of the mean

For simplicity the following variables, were left deterministic (i.e. were not varied in the probabilistic analysis): discount rate and cost-effectiveness threshold (which were deemed to be fixed by NICE) and drug prices.

In addition, various **deterministic sensitivity analyses** were undertaken to test the robustness of model assumptions and data sources. In these one or more inputs were changed and the model rerun to see the impact on results.

2.3 Model inputs

2.3.1 Summary table of model inputs (details in subsequent sections)

Table 2 - Summary of parameters used in the model

Description of variable	Point estimate	Probability distribution	Parameters for the probability distribution	Source
a) Probability of events (see 2.3.2)				
Probability of death after CABG – 1 year	2.68%	Beta	$\alpha = 63$ $\beta = 2288$	Systematic review of clinical effectiveness (Appendix K)
Probability of death after CABG – from 1 to 2 years	0.37%	Beta	$\alpha = 0.4$ $\beta = 1075$	See 2.3.2

Probability of death after CABG – from 2 to 3 years	1.97%	Beta	α = 11.6 β = 577	See 2.3.2
Probability of death after CABG – from 3 to 5 years	4.49%	Beta	α = 34.6 β = 736	See 2.3.2
Probability of death after CABG – from 5 to 10 years	17.79%	Beta	α = 32.9 β = 152	See 2.3.2
Probability of MI after CABG – 1 year	4.44%	Beta	α = 102 β = 2197	Systematic review of clinical effectiveness (Appendix K)
Probability of MI after CABG – from 1 to 2 years	0.72%	Beta	α = 4.2 β = 574	See 2.3.2
Probability of MI after CABG – from 2 to 3 years	0.52%	Beta	α = 3 β = 571	See 2.3.2
Probability of MI after CABG – from 3 to 5 years	3.49%	Beta	α = 26.6 β = 736	See 2.3.2
Probability of MI after CABG – from 5 to 10 years	1.57%	Beta	α = 2.9 β = 182	See 2.3.2
Probability of repeating revascularisation after CABG – 1 year	4.59%	Beta	α = 85 β = 1767	Systematic review of clinical effectiveness (Appendix K)
Probability of repeating revascularisation after CABG – from 1 to 2 years	0.69%	Beta	α = 7.3 β = 1047	See 2.3.2
Probability of repeating revascularisation after CABG – from 2 to 3 years	1.43%	Beta	α = 8.2 β = 565	See 2.3.2
Probability of repeating revascularisation after CABG – from 3 to 5 years	0.87%	Beta	α = 6.6 β = 748	See 2.3.2

Probability of freedom from angina symptoms after CABG – 6 months	85.20%	Beta	α = 121 β = 21	Systematic review of clinical effectiveness (Appendix K)
Probability of freedom from angina symptoms after CABG – 1 year	80.94%	Beta	α = 1168 β = 275	Systematic review of clinical effectiveness (Appendix K)
Probability of freedom from angina symptoms after CABG – 2 years	87.20%	Beta	α = 508 β = 75	Systematic review of clinical effectiveness (Appendix K)
Probability of freedom from angina symptoms after CABG – 3 years	87.20%	Beta	α = 503 β = 74	Systematic review of clinical effectiveness (Appendix K)
Probability of freedom from angina symptoms after CABG – 5 years	78.84%	Beta	α = 637 β = 171	Systematic review of clinical effectiveness (Appendix K)
Probability of freedom from angina symptoms after CABG – 10 years	64.04%	Beta	α = 130 β = 73	Systematic review of clinical effectiveness (Appendix K)
Relative risk of death at 1 year – PCI vs. CABG	1.18	Log-normal	μ = 0.166 SD(μ) = 0.168	Systematic review of clinical effectiveness (Appendix K)
Relative risk of death at 2 years – PCI vs. CABG	1.32	Log-normal	μ = 0.278 SD(μ) = 0.238	Systematic review of clinical effectiveness (Appendix K)
Relative risk of death at 3 years – PCI vs. CABG	0.79	Log-normal	μ = -0.236 SD(μ) = 0.278	Systematic review of clinical effectiveness (Appendix K)
Relative risk of death at 5 years – PCI vs. CABG	1.11	Log-normal	μ = 0.104 SD(μ) = 0.154	Systematic review of clinical effectiveness (Appendix K)
Relative risk of death at 10 years – PCI vs. CABG	0.95	Log-normal	μ = -0.051 SD(μ) = 0.173	Systematic review of clinical effectiveness (Appendix K)

Relative risk of MI at 1 year – PCI vs. CABG	1.20	Log-normal	μ = 0.182 SD(μ) = 0.130	Systematic review of clinical effectiveness (Appendix K)
Relative risk of MI at 2 years – PCI vs. CABG	1.30	Log-normal	μ = 0.262 SD(μ) = 0.231	Systematic review of clinical effectiveness (Appendix K)
Relative risk of MI at 3 years – PCI vs. CABG	1.30	Log-normal	μ = 0.262 SD(μ) = 0.220	Systematic review of clinical effectiveness (Appendix K)
Relative risk of MI at 5 years – PCI vs. CABG	1.36	Log-normal	μ = 0.307 SD(μ) = 0.146	Systematic review of clinical effectiveness (Appendix K)
Relative risk of MI at 10 years – PCI vs. CABG	1.27	Log-normal	μ = 0.239 SD(μ) = 0.276	Systematic review of clinical effectiveness (Appendix K)
Relative risk of repeating revascularisation at 1 year – PCI vs. CABG	3.55	Log-normal	μ = 1.267 SD(μ) = 0.117	Systematic review of clinical effectiveness (Appendix K)
Relative risk of repeating revascularisation at 2 years – PCI vs. CABG	4.42	Log-normal	μ = 1.486 SD(μ) = 0.139	Systematic review of clinical effectiveness (Appendix K)
Relative risk of repeating revascularisation at 3 years – PCI vs. CABG	4.03	Log-normal	μ = 1.393 SD(μ) = 0.167	Systematic review of clinical effectiveness (Appendix K)
Relative risk of repeating revascularisation at 5 years – PCI vs. CABG	4.15	Log-normal	μ = 1.423 SD(μ) = 0.135	Systematic review of clinical effectiveness (Appendix K)
Relative risk of freedom from angina symptoms at 6 months – PCI vs. CABG	1.01	Log-normal	μ = 0.010 SD(μ) = 0.048	Systematic review of clinical effectiveness (Appendix K)
Relative risk of freedom from angina symptoms at 1 year – PCI vs. CABG	0.87	Log-normal	μ = -0.139 SD(μ) = 0.020	Systematic review of clinical effectiveness (Appendix K)

Relative risk of angina symptoms at 2 years – PCI vs. CABG	0.92	Log-normal	μ = -0.083 SD(μ) = 0.025	Systematic review of clinical effectiveness (Appendix K)
Relative risk of angina symptoms at 3 years – PCI vs. CABG	0.94	Log-normal	μ = -0.062 SD(μ) = 0.025	Systematic review of clinical effectiveness (Appendix K)
Relative risk of angina symptoms at 5 years – PCI vs. CABG	0.92	Log-normal	μ = -0.083 SD(μ) = 0.027	Systematic review of clinical effectiveness (Appendix K)
Relative risk of angina symptoms at 10 years – PCI vs. CABG	0.91	Log-normal	μ = -0.094 SD(μ) = 0.081	Systematic review of clinical effectiveness (Appendix K)
b) Quality of life values (see 2.3.3)				
Utility of No Angina	0.87	Beta	α = 348 λ = 52	Melsop 2003[13]
Utility decrement of Angina vs. No angina	-0.167	Gamma	α = 2.678 λ = 16.04	See 2.3.3
Utility decrement after MI	-0.24	Gamma	α = 177.78 λ = 740.74	See 2.3.3
Utility decrement of CABG vs. PCI	-0.06	Gamma	α = 39.81 λ = 663.46	See 2.3.3
c) Costs (see 2.3.4)				
Cost of CABG procedure	£7,959	Gamma	α = 13.04 λ = 0.0016	NHS Reference Costs 2008-09, Elective Inpatient CABG 1st time
Cost of PCI procedure	£2,610	Gamma	α = 2.64 λ = 0.0010	NHS Reference Costs 2008-09, Elective Inpatient PCI 0 – 2 stents[14]
Cost of each stent	£300	Gamma	α = 15.19 λ = 0.0506	Experts opinion
Number of stents used	4	Triangular	Min = 2 Likeliest = 4 Max = 6	Experts opinion

Cost of Clopidogrel treatment over 12 months	£436	None		BNF 59[15]
Cost of Rehab	£550	Gamma	$\alpha = 15.19$ $\lambda = 0.0276$	Bethell 2007[16]
Cost of angiography	£841	Gamma	$\alpha = 11.66$ $\lambda = 0.0139$	2008-09 NHS Ref costs: Day cases, HRG EA41Z - Other Non-Complex Cardiac Surgery + Catheterisation[14]
Cost of MPS with SPECT	£293	Gamma	$\alpha = 15.19$ $\lambda = 0.0518$	Chest Pain guideline[17]
Cost of medications over 6 months	£61.37	None		See 2.3.4.2
Cost of treatment of MI	£1,783	Gamma	$\alpha = 15.19$ $\lambda = 0.00852$	Acute Coronary Syndromes Guideline[18]
Cost of referral	£112	Gamma	$\alpha = 15.19$ $\lambda = 0.1356$	2008-09 NHS Reference Costs- Consultant Led: Follow up Attendance Non-Admitted Face to Face - Cardiology[14]
d) Other parameters and assumption				
Discount rate (cost and QALYs)	3.5%	none		NICE reference case

2.3.2 Baseline event rates and relative treatment effects

CABG was used as the baseline arm of the model. Data on event rates in this arm were derived from the systematic review of clinical effectiveness (Appendix K). Events in the model were total MI (both fatal and non-fatal), repeat revascularisation, and death. Only studies of CABG versus PCI with stents were included and the probabilities of events for each available time point (1 year, 3 years, 5 years, and 10 years) were calculated as:

$$P = r/n$$

Where r is the number of events in the CABG arm and n is the total number of patients randomised to CABG.

Probabilities of events at year 1 were taken directly from the meta-analysis for that time point. Probabilities at subsequent time points were calculated as follows:

$$p_{t2\text{-}t1} = \frac{p_{t2} - p_{t1}}{1 - p_{t1}}$$

Where

$p_{t2\text{-}t1}$ is the probability of an event between an initial time t1 and a subsequent time t2

p_{t1} is the total probability of events at the initial time t1

and p_{t2} is the total probability of events at the subsequent time t2.

Among the patients alive at follow-up, the proportions of those who had angina symptoms were obtained from those studies reporting the number or proportion of patients with angina or no angina. In some papers results were expressed as mean CCS score (e.g. Buszman et al. (2008)[19]) and were excluded. If papers reported the number of patients in each CCS scores we combined CCS 0 + I to represent the 'No Angina' state, and II + III + IV to represent the 'Angina' state. The overall proportion of patients with or without angina at a time-point is used in the model to determine the angina/no angina health state for the whole cohort reaching the end nodes. We assumed that the proportion in each cycle was the same as the proportion at the following available time point. For example, in cycles 6 to 9 (corresponding to 3.5. up to 5 years) 78.84% of patients who are still alive have no angina in the CABG arm; this figure corresponds to the probability of being angina-free at 5 years.

Table 3 summarises the clinical effectiveness data used in the model.

Table 3 - Summary of estimates of effectiveness used in the base case model

Parameter	Time point	Probability at time x – CABG arm	Probability from time (x-n) to time x	RR PCI vs. CABG	Source
Death (all)	1 year	2.68%	-	1.18	Sigwart et al. 2002[20], Eefting et al. (2003)[3], Serruys et al. (2001)[21], Buszman et al. (2008)[19], Serruys et al. (2009)[22], Hueb et al. (2004)[23]
	2 years	2.71%	0.37%	1.32	Unger et al. (2003)[24], Booth et al. (2008)[25]
	3 years	4.63%	1.97%	0.79	Serruys et al. (2005)[26]
	5 years	8.91%	4.49%	1.11	Serruys et al. (2005)[26], Hueb et al. (2007)[27]
	10 years	25.12%	17.79%	0.95	Hueb et al. (2010)[28]
MI (all)	1 year	4.44%	-	1.20	Sigwart et al. 2002[20], Eefting et al. (2003)[3], Serruys et al.

					(2001)[21], Serruys et al. (2009)[22], Hueb et al. (2004)[23]
	2 years	5.12%	0.73%	1.30	Unger et al. (2003)[24], Booth et al. (2008)[25]
	3 years	5.62%	0.52%	1.30	Serruys et al. (2005)[26]
	5 years	8.91%	3.49%	1.36	Serruys et al. (2005)[26], Hueb et al. (2007)[27]
	10 years	10.34%	1.57%	1.27	Hueb et al. (2010)[28]
Repeat revascularisation	1 year	4.59%	-	3.55	Eefting et al. (2003)[3], Serruys et al. (2001)[21], Buszman et al. (2008)[19], Serruys et al. (2009)[22], Hueb et al. (2004)[23]
	2 years	5.70%	0.69%	4.42	Unger et al. (2003)[24], Booth et al. (2008)[25]
	3 years	6.61%	1.43%	4.03	Serruys et al. (2005)[26]
	5 years	7.43%	0.87%	4.15	Serruys et al. (2005)[26], Hueb et al. (2007)[27]
Patients free of angina	6 months	85.20%	-	1.01	Eefting et al. (2003)[3]
	1 year	80.94%	-	0.87	Sigwart et al. 2002[20], Eefting et al. (2003)[3], Serruys et al. (2001)[21], Hueb et al. (2004)[23]
	2 years	87.20%		0.92	Unger et al. (2003)[24]
	3 years	87.20%	-	0.94	Legrand et al. (2004)[4]
	5 years	78.84%	-	0.92	Serruys et al. (2005)[26], Hueb et al. (2007)[27]
	10 years	64.04%	-	0.91	Hueb et al. (2010)[28]

* Data not used in the model as inconsistent with the trend.

Probability of death at 6 years was available from the study by Booth et al. (2008)[25]; however these data showed some inconsistencies when compared to the meta-analysis of all the studies at previous time points (i.e. lower mortality rate compared to previous year) and we decided not to use it in the model. The same decision was made for the repeat revascularisation at 10 years from Hueb et al. (2010)[28], where the overall proportion of

patients experiencing a repeat revascularisation was lower than that at 5 years as defined by the meta-analysis, which included the 5-year follow-up of the same study[27].

2.3.3 Utilities

For economic evaluation, a specific measure of HRQoL known as utility is required to calculate QALYs. Utilities indicate the preference for health states on a scale from 0 (death) to 1 (perfect health). The NICE reference case specifies that the preferred way for this to be assessed is by the EQ-5D instrument.

Utilities were attached to the health states in the model (angina, no angina, death) and decrements in HRQoL (disutilities) were calculated for the transitional events in the model (MI and initial revascularisation, in a sensitivity analysis also repeat revascularisation).

A systematic search identified few studies with de novo utility measures. We selected only those studies reporting utility values separately in patients with and without symptoms of angina. Serruys et al. (2001)[21] reported EQ-5D scores in a randomised trial of PCI versus CABG, but did not report EQ-5D scores separately for patients with or without angina. We therefore decided to use the utilities from another RCT[13] on patients with multivessel coronary artery disease and angina or documented ischemia. In this study time trade-off scores in 400 patients with angina and in 58 patients without angina were obtained through telephone interviews in the USA. Scores in patients free of angina were significantly higher than scores in patients with angina ($p<0.01$). Disutility of CABG was calculated as a differential from the PCI intervention based on the study by Serruys et al. (2001)[21]. In this RCT, one month after the intervention patients in the surgery group had a EQ-5D score of 0.78 (SD $\pm$0.17) compared to 0.84 (SD $\pm$0.16) in patients one month after PCI. We assumed the difference in utility lasts only for one month as data up to this point was available. The total QALY loss is calculated as follows:

QALY loss = (uPCI – uCABG)/(12 months) = (0.84 – 0.86)/12 = 0.005

Where
uPCI is the EQ-5D score in the PCI group one month after the intervention
and uCABG is the EQ-5D score in the CABG group one month after the intervention.

However in a study by Scuffham et al. (2006)[29], the recovery time after CABG was considered to be 2.5 months. Compared to this study, we have underestimated the decrement in HRQoL after surgery.

To estimate the disutility after a MI, we used the value reported in the HTA by Ward et al. (2007)[30]; this was obtained from personal communication with the author of a RCT[31]. In this study[31] EQ-5D questionnaires were administered to patients with chest pain for whom a record of diagnosis including MI was available. The EQ-5D scores for patients with MI was 0.760 (uMI); as 1 was the utility representing perfect health (uPH), the disutility due to MI (disMI) corresponds to:

disMI = -(uPH – uMI) = -(1-0.760) = -0.24

This figure was divided by 2 to reflect the six-month cycle length.

Utilities used in the base case analysis are reported in Table 4.

Table 4 - Utility values used in the model

Parameter	Base case value	Source
Utility no angina	0.87 (SE 0.0435)	Melsop 2003[13]
Utility angina	0.703 (SE 0.0923)	Melsop 2003[13]
Immediate disutility CABG (QALYs lost)	-0.005	Calculated from Serruys2001[21]
Immediate disutility MI (QALYs lost)	-0.24	Calculated from Ward2007[30]

While in the base case the disutility from CABG was estimated as a differential from PCI and no disutility was attached to PCI, in a sensitivity analysis we have calculated the disutility from both PCI and CABG as differentials from the No Angina state. In this way we incorporated an estimate of the disutility associated with the repeat PCI during follow-up (see 3.2).
In another study identified in our search[32], EQ-5D scores were calculated for patients in the procedure subgroups: event free, repeat PCI, repeat CABG. In a sensitivity analysis we used the differential utility between the event free group (0.85) and the repeat PCI group (0.77) to estimate the disutility associated with the repeat revascularisation, assuming it lasts for one month. Results are reported in 3.2.

2.3.4 Resource use and cost

Costs are associated either with initial strategy (CABG or PCI), health states ('angina' or 'no angina'), or transitional events (MI, revascularisation, and development of angina).

2.3.4.1 Cost of initial strategy

The cost of the initial strategy is used in the first cycle of the model (cycle 0). Cost components are described in Table 5 and comprise the cost of initial procedure, necessary medical therapy following PCI, cost of medical treatment as for the 'no angina' state (see 2.3.4.2) and rehabilitation. In a study by Bethell et al. (2007)[16] a different proportion of patients have rehabilitation after CABG compared to PCI. However in the model we assume everyone undergoes rehabilitation regardless of their initial intervention.

Table 5 - Initial cost of intervention

	CABG	PCI	Source
Cost of initial procedure - CABG	£7,959	-	NHS Reference Costs 2008-09, Elective Inpatient CABG 1st time[14]
Cost of initial procedure - PCI	-	£2,610	NHS Reference Costs 2008-09, Elective Inpatient PCI 0 – 2 stents Or PCI 3 or more stents (EA49Z)[14]

Cost of additional stents	-	4 * £300	Experts opinion
Treatment with Clopidogrel for 12 months*	-	12*£36.35	BNF 59[15]
Medical treatment (no Angina)	£43	£42.55	BNF 59[15]
Rehabilitation	£550	£550	Bethell et al. (2007)[16]
TOTAL	**£8,552**	**£4,839**	

* the total 12 month cost of the treatment was added to the first 6-month cycle

In the NHS reference costs[14], the cost of PCI procedure includes the cost of 0 to 2 stents. In our model, patients had multi-vessel disease and would have more than two stents. We asked the experts of our GDG to estimate the average number of stents required in this intervention for the included population (4 stents). We could not find the cost of stents from publicly available sources therefore the GDG experts provided us with this estimate as well (£300 each).

In the review of the economic literature we found a study[11] comparing the one-year costs of PCI and CABG in patients enrolled in the SoS trial, which was included in our review of clinical effectiveness (see Appendix E and Appendix G). In this study the cost of the initial procedure including hospitalisation and ward costs was higher in the CABG group compared to the PCI group (£7,321 vs. £3,884; $p<0.05$). These figures are very similar to the initial cost calculated in our model.

2.3.4.2 Cost of health states

The possible health states in which a patient could be in the model are 'angina', 'no angina' and 'death'. We collected information on the resources used while in these states from the GDG experts (data on medications use from a GP practice) which were supported by the estimates of medications used in patients randomised to optimal medical treatment in the COURAGE trial[33]. We estimated the 6-month costs of the defined medical treatment based on national sources of unit costs[15].

Patients who still have angina symptoms after the intervention are treated medically according to the treatment profile reported in Table 6.

Table 6 - Resources and cost of medical treatment in patients with angina

Class of drug	Name of drug [a]	Proportion of patients treated [b]	Total cost for 6 months [c]
Statins	Simvastatin 40mg 1/day	100%	£9.15
Aspirin	Aspirin 75 mg, 1/day	100%	£6.40
BB and CCB	Bisoprolol 5mg 1/day Amlodipine 10mg 1/day	Total 100% (BB 85%, CCB 15%)	£7.85
Ivabradine	Ivabradine 5mg, 2/day	2%	£5.10
ACE inhibitors and ARB	Ramipril 5mg 1/day Losartan 50mg 1/day	Total 100% (ACE 75%, ARB 25%)	£27.00
Other drugs	Nicorandil 20mg, 2/day	5%	£4.75

Nitrates	Isosorbide mononitrate 20mg, 2/day	16%	£1.14
Total			**£61.39**

a) The most commonly used drug within the same class was identified by the GDG experts
b) Data from a GP practice (personal communications).
c) Source of cost BNF 59[15]. Cost of drugs was calculated using the lowest cost of non-proprietary medicines. E.g. if capsules were cheaper than tablets then the cost of capsules was used.

In a sensitivity analysis we have increased the cost of medications in the angina state based on the annual cost reported in the study by Ward et al. (2007)[30] which was £171; we added the cost of statins (reported in Table 6) to this figure.

In the model, patients with no angina would still be medically treated to prevent cardiovascular events. Drugs used and the computation of their cost are reported in Table 7.

Table 7 - Resources and cost of medical treatment in patients with no angina symptoms

Class of drug	Name of drug	Proportion of patients	Total cost for 6 months*
Statins	Simvastatin 40mg 1/day	100%	£9.15
Aspirin	Aspirin 75 mg, 1/day	100%	£6.40
ACE inhibitors and ARB	Ramipril 5mg 1/day Losartan 50mg 1/day	Total 100% (ACE 75%, ARB 25%)	£27.00
Total			**£42.55**

* Source of cost BNF 59[15]. Cost of drugs was calculated using the lowest cost of non-proprietary medicines. E.g. if capsules were cheaper than tablets then the cost of capsules was used.

No costs were associated with the death state.

2.3.4.3 Cost of transitional events

Transitional events in the model were MI, further revascularisation, and the appearance of angina symptoms (event preceding the 'angina' health state).
Each of these events is associated with some costs (Table 8).

The cost of MI was obtained from the Acute Coronary Syndromes Guideline[18], and it incorporates the cost of hospital stay, ambulance and A&E.

When a further revascularisation was required according to the clinical probability (2.3.2), this was assumed to be a PCI and its cost as calculated in 2.3.4.1 was used. This assumption was varied in a one-way sensitivity analysis where we increased the proportion of CABG/PCI as revascularisation procedure up to 1. The cost of CABG was used for the selected proportion of patients undergoing this procedure.

Patients who transit from the 'no angina' state to the 'angina' state are all assumed to incur the costs of a cardiology outpatient consultation, myocardial perfusion scan with SPECT, and coronary angiography as reported in Table 8.

Table 8 - Cost of transitional events in the model

Event in the model	Resource	Cost	Source
MI	Hospital stay, ambulance and A&E	£1,783	Acute Coronary Syndromes Guideline[18]
		TOTAL £1,783	
Further revascularisation	*PCI procedure*	*£2,610*	NHS Reference Costs 2008-09, Elective Inpatient PCI 0 – 2 stents Or PCI 3 or more stents (EA49Z)[14]
	Stents	*4*£300*	Experts opinion
		TOTAL £3,810	
Transition to 'angina' state	*Referral to cardiologist*	*£112*	NHS Reference Costs 2008-09 - Consultant Led: Follow up Attendance Non-Admitted Face to Face - Cardiology[14]
	Invasive coronary angiography	*£841*	NHS Reference Costs 2008-09, Day cases, HRG EA41Z - Other Non-Complex Cardiac Surgery + Catheterisation[14]
	Myocardial perfusion scan with SPECT	*£293*	Chest Pain guideline[17]
		TOTAL £1,246	

2.4 Computations

The mean cost and effectiveness of the two strategies were calculated using TreeAge Pro 2008. The incremental cost-effectiveness ratio was calculated in Microsoft Office Excel 2007.

2.4.1 Calculating QALYs gained

For each strategy, the expected QALYs per cohort of patients are calculated as follows:

$$\text{Expected QALYs} = DisU_{p} + \sum_{j=1}^{19}\sum_{i=1}^{3} U_{i} P_{ij} + \sum_{j=1}^{19}\sum_{x=1}^{3} DisU_{x} P_{xj}$$

where

$DisU_p$ = the disutility for the initial intervention p

U_i = the utility score for health state i

P_{ij} = the proportion of patients in health state i at cycle j

$DisU_x$ = the disutility of event x

P_{xj} = the probability of event x at cycle j

and where

intervention p could be either PCI or CABG,

health state i could be any of the health states represented by the green boxes in Figure 1 (angina, no angina, death)

and event x could be MI or further revascularisation.

The proportion of patients in each health state depends on the effectiveness of the treatment, in terms of mortality and improvement of symptoms.

QALYs were then discounted to reflect time preference. QALYs during cycle 0 were not discounted. The total discounted QALYs was the sum of the discounted QALYs per cycle.

The overall 10-year expected QALYs are given by the sum of the discounted QALYs calculated for each cycle. The *incremental QALYs gained* associated with a treatment strategy are calculated as the difference between the expected QALYs with that strategy and the expected QALYs with the comparator.

2.4.2 Calculating costs

For each strategy, the expected cost per cohort of patients is calculated as follows:

$$\text{Expected cost} = C_s + \sum_{j=1}^{19} \sum_{i=1}^{3} C_i P_{ij} + \sum_{j=1}^{19} \sum_{x=1}^{3} C_x P_{xj}$$

where

C_s = cost of the initial strategy (PCI or CABG)

C_i = cost of health state i

P_{ij} = proportion of patients in health state i in cycle j

C_x =cost of event x

P_{xj} = probability of event x in cycle j

and where health state i could be any of the health states represented by the green boxes in

Figure 1 (death, angina, no angina), and event x could be any of the events described in Table 8.

The proportion of patients in each health state depends on the effectiveness of the treatment, in terms of mortality and improvement of symptoms.

Future costs (those occurring after cycle 1) were discounted to reflect time preference.

The overall 10-year expected costs are given by the sum of the discounted costs calculated for each cycle. The incremental cost associated with a treatment strategy is calculated as the difference between the expected cost with that strategy and the expected cost with the comparator.

2.4.3 Calculating cost-effectiveness

The widely used cost-effectiveness metric is the incremental cost-effectiveness ratio (ICER). This is calculated by dividing the difference in costs associated with two alternatives by the difference in QALYs. The decision rule then applied is that if the ICER falls below a given cost per QALY threshold then the result is considered to be cost-effective. If both costs are lower and QALYs are higher the option is said to dominate and an ICER is not calculated.

$$ICER = \frac{Costs\ (B) - Costs\ (A)}{QALYs\ (B) - QALYs\ (A)}$$

Where:

Costs/QALYs(X) = total discounted costs/QALYs for option X

Option B is cost-effective if: ICER < Threshold

It is also possible, for a particular cost-effectiveness threshold, to re-express cost-effectiveness results in term of net benefit (NB). This is calculated by multiplying the total QALYs for a comparator by the threshold cost per QALY value (for example, £20,000) and then subtracting the total costs. The decision rule then applied is that the comparator with the highest NB is the most cost-effective option at the specified threshold. That is the option that provides the highest number of QALYs at an acceptable cost. For ease of computation NB is used to identify the optimal strategy in the probabilistic analysis simulations.

$$Net\ Benefit\ (X) = QALYs\ (X) \times D - Costs\ (X)$$

Where: Costs/QALYs(X) = total discounted costs/QALYs for option X; D = cost-effectiveness threshold

The probabilistic analysis was run for 10,000 simulations. For each simulation, total discounted costs and total discounted QALYs were calculated for each treatment option. The net benefit was also calculated and the most cost-effective option identified (that is, the one with the highest net benefit), at a threshold of £20,000 per QALY gained.

The results of the probabilistic analysis were summarised in terms of mean discounted costs and QALYs with confidence intervals, where means were the average of the 10,000 simulated estimates and the 95% confidence intervals are the 2.5 and 97.5 percentiles. A cost-effectiveness ratio was calculated from the mean costs and QALYs. The percentage of simulations where each strategy was the most cost-effective gives an indication of the strength of evidence in favour of that strategy being cost-effective.

2.4.4 Interpreting results

Our analysis was built around clinical data and costs for patients with multi-vessel disease who are eligible for both procedures. Consideration will be given to the fact that in patients with single vessel disease PCI is likely to be less costly and have the same effectiveness. In many parameters of our model we have favoured CABG, e.g. we excluded stroke from the outcomes, and we have included RCTs where a mix of stent and non-stent PCI was used (MASS-II trial)[28].

3 Results

3.1 Base case results

The base case results show that CABG generates more QALYs than PCI over a ten-year period but it generates more costs too (Table 9). The ICER is above what NICE considers to be cost-effective (£20,000/QALY). Therefore PCI is the most cost-effective choice among these two procedures for patients with characteristics similar to the ones enrolled in the trials included in the analysis.

Table 9 - Results of base case analysis

Strategy	Cost	Incr Cost	Eff	Incr Eff	ICER
PCI Stents	£10,638		6.1167		
CABG	£13,085	£2,447	6.1992	0.0825	£29,661

Table 10 reports the costs associated with the different types of resources considered in the model.

Table 10 – Cost breakdown – discounted cost per patient in the PCI and CABG strategy

Cost category	PCI	CABG
Procedures (including repeats)	£4,816	£8,221
Drugs	£1,165	£715
Further assessments	£3,895	£3,431
Treating MI	£212	£168
Rehabilitation	£500	£500
TOTAL	£10,638	£13,085

Overall CABG decreases those costs which occur later in the model (medication, further assessments, and treatment of MI) but in terms of cost of procedures CABG largely exceeds the cost in the PCI group even when the probability of repeating the procedure (higher in the PCI group) is accounted for.

3.2 Sensitivity analysis

3.2.1 Deterministic sensitivity analyses

The main driver of the results was the high initial cost of the CABG procedure.

Since PCI is associated with higher rates of repeat revascularisation, we have explored if results were sensitive to the future costs both by eliminating the discounting for costs and effectiveness (which in the base case favours interventions with low initial costs even if associated with higher future costs) and by changing the assumption around the type of procedure used as a repeat revascularisation (PCI in all the cases in the base case; CABG was possible in the sensitivity analysis).

In the base case the initial disutility associated with the CABG intervention was calculated incrementally compared to PCI; in a sensitivity analysis we have incorporated the disutility of repeating PCI by calculating the decrement in HRQoL as a differential from the 'no angina' state. We have also used alternative data on disutilities obtained from a separate study[32].

Our clinical data were limited to a 10-year period; however we could extrapolate data to a lifetime horizon assuming a constant rate of events except for death which was assumed to be equal to the general population after 10 years from the intervention and therefore did not vary according to the initial intervention.

The results of the sensitivity analyses conducted are reported in Table 11.

Table 11 - Results of sensitivity analyses

Type of sensitivity analysis	Result
No discount rate	ICER CABG vs. PCI = £24,016/QALY
Threshold analysis on proportion of CABG as repeat revascularisation procedure	PCI is the most cost-effective initial strategy if less than 85% of the repeat revascularisation procedures are CABG
Disutilities of PCI and CABG calculated as differential from 'no angina' state	ICER CABG vs. PCI = £28,850/QALY
Threshold analysis on proportion of CABG as repeat revascularisation procedure after disutilities of PCI and CABG were calculated as differential from 'no angina' state	PCI is the most cost-effective initial strategy if less than 83% of the repeat revascularisation procedures are CABG
Disutility of PCI calculated from Shrive et al. (2007)[32]	ICER CABG vs. PCI = £27,070/QALY
Cost of medication in the angina state = £171 per year excluding simvastatin[30]	ICER CABG vs. PCI = £29,354/QALY
Lifetime horizon (mean patient's age = 65)	ICER CABG vs. PCI = £20,050/QALY

3.2.2 Probabilistic sensitivity analysis

The results of the PSA show the uncertainty over the base case results (Table 12). In non-linear models, such as Markov models, there is often a difference between the deterministic and probabilistic results and in such cases the probabilistic results should take precedence.

If we consider a 95% confidence interval the base case results did not reach statistical significance.

Table 12 - Results of PSA - CABG vs. PCI

Mean cost (£)	Mean QALYs	Mean ICER (£/QALY)	95% CI – lower limit (£/QALY)	95% CI – upper limit (£/QALY)	Probability of being cost-effective at £20,000/QALY
PCI 10,555 CABG 12,982	PCI 6.0857 CABG 6.1551	34,971	CABG dominates	PCI dominates	PCI 63% CABG 37%

At a willingness to pay of £20,000/QALY PCI has only a 63% probability of being cost-effective; the two interventions have a similar probability (54% and 46% respectively for PCI and CABG) when a £30,000/QALY threshold is adopted (Figure 2).

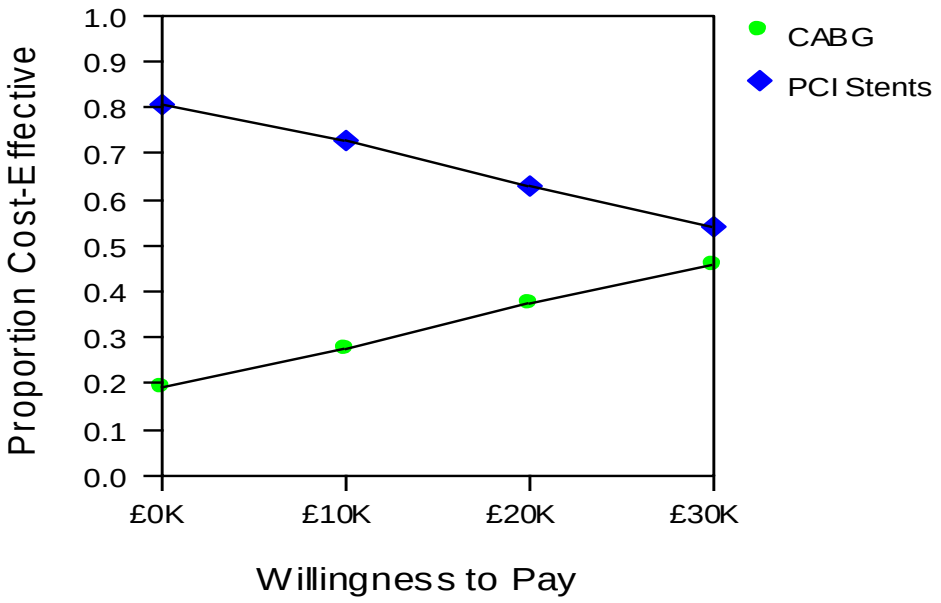


Figure 2 - Acceptability curve of PCI and CABG

The uncertainty can also be graphically represented by plotting the results of the incremental analysis for all the 10,000 simulations into a cost-effectiveness plane (Figure 3). Each point represents the ICER of CABG vs. PCI for each simulation. The dotted line represents the £20,000/QALY threshold: the dots below the line indicate a simulation where CABG was cost-effective and those above the line where CABG was not cost-effective. The ellipse delimits the 95% confidence area.

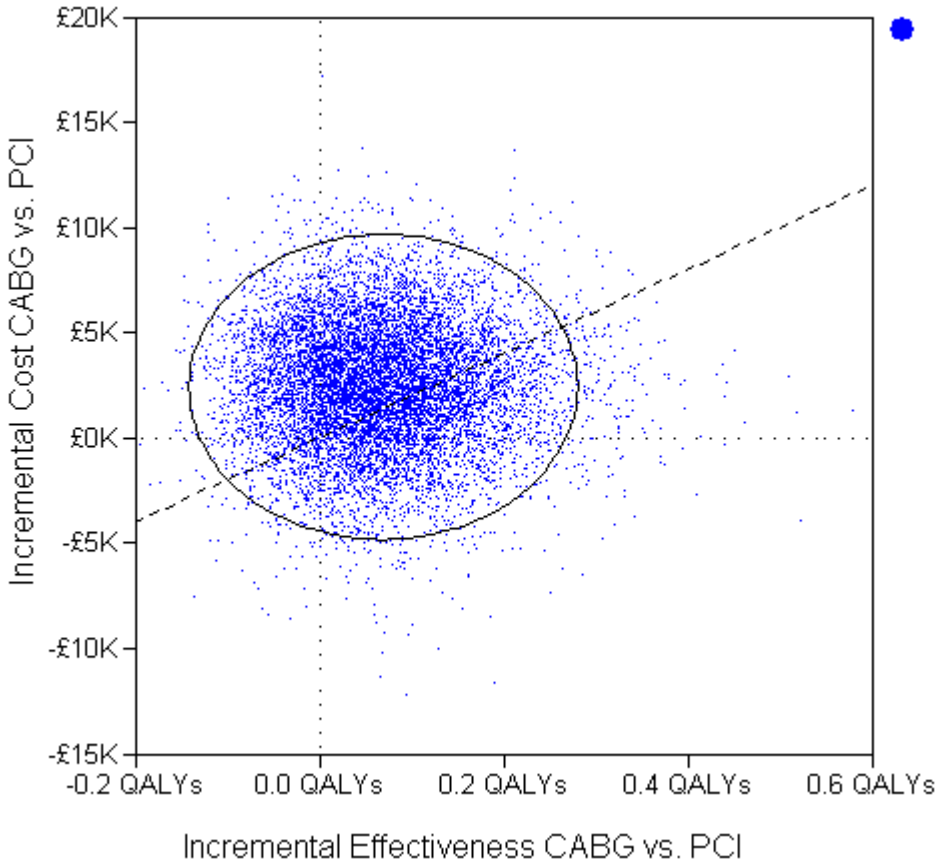


Figure 3 - Incremental cost-effectiveness scatterplot - CABG vs. PCI

4 Discussion

4.1 Summary of results

A new cost-utility analysis was developed which compared CABG and PCI as a revascularisation procedure for patients with angina who are eligible for both. This was based on the RCT data identified in the clinical review; the clinical outcomes incorporated in the model were mortality, myocardial infarction, repeat revascularisation, and presence of angina symptoms. Costs and QALYs were considered from a NHS and personal social services perspective.

We found that CABG was not cost effective when compared to PCI. This conclusion was robust to various deterministic sensitivity analyses; however, when parameters were varied simultaneously in a PSA the results were uncertain.

4.2 Limitations & interpretation

The analysis is based on clinical studies and therefore issues concerning the interpretation of the clinical studies also apply to the interpretation of the economic analysis. One of the main limitations of the model is the possibility that the included population is not representative of the general population of patients with angina. Moreover, the trials in the analysis were conducted over a long time period and the use of different surgical and percutaneous

techniques may have influenced the relative risks and benefits of the two revascularisation strategies.

The model structure was kept simple and did not incorporate the different mortality rate in patients with MI or angina. This was a pragmatic approach because the trials did not report different mortality rates in people with MI or angina in each arm.

We had to disregard some clinical data (i.e. mortality at 6 years from the SoS trial, and repeat revascularisation at 10 years from MASS-II trial) because they were inconsistent with the trend from the meta-analysis of all the studies at previous time points; in fact, the cumulative proportion of patients who were alive in the SoS trial or who had a repeat procedure in the MASS-II trial was smaller than the proportion at the previous time point calculated from the meta-analysis of clinical studies. In the latter example, the meta-analysis at a previous time point included the MASS-II trial as well.

HRQoL data were not available from most of the trials; some values were available from the ARTS study[4]; however, had we used HRQoL outcomes from one trial we would have had to disregard the intermediate clinical outcomes (incidence of MI, angina symptoms) from other trials. In our model we used one estimate of utility attached to the 'angina' health state, thus we did not capture the possible impact of differences in symptom severity.

We decided not to include stroke in the analysis because of concern about heterogeneity in the definition of stroke across the studies. Furthermore many assumptions on the severity and cost of treatment for stroke would have had to be made. Since the results of the model showed that PCI was more cost-effective and stroke was more frequent in the CABG group (see chapter 12) inclusion of stroke in the model would not have changed the overall result.

Furthermore, our analysis has been unfavourable to PCI as we added the cost of additional stents to the basic cost of the procedure, which already included the use of some stents. In addition, for every patient developing angina in any cycle after the initial intervention we included the costs of a referral, myocardial perfusion scan with SPECT, and coronary angiography, and this is likely to overestimate the true requirement for these additional procedures.

4.3 Generalisability to other populations / settings

Individuals participating in the trials included in the analysis were a highly selected population. The analysis was based on randomised trials of PCI versus CABG and the results only directly apply to patients considered eligible for either revascularisation procedure.

A validated risk score for patients with stable angina is not available and therefore a stratified analysis on different baseline risk was not performed as in practice the baseline risk cannot be precisely quantified.

Patients in the trials had multi-vessel disease; in single vessel disease the repeat revascularisation rate is generally lower compared to multi-vessel disease and PCI is likely to be an even more cost-effective option for this group of patients.

4.4 Comparisons with published studies

All the studies identified in our review (see Chapter 12 and economic evidence tables in Appendix G) consistently reported higher cost of CABG compared to PCI. The difference in costs tends to decrease when a longer follow-up time was considered (e.g. in the ARTS study[4], RITA trial[7]). Of the other three cost-utility analyses[3,10,11], two[3,11] showed that CABG was not cost-effective but their analysis was limited to a one-year time horizon. The other analysis[10] concluded that CABG was cost-effective in patients suitable for both procedures; however this study was based on non-randomised data and probably most of the PCI procedures were without stents.

Our analysis included the routine use of stent during PCI procedures, and combines short and long follow-up data from a systematic review of RCTs.

4.5 Conclusion= Evidence statement

Our analysis suggests that CABG is effective but not cost-effective compared with PCI for patients eligible for both procedures but there is some uncertainty around this conclusion.

4.6 Implications for future research

Had a validated score for risk stratification for stable angina been available at the time of our analysis we could have identified the most appropriate population for each of the interventions compared. This would mean the resources are distributed more cost-effectively (i.e. offering CABG or PCI only to those patients that would benefit more from the intervention).

Reference List

1 Abizaid A, Costa MA, Centemero M, et al. Clinical and economic impact of diabetes mellitus on percutaneous and surgical treatment of multivessel coronary disease patients: insights from the Arterial Revascularization Therapy Study (ARTS) trial. Circulation 2001 Jul 31;104:533-8.

2 de Feyter PJ, Serruys PW, Unger F, et al. Bypass surgery versus stenting for the treatment of multivessel disease in patients with unstable angina compared with stable angina. Circulation 2002;105:2367-72.

3 Eefting F, Nathoe H, van Dijk D, et al. Randomized comparison between stenting and off-pump bypass surgery in patients referred for angioplasty. Circulation 2003 Dec 9;108:2870-6.

4 Legrand VM, Serruys PW, Unger F, et al. Three-year outcome after coronary stenting versus bypass surgery for the treatment of multivessel disease. Circulation 2004 Mar 9;109:1114-20.

5 Weintraub WS, Mauldin PD, Becker E, et al. A comparison of the costs of and quality of life after coronary angioplasty or coronary surgery for multivessel coronary artery disease. Results from the Emory Angioplasty Versus Surgery Trial (EAST). Circulation 1995 Nov 15;92:2831-40.

6 Weintraub WS, Becker ER, Mauldin PD, et al. Costs of revascularization over eight years in the randomized and eligible patients in the Emory Angioplasty versus Surgery Trial (EAST). Am J Cardiol 2000 Oct 1;86:747-52.

7 Henderson RA, Pocock SJ, Sharp SJ, et al. Long-term results of RITA-1 trial: clinical and cost comparisons of coronary angioplasty and coronary-artery bypass grafting. Lancet 1998 Oct 31;352:1419-25.

8 Sculpher MJ, Seed P, Henderson RA, et al. Health service costs of coronary angioplasty and coronary artery bypass surgery: the Randomised Intervention Treatment of Angina (RITA) trial. Lancet 1994;344:927-33.

9 Zhang Z, Mahoney EM, Spertus JA, et al. The impact of age on outcomes after coronary artery bypass surgery versus stent-assisted percutaneous coronary intervention: one-year results from the Stent or Surgery (SoS) trial. Am Heart J 2006 Dec;152:1153-60.

10 Griffin SC, Barber JA, Manca A, et al. Cost effectiveness of clinically appropriate decisions on alternative treatments for angina pectoris: prospective observational study. Br Med J 2007;334:624-8.

11 Weintraub WS, Mahoney EM, Zhang Z, et al. One year comparison of costs of coronary surgery versus percutaneous coronary intervention in the stent or surgery trial. Heart 2004 Jul;90:782-8.

12 National Institute for Health and Clinical Excellence. The Guidelines Manual 2009. London: National Institute for Health and Clinical Excellence; 2009.

13 Melsop KA, Boothroyd DB, Hlatky MA. Quality of life and time trade-off utility measures in patients with coronary artery disease. Am Heart J 2003 Jan;145:36-41.

14 Department of Health. NHS Reference Costs 2008-09. UK: Department of Health; 2010 Oct 25.

15 Royal Pharmaceutical Society of Great Britain. British National Formulary. 59 ed. London: Pharmaceutical Press; 2010.

16 Bethell H, Lewin R, Dalai H. Cardiac rehabilitation in the United Kingdom. Heart 2009;95:271-5.

17 National Clinical Guideline Centre for Acute and Chronic Conditions. Chest pain of recent onset: assessment and diagnosis of recent onset chest pain or discomfort of suspected cardiac origin. London: National Insititute for Health and Clincial Excellence; 2010 Mar. Report No.: CG95.

18 National Clinical Guideline Centre for Acute and Chronic Conditions. Unstable Angina and NSTEMI: the early management of unstable angina and non-ST-segment-elevation myocardial infarction. London: National Institute for Health and Clincial Excellence; 2010 Mar. Report No.: CG94.

19 Buszman PE, Kiesz SR, Bochenek A, et al. Acute and late outcomes of unprotected left main stenting in comparison with surgical revascularization. J Am Coll Cardiol 2008 Feb 5;51:538-45.

20 Sigwart U, Stables R, Booth J, et al. Coronary artery bypass surgery versus percutaneous coronary intervention with stent implantation in patients with multivessel coronary artery disease (the Stent or Surgery trial): A randomised controlled trial. Lancet 2002;360:965-70.

21 Serruys PW, Unger F, Sousa JE, et al. Comparison of coronary-artery bypass surgery and stenting for the treatment of multivessel disease. N Engl J Med 2001;344:1117-24.

22 Serruvs PW, Morice MC, Kappetein AP, et al. Percutaneous coronary intervention versus coronary-artery bypass grafting for severe coronary artery disease. N Engl J Med 2009;360:961-72.

23 Hueb W, Soares PR, Gersh BJ, et al. The Medicine, Angioplasty, or Surgery Study (MASS-II): a randomized, controlled clinical trial of three therapeutic strategies for multivessel coronary artery disease. One-year results. J Am Coll Cardiol 2004;43:1743-51.

24 Unger F, Serruys PW, Yacoub MH, et al. Revascularization in multivessel disease: comparison between two-year outcomes of coronary bypass surgery and stenting. J Thorac Cardiovasc Surg 2003 Apr;125:809-20.

25 Booth J, Clayton T, Pepper J, et al. Randomized, controlled trial of coronary artery bypass surgery versus percutaneous coronary intervention in patients with multivessel coronary artery disease: six-year follow-up from the Stent or Surgery Trial (SoS). Circulation 2008 Jul 22;118:381-8.

26 Serruys PW, Ong AT, van Herwerden LA, et al. Five-year outcomes after coronary stenting versus bypass surgery for the treatment of multivessel disease: the final analysis

of the Arterial Revascularization Therapies Study (ARTS) randomized trial. J Am Coll Cardiol 2005 Aug 16;46:575-81.

27 Hueb W, Lopes NH, Gersh BJ, et al. Five-year follow-up of the Medicine, Angioplasty, or Surgery Study (MASS II): A randomized controlled clinical trial of 3 therapeutic strategies for multivessel coronary artery disease. Circulation 2007;115:1082-9.

28 Hueb W, Lopes N, Gersh BJ, et al. Ten-year follow-up survival of the Medicine, Angioplasty, or Surgery Study (MASS II). A randomized controlled clinical trial of 3 therapeutic strategies for multivessel coronary artery disease. Circulation 2010 Aug 23;122:943-5.

29 Scuffham PA, Kosa J. The cost-effectiveness of fluvastatin in Hungary following successful percutaneous coronary intervention. Cardiovasc Drugs Ther 2006 Aug;20:309-17.

30 Ward S, Lloyd-Jones M, Pandor A, et al. A systematic review and economic evaluation of statins for the prevention of coronary events. Health Technology Assessment 11[14], 1-160. 2004.

31 Goodacre SW, Nicholl J, Dixon S, et al. Randomised controlled trial and economic evaluation of a chest pain observation unit compared with routine care. Br Med J 2004;328:254-7.

32 Shrive FM, Ghali WA, Johnson JA, et al. Use of the US and UK scoring algorithm for the EuroQol-5D in an economic evaluation of cardiac care. Med Care 2007;45:269-73.

33 Weintraub WS, Boden WE, Zhang Z, et al. Cost-effectiveness of percutaneous coronary intervention in optimally treated stable coronary patients. Circulation Cardiovascular Quality and Outcomes 2008 Sep;1:12-20.

Appendix I

Criteria for selecting key priorities for implementation

Key priorities for implementation	Selection criteria used
Explore and address issues according to the person's needs, which may include: – self-management skills such as pacing their activities and goal setting – concerns about the impact of stress, anxiety or depression on angina – advice about physical exertion including sexual activity.	• have a high impact on outcomes that are important to patients
Offer people optimal drug treatment for the initial management of stable angina. Optimal drug treatment consists of one or two anti-anginal drugs as necessary plus drugs for secondary prevention of cardiovascular disease.	• lead to more efficient use of NHS resources • have a high impact on reducing variation in care and outcomes • have a high impact on outcomes that are important to patients
Consider revascularisation (coronary artery bypass graft [CABG] or percutaneous coronary intervention [PCI]) for people with stable angina whose symptoms are not satisfactorily controlled with optimal medical treatment.	• have a high impact on reducing variation in care and outcomes • have a high impact on outcomes that are important to patients
When either procedure would be appropriate, offer PCI in preference to CABG for people with anatomically less complex disease whose symptoms are not satisfactorily controlled with optimal medical treatment, unless the person expresses a preference for CABG.	• lead to more efficient use of NHS resources • highlights the need for practice to change • may be viewed as potentially contentious, or difficult to implement for other reasons
When either procedure would be appropriate, take into account the potential survival advantage of CABG over PCI for people with multivessel disease whose symptoms are not satisfactorily controlled with optimal medical treatment and	• have a high impact on outcomes that are important to patients

who: – have diabetes **or** – are over 65 years **or** – have anatomically complex three-vessel disease, with or without involvement of the left main stem.	
Consider the relative risks and benefits of CABG and PCI for people with stable angina using a systematic approach to assess the severity and complexity of the person's coronary disease, in addition to other relevant clinical factors and comorbidities.	• lead to more efficient use of NHS resources • have a high impact on outcomes that are important to patients
Ensure that there is a regular multidisciplinary team meeting to discuss the risks and benefits of continuing drug treatment or the revascularisation strategy (CABG or PCI) for people with stable angina. The team should include cardiac surgeons and interventional cardiologists. Treatment strategy should be discussed for the following people, including but not limited to: – people with left main stem or anatomically complex three-vessel disease – people in whom there is doubt about the best method of revascularisation because of the complexity of coronary anatomy, the extent of stenting required or other relevant clinical factors and comorbidities.	• lead to more efficient use of NHS resources • have a high impact on reducing variation in care and outcomes • may be viewed as potentially contentious, or difficult to implement for other reasons
Ensure people with stable angina receive balanced information and have the opportunity to discuss the benefits, limitations and risks of continuing drug treatment, CABG and PCI to help them make an informed decision about their treatment. When either revascularisation procedure is appropriate, explain to the person: – The main purpose of revascularisation is to improve the symptoms of stable angina. – CABG and PCI are effective in relieving symptoms. – Repeat revascularisation may be necessary after either CABG or PCI and the rate is lower after CABG. – Stroke is uncommon after either CABG or PCI, and the incidence is similar between the two procedures. – There is a potential survival advantage with CABG for some people with multivessel disease.	• promote patient choice

Discuss the following with people whose symptoms are satisfactorily controlled with optimal medical treatment: – their prognosis without further investigation – the likelihood of having left main stem disease or proximal three-vessel disease – the availability of CABG to improve the prognosis in a subgroup of people with left main stem or proximal three-vessel disease – the process and risks of investigation – the benefits and risks of CABG, including the potential survival gain.	• promote patient choice

Criteria for selecting high priority research recommendations

1.1 Adding a newer anti-anginal drug to a calcium channel blocker

Research question:

What is the clinical and cost effectiveness of adding a newer anti-anginal drug (nicorandil, ivabradine or ranolazine) to a calcium channel blocker for treating stable angina?

Why this is important:

We do not know the clinical and cost effectiveness of adding a newer anti-anginal drug to a calcium channel blocker in people with stable angina. We propose a double-blind placebo-controlled randomised trial comparing the addition of a newer anti-anginal drug to a calcium channel blocker with a calcium channel blocker alone in people with stable angina whose symptoms are not being controlled. Endpoints would include symptom severity, quality of life, long-term morbidity and mortality, and cost effectiveness. The results of the trial would influence clinical practice and inform future updates of key recommendations in this guideline.

Criteria for selecting high-priority research recommendations:

Importance to patients or the population. What would be the impact on the population of any new or altered guidance? (for example, acceptability to patients, quality of life, morbidity or disease prevalence, severity of disease or mortality).	It is important to find out the additional benefit that can be gained from using a newer anti-anginal agent with a Calcium Channel Blocker in patients with Angina because it may provide them with an alternative treatment that would alleviate the severity of their disease and a better quality of life.
Relevance to NICE guidance How would the answer to this question change future NICE guidance (that is, generate new knowledge and/or evidence)?	This knowledge will help in updating the NICE Guidance in the treatment of Stable Angina.
Relevance to the NHS What would be the impact on the NHS and (where relevant) the public sector of any new or altered guidance (for example, financial advantage, effect on staff, impact on strategic planning or service delivery)?	Providing a better control of Angina would also help in reducing the complications of the disease, GP and Hospital attendance, thereby saving the NHS unnecessary expenditure.
National priorities Is the question relevant to a national priority area (such as a national service framework or white paper)?	This is very relevant to the CHD NHS service Framework and to the current Stable Angina Guidance.

The relevant document should be specified.	
Current evidence base What are the problems with the current evidence base? (that is, why is further research required?) Reference should be made to the section of the full guideline that describes the current evidence base, including details of trials and systematic reviews.	Often newer agents can safely be added to B-Blockers. However, currently, there is no evidence of any trial that has been conducted to elucidate the benefit of adding one of the newer Anti-anginal drugs mentioned before, to a Calcium Channel Blocker.
Equality Does the research recommendation address equality issues? For example, does it focus on groups that need special consideration, or focus on an intervention that is not available for use by people with certain disabilities?	The proposed trial will focus on groups of patients with Angina in whom a second anti-anginal agent is needed and also on those in whom B-Blockers are not tolerated or contraindicated.
Study design It should also specify the most appropriate study design to address the proposed question(s). Primary research or secondary research (for example, systematic reviews) can be recommended.	This will be a primary research and should take the style of Double-blind RCT.
Feasibility Can the proposed research be carried out in a realistic timescale and at an acceptable cost? Are there any ethical or technical issues?	This proposed research can be carried out in 1-2 years at an acceptable cost with the help of the relevant pharmaceutical firms and has to comply with the ethical standards of research in the UK.
Other comments Any other important issues should be mentioned, such as potential funders or outcomes of previous attempts to address this issue or methodological problems. However, this is not a research protocol.	
Importance How important is the question to the overall guideline? The research recommendation should be categorised into one of the following categories of importance: • High: the research is essential to inform future updates of key	High Importance

recommendations in the guideline • Medium: the research is relevant to the recommendations in the guideline, but the research recommendations are not key to future updates • Low: the research is of interest and will fill existing evidence gaps.	

1.2 Management of stable angina in people with evidence of ischaemia on non-invasive functional testing

Research question:

Do people with stable angina and evidence of reversible ischaemia on non-invasive functional testing who are on optimal drug treatment benefit from routine coronary angiography with a view to revascularisation?

Why this is important:

Revascularisation has traditionally been offered to people with stable angina who have evidence of reversible ischaemia on non-invasive functional testing. Recent trials in people with stable angina (COURAGE, BARI-2D, MASS II) have not shown survival benefit from revascularisation compared with drug treatment. In the nuclear substudy of COURAGE (n = 314), PCI was shown to be more effective in treating ischaemia than optimal drug treatment, and in multivariate analyses reduction of ischaemia was associated with greater event-free survival. It is unclear, however, whether people on optimal drug treatment who have evidence of inducible ischaemia on non-invasive functional testing should routinely have coronary angiography and revascularisation. This question is particularly relevant for people who have responded adequately (say Canadian Cardiovascular Class 1 or 2) to optimal drug treatment and in whom, based on symptoms alone, revascularisation is not indicated. To answer this question we recommend a randomised trial of interventional management versus continued drug treatment in people with stable angina and myocardial ischaemia on non-invasive functional testing, with all-cause mortality and cardiovascular mortality as the primary endpoints.

Criteria for selecting high-priority research recommendations:

<u>Importance to patients or the population.</u> What would be the impact on the population of any new or altered guidance? (for example, acceptability to patients, quality of life, morbidity or disease prevalence, severity of disease or mortality).	Uncertainty remains, about whether decisions for cardiac catheterisation in patients on optimal medical treatment should be driven by symptoms alone or by the results of non-invasive ischaemia testing. Research is aimed to address this

	uncertainty
Relevance to NICE guidance How would the answer to this question change future NICE guidance (that is, generate new knowledge and/or evidence)?	Will inform future updates of key recommendations in the guideline
Relevance to the NHS What would be the impact on the NHS and (where relevant) the public sector of any new or altered guidance (for example, financial advantage, effect on staff, impact on strategic planning or service delivery)?	Identifying the optimal diagnostic procedures required prior to PCI can help optimise resource utilisation within the NHS and minimise variation in clinical practice and outcomes
National priorities Is the question relevant to a national priority area (such as a national service framework or white paper)? The relevant document should be specified.	.
Current evidence base What are the problems with the current evidence base? (that is, why is further research required?) Reference should be made to the section of the full guideline that describes the current evidence base, including details of trials and systematic reviews.	Recent trials that have recruited patients with stable angina (COURAGE, BARI-2D, MASS II), have failed to confirm survival benefit for revascularisation strategies compared with medical treatment. In the nuclear substudy of COURAGE, percutaneous intervention produced more effective resolution of ischaemia than optimal medical treatment but only 314 patients were recruited and risk-adjusted mortality was similar for the two groups.
Equality Does the research recommendation address equality issues? For example, does it focus on groups that need special consideration, or focus on an intervention that is not available for use by people with certain disabilities?	
Study design It should also specify the most appropriate study design to address the proposed question(s). Primary research or secondary research (for example, systematic reviews) can be recommended.	The question is particularly relevant in the group of patients that has responded adequately (say CCS class 1 or 2) to optimal medical treatment in whom revascularisation on symptomatic grounds is not indicated. To answer the question in this group we recommend a randomised trial of interventional versus continuing

	medical management in with all cause and cardiovascular mortality as the primary endpoints.
Feasibility Can the proposed research be carried out in a realistic timescale and at an acceptable cost? Are there any ethical or technical issues?	
Other comments Any other important issues should be mentioned, such as potential funders or outcomes of previous attempts to address this issue or methodological problems. However, this is not a research protocol.	
Importance How important is the question to the overall guideline? The research recommendation should be categorised into one of the following categories of importance: • High: the research is essential to inform future updates of key recommendations in the guideline • Medium: the research is relevant to the recommendations in the guideline, but the research recommendations are not key to future updates • Low: the research is of interest and will fill existing evidence gaps.	High importance.

1.3 Early revascularisation strategy for people with angina and multivessel disease

Research question:

In people with stable angina and multivessel disease (including left main stem [LMS] disease) whose symptoms are controlled with optimal drug treatment, would an initial treatment strategy of revascularisation be clinically and cost effective compared with continued drug treatment?

Why this is important:

Research is needed to determine whether early investigation and revascularisation can improve longer term survival. People with stable angina may be disadvantaged if they do not have tests to identify whether they have a higher risk profile for early cardiac death, which could be reduced by revascularisation. This disadvantage could be magnified when people who are deemed to fall into very high risk groups (for example, LMS stenosis > 50% in the MASS II trial) are excluded from randomised trials, resulting in the benefits of revascularisation being underestimated. We propose a randomised trial comparing an initial strategy of revascularisation (PCI or CABG) with an initial strategy of continued drug treatment in people with multivessel disease (including LMS disease) in whom revascularisation is not needed for symptom relief. The trial should use drug-eluting stents and wider inclusion criteria than BARI-2D and COURAGE.

Criteria for selecting high-priority research recommendations:

Importance to patients or the population. What would be the impact on the population of any new or altered guidance? (for example, acceptability to patients, quality of life, morbidity or disease prevalence, severity of disease or mortality).	Potentially improved survival, fewer myocardial infarctions, and fewer hospitalisations for repeat interventions
Relevance to NICE guidance How would the answer to this question change future NICE guidance (that is, generate new knowledge and/or evidence)?	Could significantly change the recommendations by encouraging earlier investigation or provide a reliable evidence base for not doing so.
Relevance to the NHS What would be the impact on the NHS and (where relevant) the public sector of any new or altered guidance (for example, financial advantage, effect on staff, impact on strategic planning or service delivery)?	Advancing the treatment of coronary artery disease to the highest international standards.
National priorities Is the question relevant to a national priority area (such as a national service framework or white paper)? The relevant document should be specified.	Contributes to implementation of the NSF for Coronary Heart Disease
Current evidence base What are the problems with the current evidence base? (that is, why is further research required?) Reference	This question has not been formally addressed leaving a significant gap in the evidence base.

should be made to the section of the full guideline that describes the current evidence base, including details of trials and systematic reviews.	
Equality Does the research recommendation address equality issues? For example, does it focus on groups that need special consideration, or focus on an intervention that is not available for use by people with certain disabilities?	Current practice for investigation of stable coronary disease is patchy and a reliable evidence base would improve equality of care
Study design It should also specify the most appropriate study design to address the proposed question(s). Primary research or secondary research (for example, systematic reviews) can be recommended.	A randomised study of patients in primary and secondary care whose symptoms are apparently adequately controlled with medication
Feasibility Can the proposed research be carried out in a realistic timescale and at an acceptable cost? Are there any ethical or technical issues?	No major stumbling blocks evident.
Other comments Any other important issues should be mentioned, such as potential funders or outcomes of previous attempts to address this issue or methodological problems. However, this is not a research protocol.	
Importance How important is the question to the overall guideline? The research recommendation should be categorised into one of the following categories of importance: • High: the research is essential to inform future updates of key recommendations in the guideline • Medium: the research is relevant to the recommendations in the guideline, but the research recommendations are not key to future updates • Low: the research is of interest and	High

will fill existing evidence gaps.	

1.4 Cardiac Rehabilitation

Research question:

Is an 8-week, comprehensive, multidisciplinary, cardiac rehabilitation service more clinically and cost effective for managing stable angina than current clinical practice?

Why this is important:

Cardiac rehabilitation programmes are an established treatment strategy for certain heart conditions, such as for people who have had a heart attack. However, there is no evidence to suggest that cardiac rehabilitation is clinically or cost effective for managing stable angina. Research to date has looked at short-term outcomes, such as a change in diet or exercise levels, but the effect on morbidity and mortality has not been studied. A randomised controlled trial is required to compare comprehensive cardiac rehabilitation with standard care in people with stable angina, with measures of angina severity (exercise capacity, angina frequency, use of a short-acting nitrate), and long-term morbidity and mortality as endpoints.

Criteria for selecting high-priority research recommendations:

<u>Importance to patients or the population.</u> What would be the impact on the population of any new or altered guidance? (for example, acceptability to patients, quality of life, morbidity or disease prevalence, severity of disease or mortality).	It would help optimise and standardise care for patients with stable angina and reduce variation. It would provide a structured comprehensive MDT service accessible to stable angina patients.
<u>Relevance to NICE guidance</u> How would the answer to this question change future NICE guidance (that is, generate new knowledge and/or evidence)?	There is no comprehensive evidence base currently.
<u>Relevance to the NHS</u> What would be the impact on the NHS and (where relevant) the public sector of any new or altered guidance (for example, financial advantage, effect on staff, impact on strategic planning or service delivery)?	Identifying whether CR is clinically and cost effective for patients with stable angina, will help determine pathways for stable angina patients that will standardise their care, and reduce variation.
<u>National priorities</u> Is the question relevant to a national priority area (such as a national	The NSF for CHD was unable to clarify if CR was appropriate for stable angina patients; Consequently this research work

service framework or white paper)? The relevant document should be specified.	could provide structure to National Frameworks.
Current evidence base What are the problems with the current evidence base? (that is, why is further research required?) Reference should be made to the section of the full guideline that describes the current evidence base, including details of trials and systematic reviews.	There is no evidence that evaluates the whole package that CR could potentially provide.
Equality Does the research recommendation address equality issues? For example, does it focus on groups that need special consideration, or focus on an intervention that is not available for use by people with certain disabilities?	Research can address equality issues e.g. evidence can minimise variation in the management and resulting outcomes for stable angina patients
Study design It should also specify the most appropriate study design to address the proposed question(s). Primary research or secondary research (for example, systematic reviews) can be recommended.	Previous studies that have looked at aspects of cardiac rehabilitation to angina patients, have been small, with only short term follow up. Therefore it is suggested that a Randomised Control Study, with follow up at 5 years, will help to address this gap. Sample groups should be greater than 100.
Feasibility Can the proposed research be carried out in a realistic timescale and at an acceptable cost? Are there any ethical or technical issues?	There is a large stable angina population across the UK as well as numerous establishments that currently provide CR services to stable angina patients.
Other comments Any other important issues should be mentioned, such as potential funders or outcomes of previous attempts to address this issue or methodological problems. However, this is not a research protocol.	The University of Glamorgan has supported a similar research project that addressed the issue of Heart Failure and CR; they may consider supporting this research. The British Heart Foundation may be a potential supporter
Importance How important is the question to the overall guideline? The research recommendation should be categorised into one of the following categories of importance:	Medium to high importance.

• High: the research is essential to inform future updates of key recommendations in the guideline • Medium: the research is relevant to the recommendations in the guideline, but the research recommendations are not key to future updates • Low: the research is of interest and will fill existing evidence gaps.	

1.5 Patient self-management plans

Research question:

What is the clinical and cost effectiveness of a self-management plan for people with stable angina?

Why this is important:

Stable angina is a chronic condition. Evidence suggests that addressing people's beliefs and behaviours in relation to angina may improve quality of life, and reduce morbidity and use of resources. Self-management plans could include: educating people with stable angina about the role of psychological factors in pain and pain control; and teaching people self-management skills to modify cognitions, behaviours and affective responses in order to control chest pain. These skills may include pacing of physical activities, modifying stress using cognitive reframing and problem-solving techniques, and relaxation training or mindfulness techniques. The proposed study is a randomised controlled trial in primary care that would assess the clinical and cost effectiveness of self-management plans. This research would inform future updates of key recommendations in the guideline. Furthermore the research would be relevant to a national priority area (National service framework for coronary heart disease [NSF CHD] chapter 4: stable angina and chapter 7: cardiac rehabilitation) as well as the Coalition White Paper 2010 (Equity and excellence: liberating the NHS) that emphasize the importance of increasing people's choice and control in managing their condition.

Criteria for selecting high-priority research recommendations:

<u>Importance to patients or the population.</u> What would be the impact on the population of any new or altered guidance? (for example, acceptability to patients, quality of life, morbidity or disease prevalence, severity of disease or mortality).	Improved quality of life Improved survival Less use of medication Reduced side effects of medication and

	coronary intervention(PCI and CABG)
Relevance to NICE guidance How would the answer to this question change future NICE guidance (that is, generate new knowledge and/or evidence)?	It would strengthen the evidence for such a plan. If cost effective it would need to be cheaper in resource terms than the status quo ie no effective self management plan in place
Relevance to the NHS What would be the impact on the NHS and (where relevant) the public sector of any new or altered guidance (for example, financial advantage, effect on staff, impact on strategic planning or service delivery)?	It should apply to all stable angina patients whether being seen in primary secondary or tertiary care
National priorities Is the question relevant to a national priority area (such as a national service framework or white paper)? The relevant document should be specified.	NSF CHD chapters 4 (stable angina) and chapter 7 (cardiac rehabilitation) Coalition White Paper 2010: Equity and excellence: Liberating the NHS: Putting patients and public first : We will put patients at the heart of the NHS, through an information revolution and greater choice and control: Shared decision-making will become the norm: no decision about me without me. Patients will have access to the information they want, to make choices about their care. They will have increased control over their own care records.
Current evidence base What are the problems with the current evidence base? (that is, why is further research required?) Reference should be made to the section of the full guideline that describes the current evidence base, including details of trials and systematic reviews.	No UK based studies No primary care based studies No RCTs
Equality Does the research recommendation address equality issues? For example, does it focus on groups that need	Covers all patients

special consideration, or focus on an intervention that is not available for use by people with certain disabilities?	
Study design It should also specify the most appropriate study design to address the proposed question(s). Primary research or secondary research (for example, systematic reviews) can be recommended.	RCT with health economics analysis
Feasibility Can the proposed research be carried out in a realistic timescale and at an acceptable cost? Are there any ethical or technical issues?	RCT in primary care
Other comments Any other important issues should be mentioned, such as potential funders or outcomes of previous attempts to address this issue or methodological problems. However, this is not a research protocol.	
Importance How important is the question to the overall guideline? The research recommendation should be categorised into one of the following categories of importance: • High: the research is essential to inform future updates of key recommendations in the guideline • Medium: the research is relevant to the recommendations in the guideline, but the research recommendations are not key to future updates • Low: the research is of interest and will fill existing evidence gaps.	High

1 Declarations of interests

1.1 Introduction

All members of the GDG and all members of the NCGC staff were required to make formal declarations of interest at the outset of each meeting, and these were updated at every subsequent meeting throughout the development process. No interests were declared that required actions.

1.2 Declarations of interests of the GDG members

1.2.1 Sotiris Antoniou

GDG meeting	*Declaration of Interests*
GDG Application	No interests to declare
First GDG meeting (10th July 2009)	No change in declaration
Second GDG Meeting (04th September 2009)	No change in declaration
Third GDG Meeting (14th October 2009)	No change in declaration
Fourth GDG Meeting (27th November 2009)	No change in declaration
Fifth GDG Meeting (13th January 2010)	No change in declaration
Sixth GDG Meeting (26th February 2010)	SA declared the following item of **personal pecuniary interest:** • Attended a study event (state of the heart) which was sponsored by Astra Zeneca; The event was unrelated to stable angina and any of the drugs associated with stable angina
Seventh GDG Meeting (26th March 2010)	SA declared the following item of **personal pecuniary interest:** • Receipt of honoraria for participation in an Advisory Board for Astra Zeneca for a drug unrelated to stable angina.
Eighth GDG Meeting (14th May 2010)	SA declared the following item of **personal pecuniary interest:** • Receipt of honorarium from GSK for presentation on a drug unrelated to the treatment of stable angina • Receipt of honoraria for participation in an Advisory Board for Bayer for a drug unrelated to stable angina.
Ninth GDG Meeting (18th June 2010)	No change in declaration
Tenth GDG Meeting (23rd July 2010)	No change in declaration
Eleventh GDG Meeting (08th September 2010)	SA declared the following item of **personal pecuniary interest:** • Receipt of honoraria for participation in an Advisory Board on the development of an Integrated Care Pathway unrelated to Stable angina sponsored by Chiesi.
Twelfth GDG Meeting (22nd October 2010)	SA declared the following item of **personal pecuniary interest:** • Presented at HRC meeting and was sponsored by Sanofi Aventis
Thirteenth GDG Meeting (4th March 2011)	No change in declaration

1.2.2 Christopher Blauth

GDG meeting	*Declaration of Interests*
GDG Application	No interests to declare
First GDG meeting (10th July 2009)	No change in declaration
Second GDG Meeting (04th September 2009)	No change in declaration
Third GDG Meeting (14th October 2009)	No change in declaration
Fourth GDG Meeting (27th November 2009)	No change in declaration

GDG meeting	*Declaration of Interests*
Fifth GDG Meeting (13th January 2010)	No change in declaration
Sixth GDG Meeting (26th February 2010)	No change in declaration
Seventh GDG Meeting (26th March 2010)	No change in declaration
Eighth GDG Meeting (14th May 2010)	No change in declaration
Ninth GDG Meeting (18th June 2010)	No change in declaration
Tenth GDG Meeting (23rd July 2010)	No change in declaration
Eleventh GDG Meeting (08th September 2010)	No change in declaration
Twelfth GDG Meeting (22nd October 2010)	No change in declaration
Thirteenth GDG Meeting (4th March 2011)	No change in declaration

1.2.3 Liz Clark

GDG meeting	*Declaration of Interests*
GDG Application	No interests to declare
First GDG meeting (10th July 2009)	LC declared the following item of **personal pecuniary interest:** • Will be undertaking 3 or 4 days work for Mid Devon PCT to help them set up a structure for patient involvement and will be paid a small fee
Second GDG Meeting (04th September 2009)	No change in declaration
Third GDG Meeting (14th October 2009)	No change in declaration
Fourth GDG Meeting (27th November 2009)	No change in declaration
Fifth GDG Meeting (13th January 2010)	No change in declaration
Sixth GDG Meeting (26th February 2010)	No change in declaration
Seventh GDG Meeting (26th March 2010)	No change in declaration
Eighth GDG Meeting (14th May 2010)	No change in declaration
Ninth GDG Meeting (18th June 2010)	No change in declaration
Tenth GDG Meeting (23rd July 2010)	No change in declaration
Eleventh GDG Meeting (08th September 2010)	No change in declaration
Twelfth GDG Meeting (22nd October 2010)	LC declared the following item of **personal non-pecuniary interest:** • Will be a Lay Representative on the Scottish Computed Tomography of the Heart Trail as from Wednesday 13th October, 2010
Thirteenth GDG Meeting (4th March 2011)	No change in declaration

1.2.4 Kevin Fox

GDG meeting	*Declaration of Interests*
GDG Application	No interests to declare
First GDG meeting (10th July 2009)	No change in declaration
Second GDG Meeting (04th September 2009)	No change in declaration
Third GDG Meeting (14th October 2009)	No change in declaration
Fourth GDG Meeting (27th November 2009)	No change in declaration
Fifth GDG Meeting (13th January 2010)	No change in declaration
Sixth GDG Meeting (26th February 2010)	No change in declaration
Seventh GDG Meeting (26th March 2010)	No change in declaration
Eighth GDG Meeting (14th May 2010)	No change in declaration
Ninth GDG Meeting (18th June 2010)	No change in declaration
Tenth GDG Meeting (23rd July 2010)	No change in declaration
Eleventh GDG Meeting (08th September 2010)	KF declared the following item of **personal pecuniary interest:** • Accepted invitation by Servier to comment on the recent trial of its ivabradine in heart failure at an upcoming industry sponsored meeting As a result it was agreed that KF will not participate in any further discussions on pharmacological interventions in stable angina.
Twelfth GDG Meeting (22nd October 2010)	No change in declaration
Thirteenth GDG Meeting (4th March 2011)	No change in declaration

1.2.5 Robert Henderson

GDG meeting	*Declaration of Interests*
GDG Application	RH declared the following item of **personal pecuniary interest:** • Receipt of honoraria for participation in Advisory Boards for two stent manufacturers (Cordis and Abbott) RH declared the following item of **personal non-pecuniary interest:** • Elected member of the British Cardiovascular Intervention Society council; Has contributed to the conduct of randomised trials of percutaneous coronary intervention in the management of patients with angina an coronary artery disease

GDG meeting	*Declaration of Interests*
First GDG meeting (10th July 2009)	No change in declaration
Second GDG Meeting (04th September 2009)	No change in declaration
Third GDG Meeting (14th October 2009)	No change in declaration
Fourth GDG Meeting (27th November 2009)	RH declared the following item of **personal pecuniary interest:** • Receipt of honorarium from Pfizer and Lilly UK for presentations on treatment of ACS
Fifth GDG Meeting (13th January 2010)	RH declared the following item of **personal non-pecuniary interest:** • Author of 1 of the 32 papers reviewed; however this would not result to bias as his publication referred to an older trial of limited value to today's relative merits of PCI vs CABG
Sixth GDG Meeting (26th February 2010)	RH declared the following items of **personal pecuniary interest:** • Receipt of honorarium for participation in conference (PPCI challenge, Manchester) sponsored by Lilly UK, Daichii-Sankyo UK Ltd and Boston Scientific • Receipt of honorarium for participation in conference (ACS challenge, Manchester) sponsored by Pfizer and Lilly UK
Seventh GDG Meeting (26th March 2010)	No change in declaration
Eighth GDG Meeting (14th May 2010)	RH declared the following item of **personal pecuniary interest:** • Receipt of honorarium for participation in a GSK-sponsored meeting on the NICE UA/NSTEMI guideline RH declared the following items of **personal non-pecuniary interest:** • Participation in a Lilly/Boston Scientific/Edwards sponsored meeting and in a meeting of the British Cardiovascular Intervention Society on the NICE UA/NSTEMI guideline. No honorarium was received for either of these presentations
Ninth GDG Meeting (18th June 2010)	RH declared the following item of **personal pecuniary interest:** • Sponsorship by Boston Scientific to attend EuroPCR (May 2010) conference
Tenth GDG Meeting (23rd July 2010)	No change in declaration
Eleventh GDG Meeting (08th September 2010)	No change in declaration
Twelfth GDG Meeting (22nd October 2010)	RH declared the following item of **personal pecuniary interest:** • Sponsored by Edwards Life Science to attend EuroPCR Valve Live meeting (11th to 12th October 2010)

GDG meeting	Declaration of Interests
Thirteenth GDG Meeting (4th March 2011)	RH declared the following item of **personal non-pecuniary interest:** • Attendance at the 'Cardiology and Diabetes at the Limits' Conference on 25–28 Feb 2011; sponsored by Pfizer Ltd, F.Hoffman-La Roche Ltd, Novo Nordisk, AstraZenica South Africa, Medtronic Ltd, Saiichi-Sankyo/Lilly UK, Sanofi-Aventis, Lilly UK Ltd.

1.2.6 Leonard Jacob

GDG meeting	Declaration of Interests
GDG Application	No interests to declare
First GDG meeting (10th July 2009)	No change in declaration
Second GDG Meeting (04th September 2009)	No change in declaration
Third GDG Meeting (14th October 2009)	No change in declaration
Fourth GDG Meeting (27th November 2009)	No change in declaration
Fifth GDG Meeting (13th January 2010)	LJ declared the following item of **personal pecuniary interest:** • Attended a meeting organised by B.I. in November 2009 on "Anticoagulation for the management of Atrial Fibrilation"
Sixth GDG Meeting (26th February 2010)	No change in declaration
Seventh GDG Meeting (26th March 2010)	No change in declaration
Eighth GDG Meeting (14th May 2010)	No change in declaration
Ninth GDG Meeting (18th June 2010)	No change in declaration
Tenth GDG Meeting (23rd July 2010)	No change in declaration
Eleventh GDG Meeting (08th September 2010)	No change in declaration
Twelfth GDG Meeting (22nd October 2010)	No change in declaration
Thirteenth GDG Meeting (4th March 2011)	No change in declaration

1.2.7 Aidan Mac Dermott

GDG meeting	Declaration of Interests
GDG Application	No interests to declare
First GDG meeting (10th July 2009)	No change in declaration
Second GDG Meeting (04th September 2009)	No change in declaration
Third GDG Meeting (14th October 2009)	No change in declaration
Fourth GDG Meeting (27th November 2009)	No change in declaration

GDG meeting	*Declaration of Interests*
Fifth GDG Meeting (13th January 2010)	No change in declaration
Sixth GDG Meeting (26th February 2010)	No change in declaration
Seventh GDG Meeting (26th March 2010)	No change in declaration
Eighth GDG Meeting (14th May 2010)	AD declared the following item of **personal pecuniary interest:** • Received a British Cardiovascular Society (BCS) travel training grant of £100 to attend BCS annual conference; This grant was supported by MSD and Servier
Ninth GDG Meeting (18th June 2010)	No change in declaration
Tenth GDG Meeting (23rd July 2010)	No change in declaration
Eleventh GDG Meeting (08th September 2010)	No change in declaration
Twelfth GDG Meeting (22nd October 2010)	No change in declaration
Thirteenth GDG Meeting (4th March 2011)	No change in declaration

1.2.8 Helen O'Leary

GDG meeting	*Declaration of Interests*
GDG Application	No interests to declare
First GDG meeting (10th July 2009)	No change in declaration
Second GDG Meeting (04th September 2009)	No change in declaration
Third GDG Meeting (14th October 2009)	No change in declaration
Fourth GDG Meeting (27th November 2009)	No change in declaration
Fifth GDG Meeting (13th January 2010)	No change in declaration
Sixth GDG Meeting (26th February 2010)	No change in declaration
Seventh GDG Meeting (26th March 2010)	No change in declaration
Eighth GDG Meeting (14th May 2010)	No change in declaration
Ninth GDG Meeting (18th June 2010)	No change in declaration
Tenth GDG Meeting (23rd July 2010)	No change in declaration
Eleventh GDG Meeting (08th September 2010)	No change in declaration
Twelfth GDG Meeting (22nd October 2010)	HOL declared the following item of **personal pecuniary interest:** • Received a travel training grant by Servier to attend a training event
Thirteenth GDG Meeting (4th March 2011)	No change in declaration

1.2.9 Charles Peebles

GDG meeting	*Declaration of Interests*
GDG Application	No interests to declare
First GDG meeting (10th July 2009)	No change in declaration
Second GDG Meeting (04th September 2009)	No change in declaration
Third GDG Meeting (14th October 2009)	No change in declaration
Fourth GDG Meeting (27th November 2009)	No change in declaration
Fifth GDG Meeting (13th January 2010)	No change in declaration
Sixth GDG Meeting (26th February 2010)	No change in declaration
Seventh GDG Meeting (26th March 2010)	No change in declaration
Eighth GDG Meeting (14th May 2010)	No change in declaration
Ninth GDG Meeting (18th June 2010)	No change in declaration
Tenth GDG Meeting (23rd July 2010)	No change in declaration
Eleventh GDG Meeting (08th September 2010)	No change in declaration
Twelfth GDG Meeting (22nd October 2010)	No change in declaration
Thirteenth GDG Meeting (4th March 2011)	No change in declaration

1.2.10 Maurice Pye

GDG meeting	*Declaration of Interests*
GDG Application	No interests to declare
First GDG meeting (10th July 2009)	No change in declaration
Second GDG Meeting (04th September 2009)	No change in declaration
Third GDG Meeting (14th October 2009)	No change in declaration
Fourth GDG Meeting (27th November 2009)	No change in declaration
Fifth GDG Meeting (13th January 2010)	No change in declaration
Sixth GDG Meeting (26th February 2010)	MP declared the following item of **personal pecuniary interest:** • Receipt of honorarium (£350) paid by Pfizer for speaking at meeting on Statins in Feb 2010
Seventh GDG Meeting (26th March 2010)	No change in declaration
Eighth GDG Meeting (14th May 2010)	MP declared the following item of **personal non-pecuniary interest:** • Co-author of a paper on cardiac rehabilitation in angina ○ Therefore MP did not participate in the drafting of recommendations on the topic

GDG meeting	*Declaration of Interests*
Ninth GDG Meeting (18th June 2010)	No change in declaration
Tenth GDG Meeting (23rd July 2010)	No change in declaration
Eleventh GDG Meeting (08th September 2010)	No change in declaration
Twelfth GDG Meeting (22nd October 2010)	MP declared the following item of **personal pecuniary interest:** • Receipt of honoraria by AstraZeneca and Pfizer for speaking at a conference (Oct 2010)
Thirteenth GDG Meeting (4th March 2011)	No change in declaration

1.2.11 Jonathan Shribman

GDG meeting	*Declaration of Interests*
GDG Application	No interests to declare
First GDG meeting (10th July 2009)	No change in declaration
Second GDG Meeting (04th September 2009)	No change in declaration
Third GDG Meeting (14th October 2009)	No change in declaration
Fourth GDG Meeting (27th November 2009)	No change in declaration
Fifth GDG Meeting (13th January 2010)	No change in declaration
Sixth GDG Meeting (26th February 2010)	No change in declaration
Seventh GDG Meeting (26th March 2010)	No change in declaration
Eighth GDG Meeting (14th May 2010)	No change in declaration
Ninth GDG Meeting (18th June 2010)	No change in declaration
Tenth GDG Meeting (23rd July 2010)	No change in declaration
Eleventh GDG Meeting (08th September 2010)	No change in declaration
Twelfth GDG Meeting (22nd October 2010)	No change in declaration
Thirteenth GDG Meeting (4th March 2011)	No change in declaration

1.2.12 Roger Till

GDG meeting	*Declaration of Interests*
GDG Application	No interests to declare
First GDG meeting (10th July 2009)	RT declared the following item of **non-personal pecuniary interest:** • Member of the Patient Participation Group (PPG) at the Lawson General Practice (Nuttall Street, Hackney London): The PPG has just received an Award of £3000 from the Royal College of General Practitioners to support some of the development of a Patient Information Centre at the Practice
Second GDG Meeting (04th September 2009)	No change in declaration
Third GDG Meeting (14th October 2009)	No change in declaration
Fourth GDG Meeting (27th November 2009)	No change in declaration
Fifth GDG Meeting (13th January 2010)	No change in declaration
Sixth GDG Meeting (26th February 2010)	No change in declaration
Seventh GDG Meeting (26th March 2010)	No change in declaration
Eighth GDG Meeting (14th May 2010)	No change in declaration
Ninth GDG Meeting (18th June 2010)	No change in declaration
Tenth GDG Meeting (23rd July 2010)	No change in declaration
Eleventh GDG Meeting (08th September 2010)	No change in declaration
Twelfth GDG Meeting (22nd October 2010)	RT declared the following item of **non-personal non-pecuniary interest:** • Appointed as a Trustee of N.A.P.P. (National Association for Patient Participation)
Thirteenth GDG Meeting (4th March 2011)	No change in declaration

1.2.13 Professor Adam Timmis

GDG meeting	*Declaration of Interests*
GDG Application	AT declared the following items of **non-personal pecuniary interest:** • Siemens sponsors his cardiac research fellow at London Chest Hospital (until June 2009) • NIHR Programme Grant RP-PG-0407-10314 (£1.8M 2008-2012): Improving the quality of care of patients with angina and heart attack AT declared the following items of **personal non-pecuniary interest:** • Conduct of research into the investigation and management of angina

GDG meeting	*Declaration of Interests*
First GDG meeting (10th July 2009)	AT declared the following items of **non-personal pecuniary interest:** • Research grant (£1.2m 2008-2012) by Welcome Trust: Insights into CVD from linking datasets (Hemingway H, Hingorani A, Smeeth L, Kivimaki M, Kalra D, Timmis A.) • NIHR Biomedical Research Unit Grant to develop an academic department of cardiovascular imaging which includes MSCT; Grant includes capital funding for purchase of a new MSCT scanner AT declared the following item of **personal pecuniary interest:** • Ad hoc participation in advisory board for Pfizer (5/04/2009) to discuss statin prescribing in the UK, for which an honorarium was received. No further meetings of this board have taken place
Second GDG Meeting (04th September 2009)	No change in declaration
Third GDG Meeting (14th October 2009)	AT declared the following items of **personal non-pecuniary interest:** • Author on a Ranolazine paper published in the European Heart Journal (2008) • Investigator in the BEAUTIFUL study published in the Lancet (2008)
Fourth GDG Meeting (27th November 2009)	AT declared the following item of **non-personal pecuniary interest:** • Research funded by Welcome Trust and NIHR: Electronic records to investigate causes and prognosis of chest pain and MI AT declared the following item of **personal non-pecuniary interest:** • UK representative for the QUIET trial for ACE inhibitors
Fifth GDG Meeting (13th January 2010)	No change in declaration
Sixth GDG Meeting (26th February 2010)	No change in declaration
Seventh GDG Meeting (26th March 2010)	No change in declaration
Eighth GDG Meeting (14th May 2010)	No change in declaration
Ninth GDG Meeting (18th June 2010)	AT declared the following item of **non-personal pecuniary interest:** • Entered discussions with Servier on the funding of academic research project on the valuation of an intervention in chest pain clinics
Tenth GDG Meeting (23rd July 2010)	No change in declaration
Eleventh GDG Meeting (08th September 2010)	No change in declaration
Twelfth GDG Meeting (22nd October 2010)	No change in declaration
Thirteenth GDG Meeting (4th March 2011)	No change in declaration

1.3 Declarations of interests of the NCGC members

GDG meeting	*Declaration of Interests of the NCC-AC members*
First GDG meeting (10th July 2009)	No interests to declare
Second GDG Meeting (04th September 2009)	No change in declaration
Third GDG Meeting (14th October 2009)	No change in declaration
Fourth GDG Meeting (27th November 2009)	No change in declaration
Fifth GDG Meeting (13th January 2010)	No change in declaration
Sixth GDG Meeting (26th February 2010)	No change in declaration
Seventh GDG Meeting (26th March 2010)	No change in declaration
Eighth GDG Meeting (14th May 2010)	No change in declaration
Ninth GDG Meeting (18th June 2010)	No change in declaration
Tenth GDG Meeting (23rd July 2010)	No change in declaration
Eleventh GDG Meeting (08th September 2010)	No change in declaration
Twelfth GDG Meeting (22nd October 2010)	No change in declaration
Thirteenth GDG Meeting (4th March 2011)	No change in declaration

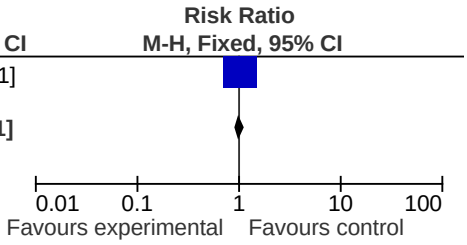
APPENDIX K

Additional analysis for the economic model – PCI vs. CABG

1. **Free of angina – 6 months**

Study or Subgroup	PCI Events	PCI Total	CABG Events	CABG Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Unger 2003 (ARTS)	119	138	121	142	100.0%	1.01 [0.92, 1.11]
Total (95% CI)		**138**		**142**	**100.0%**	**1.01 [0.92, 1.11]**
Total events	119		121			

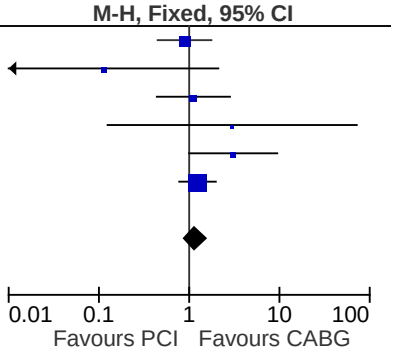
Heterogeneity: Not applicable
Test for overall effect: Z = 0.24 (P = 0.81)



2. **Death (all causes) – 1 year**

Study or Subgroup	PCI Events	PCI Total	CABG Events	CABG Total	Weight	Risk Ratio M-H, Fixed, 95% CI
ARTS 2001	15	600	17	605	26.2%	0.89 [0.45, 1.77]
Eefting 2003	0	138	4	142	6.9%	0.11 [0.01, 2.10]
Hueb 2004 (MASS II)	9	205	8	203	12.4%	1.11 [0.44, 2.83]
LEMANS 2008	1	52	0	52	0.8%	3.00 [0.13, 71.99]
SoS 2002	12	488	4	500	6.1%	3.07 [1.00, 9.46]
SYNTAX 2009	39	891	30	849	47.6%	1.24 [0.78, 1.98]
Total (95% CI)		**2374**		**2351**	**100.0%**	**1.18 [0.85, 1.64]**
Total events	76		63			

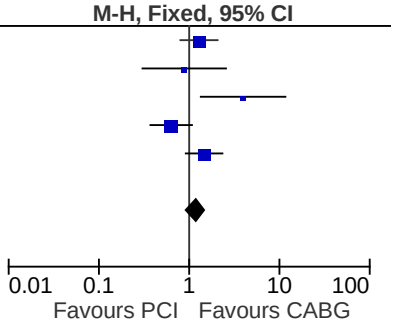
Heterogeneity: Chi² = 6.29, df = 5 (P = 0.28); I² = 21%
Test for overall effect: Z = 1.00 (P = 0.32)



3. **MI – 1 year**

Study or Subgroup	PCI Events	PCI Total	CABG Events	CABG Total	Weight	Risk Ratio M-H, Fixed, 95% CI
ARTS 2001	37	600	29	605	28.3%	1.29 [0.80, 2.06]
Eefting 2003	6	138	7	142	6.8%	0.88 [0.30, 2.56]
Hueb 2004 (MASS II)	16	205	4	203	3.9%	3.96 [1.35, 11.64]
SoS 2002	21	488	34	500	32.9%	0.63 [0.37, 1.07]
SYNTAX 2009	43	891	28	849	28.1%	1.46 [0.92, 2.33]
Total (95% CI)		**2322**		**2299**	**100.0%**	**1.20 [0.93, 1.55]**
Total events	123		102			

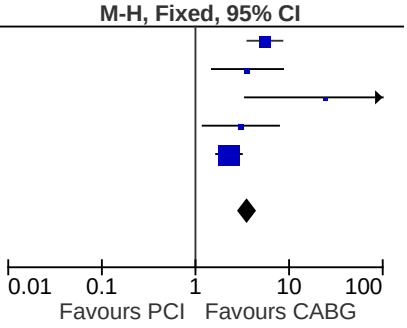
Heterogeneity: Chi² = 11.42, df = 4 (P = 0.02); I² = 65%
Test for overall effect: Z = 1.39 (P = 0.17)



4. Repeat revascularisation – 1 year

Study or Subgroup	PCI Events	PCI Total	CABG Events	CABG Total	Weight	Risk Ratio M-H, Fixed, 95% CI
ARTS 2001	126	600	23	605	26.6%	5.52 [3.59, 8.49]
Eefting 2003	21	138	6	142	6.9%	3.60 [1.50, 8.65]
Hueb 2004 (MASS II)	25	205	1	203	1.2%	24.76 [3.39, 180.98]
LEMANS 2008	15	52	5	53	5.8%	3.06 [1.20, 7.80]
SYNTAX 2009	120	891	50	849	59.6%	2.29 [1.67, 3.14]
Total (95% CI)		**1886**		**1852**	**100.0%**	**3.55 [2.82, 4.47]**
Total events	307		85			

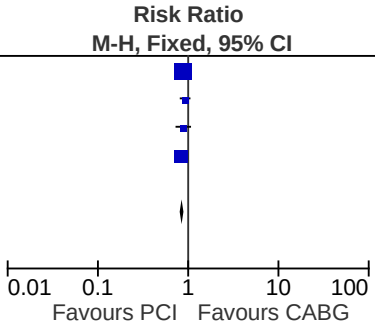
Heterogeneity: Chi² = 15.24, df = 4 (P = 0.004); I² = 74%
Test for overall effect: Z = 10.75 (P < 0.00001)



5. Free of angina – 1 year

Study or Subgroup	PCI Events	PCI Total	CABG Events	CABG Total	Weight	Risk Ratio M-H, Fixed, 95% CI
ARTS 2001	473	600	541	605	46.6%	0.88 [0.84, 0.93]
Eefting 2003	108	138	120	142	10.2%	0.93 [0.83, 1.04]
Hueb 2004 (MASS II)	107	205	120	203	10.4%	0.88 [0.74, 1.05]
SoS 2002	309	471	387	493	32.7%	0.84 [0.77, 0.91]
Total (95% CI)		**1414**		**1443**	**100.0%**	**0.87 [0.84, 0.91]**
Total events	997		1168			

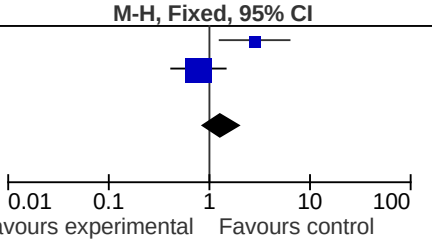
Heterogeneity: Chi² = 2.40, df = 3 (P = 0.49); I² = 0%
Test for overall effect: Z = 6.60 (P < 0.00001)



6. Death (all causes) – 2 years

Study or Subgroup	PCI Events	PCI Total	CABG Events	CABG Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Booth 2008 (SOS)	22	488	8	500	26.5%	2.82 [1.27, 6.27]
Unger 2003 (ARTS)	17	600	22	605	73.5%	0.78 [0.42, 1.45]
Total (95% CI)		**1088**		**1105**	**100.0%**	**1.32 [0.83, 2.11]**
Total events	39		30			

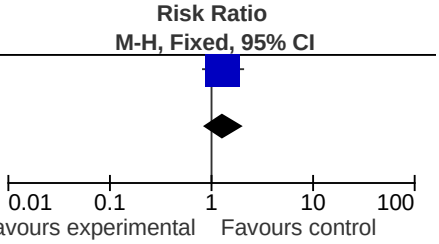
Heterogeneity: Chi² = 6.21, df = 1 (P = 0.01); I² = 84%
Test for overall effect: Z = 1.16 (P = 0.25)



7. MI – 2 years

Study or Subgroup	PCI Events	PCI Total	CABG Events	CABG Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Unger 2003 (ARTS)	40	600	31	605	100.0%	1.30 [0.83, 2.05]
Total (95% CI)		**600**		**605**	**100.0%**	**1.30 [0.83, 2.05]**
Total events	40		31			

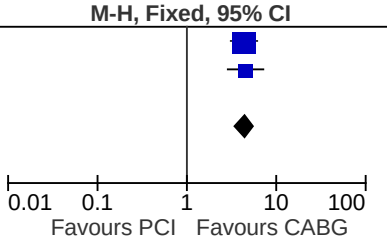
Heterogeneity: Not applicable
Test for overall effect: Z = 1.13 (P = 0.26)



8. Repeat revascularisation – 2 years

Study or Subgroup	PCI Events	PCI Total	CABG Events	CABG Total	Weight	Risk Ratio M-H, Fixed, 95% CI
ARTS 2003	160	600	37	605	64.0%	4.36 [3.11, 6.12]
SoS 2002	93	488	21	500	36.0%	4.54 [2.87, 7.16]
Total (95% CI)		**1088**		**1105**	**100.0%**	**4.42 [3.37, 5.81]**
Total events	253		58			

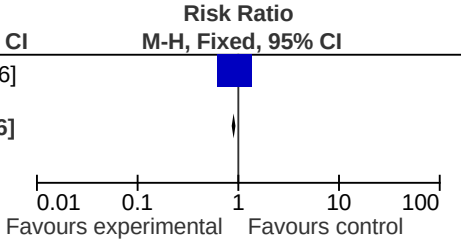
Heterogeneity: Chi² = 0.02, df = 1 (P = 0.89); I² = 0%
Test for overall effect: Z = 10.70 (P < 0.00001)



9. Free of angina – 2 years

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
ARTS 2003	465	583	508	583	100.0%	0.92 [0.87, 0.96]
Total (95% CI)		**583**		**583**	**100.0%**	**0.92 [0.87, 0.96]**
Total events	465		508			

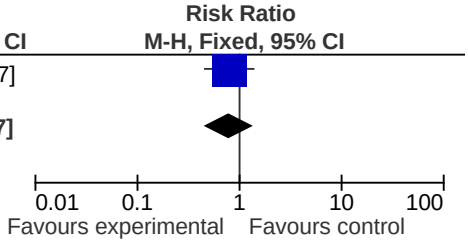
Heterogeneity: Not applicable
Test for overall effect: Z = 3.37 (P = 0.0007)



10. Death (all causes) – 3 years

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Serruys 2005 (ARTS)	22	600	28	605	100.0%	0.79 [0.46, 1.37]
Total (95% CI)		**600**		**605**	**100.0%**	**0.79 [0.46, 1.37]**
Total events	22		28			

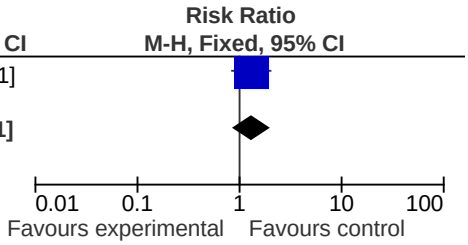
Heterogeneity: Not applicable
Test for overall effect: Z = 0.83 (P = 0.40)



11. MI – 3 years

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Serruys 2005 (ARTS)	44	600	34	605	100.0%	1.30 [0.85, 2.01]
Total (95% CI)		**600**		**605**	**100.0%**	**1.30 [0.85, 2.01]**
Total events	44		34			

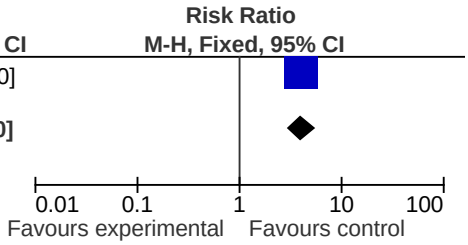
Heterogeneity: Not applicable
Test for overall effect: Z = 1.20 (P = 0.23)



12. Repeat revascularisation – 3 years

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Serruys 2005 (ARTS)	160	600	40	605	100.0%	4.03 [2.91, 5.60]
Total (95% CI)		**600**		**605**	**100.0%**	**4.03 [2.91, 5.60]**
Total events	160		40			

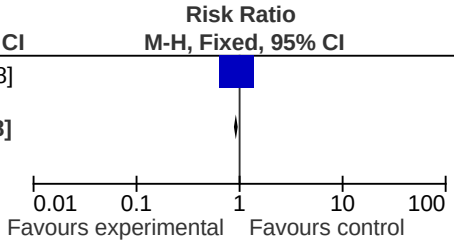
Heterogeneity: Not applicable
Test for overall effect: Z = 8.34 (P < 0.00001)



13. Free of angina – 3 years

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Legrand 2004 (ARTS)	490	600	528	605	100.0%	0.94 [0.89, 0.98]
Total (95% CI)		**600**		**605**	**100.0%**	**0.94 [0.89, 0.98]**
Total events	490		528			

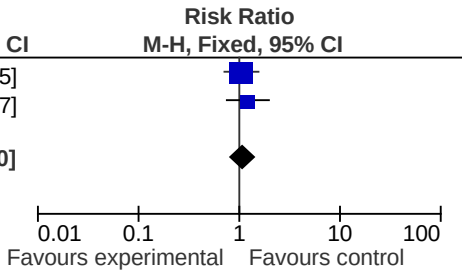
Heterogeneity: Not applicable
Test for overall effect: Z = 2.68 (P = 0.007)



14. Death (all causes) – 5 years

Study or Subgroup	PCI Events	PCI Total	CABG Events	CABG Total	Weight	Risk Ratio M-H, Fixed, 95% CI
ARTS 2005	48	600	46	605	63.7%	1.05 [0.71, 1.55]
Hueb 2007 (MASS-II)	32	205	26	203	36.3%	1.22 [0.75, 1.97]
Total (95% CI)		**805**		**808**	**100.0%**	**1.11 [0.82, 1.50]**
Total events	80		72			

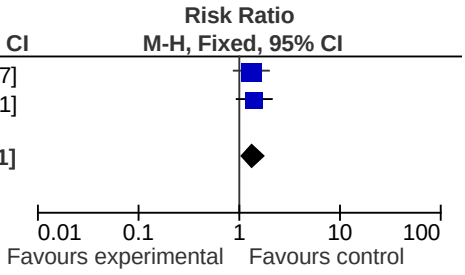
Heterogeneity: Chi² = 0.22, df = 1 (P = 0.64); I² = 0%
Test for overall effect: Z = 0.69 (P = 0.49)



15. MI – 5 years

Study or Subgroup	PCI Events	PCI Total	CABG Events	CABG Total	Weight	Risk Ratio M-H, Fixed, 95% CI
ARTS 2005	51	600	39	605	53.9%	1.32 [0.88, 1.97]
Hueb 2007 (MASS-II)	47	205	33	203	46.1%	1.41 [0.94, 2.11]
Total (95% CI)		**805**		**808**	**100.0%**	**1.36 [1.02, 1.81]**
Total events	98		72			

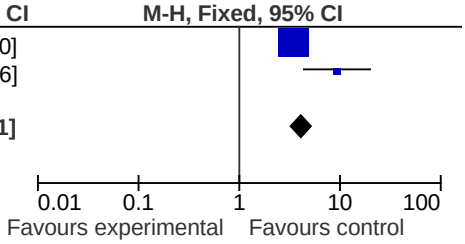
Heterogeneity: Chi² = 0.05, df = 1 (P = 0.82); I² = 0%
Test for overall effect: Z = 2.13 (P = 0.03)



16. Repeat revascularisation – 5 years

Study or Subgroup	PCI Events	PCI Total	CABG Events	CABG Total	Weight	Risk Ratio M-H, Fixed, 95% CI
ARTS 2005	182	600	53	605	88.2%	3.46 [2.61, 4.60]
Hueb 2007 (MASS-II)	66	205	7	203	11.8%	9.34 [4.39, 19.86]
Total (95% CI)		**805**		**808**	**100.0%**	**4.15 [3.19, 5.41]**
Total events	248		60			

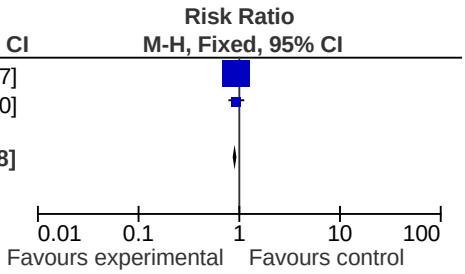
Heterogeneity: Chi² = 6.00, df = 1 (P = 0.01); I² = 83%
Test for overall effect: Z = 10.54 (P < 0.00001)



17. Free of angina – 5 years

Study or Subgroup	PCI Events	PCI Total	CABG Events	CABG Total	Weight	Risk Ratio M-H, Fixed, 95% CI
ARTS 2005	467	600	511	605	80.1%	0.92 [0.87, 0.97]
Hueb 2007 (MASS-II)	119	205	126	203	19.9%	0.94 [0.80, 1.10]
Total (95% CI)		**805**		**808**	**100.0%**	**0.92 [0.88, 0.98]**
Total events	586		637			

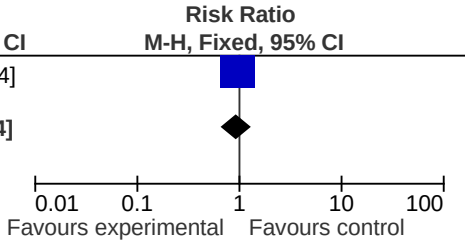
Heterogeneity: Chi² = 0.03, df = 1 (P = 0.86); I² = 0%
Test for overall effect: Z = 2.86 (P = 0.004)



18. Death (all causes) – 10 years

Study or Subgroup	PCI Events	PCI Total	CABG Events	CABG Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Hueb 2009 (MASS-II)	49	205	51	203	100.0%	0.95 [0.68, 1.34]
Total (95% CI)		**205**		**203**	**100.0%**	**0.95 [0.68, 1.34]**
Total events	49		51			

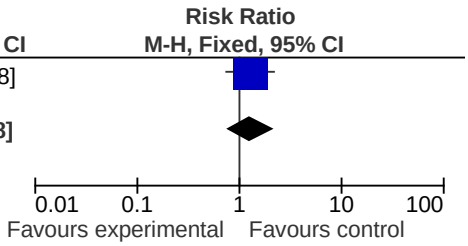
Heterogeneity: Not applicable
Test for overall effect: Z = 0.29 (P = 0.77)



19. MI (non-fatal) – 10 years

Study or Subgroup	PCI Events	PCI Total	CABG Events	CABG Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Hueb 2009 (MASS-II)	27	205	21	203	100.0%	1.27 [0.74, 2.18]
Total (95% CI)		**205**		**203**	**100.0%**	**1.27 [0.74, 2.18]**
Total events	27		21			

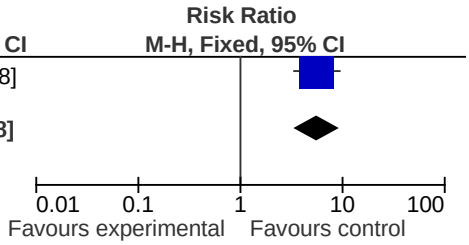
Heterogeneity: Not applicable
Test for overall effect: Z = 0.88 (P = 0.38)



20. Repeat revascularisation – 10 years

Study or Subgroup	PCI Events	PCI Total	CABG Events	CABG Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Hueb 2009 (MASS-II)	85	205	15	203	100.0%	5.61 [3.36, 9.38]
Total (95% CI)		**205**		**203**	**100.0%**	**5.61 [3.36, 9.38]**
Total events	85		15			

Heterogeneity: Not applicable
Test for overall effect: Z = 6.58 (P < 0.00001)



21. Free of angina – 10 years

Study or Subgroup	PCI Events	PCI Total	CABG Events	CABG Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Hueb 2009 (MASS-II)	120	205	130	203	100.0%	0.91 [0.78, 1.07]
Total (95% CI)		**205**		**203**	**100.0%**	**0.91 [0.78, 1.07]**
Total events	120		130			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.14 (P = 0.25)