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Medical therapy versus percutaneous coronary intervention or coronary artery bypass graft in stable coronary artery disease; a systematic review and meta-analysis of randomized clinical trials

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Meta-analysis

Abstract

BACKGROUND: Ischemic heart disease (IHD) is the first cause of mortality in the world. Stable coronary artery disease (CAD) is the most common IHD. Medical therapy (MT), percutaneous coronary intervention (PCI), and coronary artery bypass grafting (CABG) are three strategies for the management of this disease. The main aim of this study was the comparison of MT with PCI or CABG in terms of cardiovascular (CV) mortality, myocardial infarction (MI), unplanned revascularization (UR), stroke, and freedom from angina in managing stable CAD.

METHODS: The Cochrane Central Register of Controlled Trials, Embase, PubMed, and Scopus were searched. Two reviewers independently appraised the titles and abstracted data of the identified studies. After the Full-text reviewing phase, eligible studies were analyzed through the random-effect meta-analysis method. Finally, a sensitivity analysis was conducted for the robustness of findings.

RESULTS: Nine randomized controlled trials (RCTs) were included. The pooled RR of CV mortality associated with MT compared with PCI and CABG was 1.22 and 1.385, respectively. Overall, The RR of MT associated with MI, UR, stroke, and freedom from angina compared with PCI was 1.001, 1.151, 0.799, and 0.801, respectively.

CONCLUSION: Our results revealed no statistically significant difference between MT and PCI in terms of studied primary outcomes. The findings also highlighted that there is no statistically significant difference between MT and CABG in terms of CV mortality.

Keywords: Coronary Artery Disease; Myocardial infarction; Medication Therapy Management; Percutaneous coronary intervention; coronary artery bypass grafting; Meta-analysis

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Introduction

Ischemic heart disease (IHD) has remained the leading cause of death globally since 2004, accounting for 9.4 million deaths in 2016.[1] Moreover, the most common type of IHD is stable coronary artery disease (CAD).[2]

The main reason for CAD is atherosclerotic plaque aggregation in the coronary arteries,[3] which can be modified through lifestyle changes, medical therapies, and the implementation of invasive interventions.[4]

Despite the long and stable periods of CAD, it can become unstable at any time due to an acute atherothrombotic event.

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The dynamic nature of CAD leads to various clinical manifestations,[4] the most significant of which is stable angina,[5] which can be managed through medical therapy (MT), percutaneous coronary intervention (PCI), coronary artery bypass grafting (CABG), or a combination of them.[6,7]

Recently, the prognosis of stable CAD patients has notably improved due to advances in MT,[7] such as using different classes of medications for managing stable angina.[8-10] Various guidelines suggest optimal medical therapy (OMT) as the initial treatment for stable angina. OMT is applied for the three purposes of relieving angina symptoms using short-acting nitrates, prevention of secondary cardiovascular (CV) events using aspirin, statins, angiotensin-converting enzyme (ACE) inhibitors, and antihypertensive drugs, and treatment of stable CAD using beta-blockers or calcium channel-blocker, long-acting nitrates, ivabradine, nicorandil, and ranolazine.[4,8,9]

Revascularization intervention is suggested when stable CAD patients on OMT showed inadequate symptom relief, suboptimal quality of life (QOL), or the emergence of acute coronary syndrome (ACS).[9] Revascularization intervention, including CABG and PCI,[11] has been claimed to improve QOL, and decrease the risk of myocardial infarction (MI) and premature death.[12] Although guidelines mention MT as the initial treatment for stable CAD,[4,8,9] most randomized controlled trials (RCTs) have compared PCI and CABG.

However, the efficacy of PCI or CABG compared with MT in improving life expectancy or reducing the risk of a heart attack in stable CAD patients is not well established.[13] Moreover, PCI and CABG strategies have waiting lists and the high cost of the first hospitalization that could increase health system costs. Based on the abovementioned facts, comparing MT with PCI and CABG strategies in stable CAD patients is essential as it will help policymakers decide how to allocate limited resources.

We noticed that the latest meta-analysis in this field was conducted in 2013,[14] and had only compared MT with PCI. Thus, it seems necessary to conduct an updated meta-analysis regarding MT, PCI, and CABG to find a more efficient and holistic approach to these treatment strategies in the scope of CAD management. Moreover, new reports from old RCTs present a more precise image of different outcomes. Therefore, this systematic review and meta-analysis was conducted to compare MT with PCI and CABG in terms of CV mortality, MI, unplanned revascularization (UR), stroke, and freedom from angina in managing stable CAD.

Materials and Methods

Data sources and search strategy: We searched English articles published until 22 December 2020 from the Cochrane Central Register of Controlled Trials, PubMed, Embase, and Scopus databases using a systematic search query. The study protocol has been registered on PROSPERO with the registration number CRD42020157037 and can be accessed on https://www.crd.york.ac.uk/prospero/.

Systematic Review questions (PICO)

Population: Patients with proven stable CAD, who were appropriate candidates for both continued MT and PCI or CABG.

Intervention: MT including mono/combination drug therapy of beta-blockers, calcium channel blocker, aspirin, statins, ACEI/ARBs, nitrates, and vasodilator

Comparison: Revascularization (i.e., all forms of PCI or CABG)

Outcomes: Rates for CV mortality, MI, UR, stroke, and freedom from angina

Study types: Randomized controlled trials (RCTs) comparing MT with PCI or CABG in patients with stable CAD

Inclusion and exclusion criteria: Randomized controlled trials (RCTs) comparing MT with PCI or CABG in stable CAD patients were included in this study. RCTs not comparing MT with PCI or CABG in stable CAD patients were excluded.

Systematic reviews, observational studies, guidelines, short communications, conference proceedings, and articles that did not meet the quality evaluation criteria were excluded.

Study selection and data abstraction: From a total of 1978 articles identified in the literature search, 31 potentially relevant articles were selected. After applying the inclusion-exclusion criteria listed above, 9 RCTs with 6705 patients and a mean of 54 months of follow-up were found to be relevant. These 9 articles were included in the final review (Figure 1).

A data extraction sheet was developed to collect relevant information from the included studies. Then, the considered data were extracted independently from articles. Any disagreement over data extraction was resolved in consultation with the senior investigator. Each study's abstract was reviewed by 2 investigators (BF and SR) independently against prespecified inclusion and exclusion criteria.

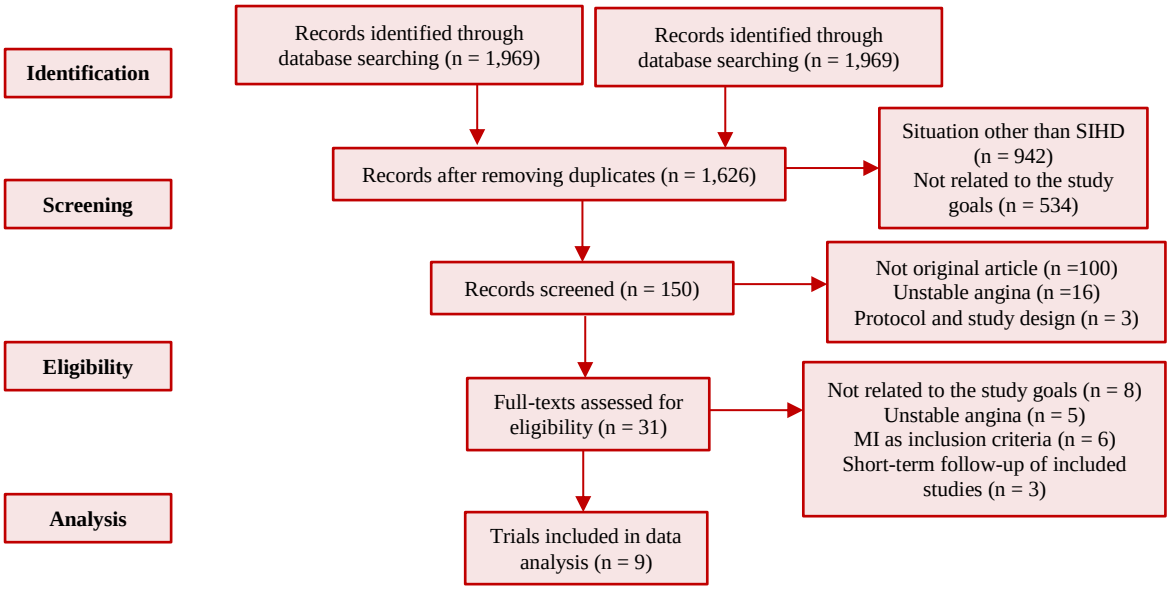

Figure 1. Flow diagram of study selection
MI: Myocardial Infarction; RCT: Randomized Clinical Trial; SIHD: Stable Ischemic Heart Disease

In case of disagreement on the quality of the article, the third author intervened in the decision.

Risk of bias: The risk of bias was assessed using the Cochrane risk of bias assessment tool for clinical trials at the study level.[15] Moreover, the overall risk of bias across studies was assessed based on each outcome of interest. To investigate publication bias for each trial, the effect was plotted by the inverse of its standard error. The symmetry of the funnel plots was assessed using Egger's test to see if the effect decreased with increasing sample size.[16,17]

Summary measures: In this study, the relative risk (RR) was measured for all outcomes of interest.

Synthesis of results: We quantitatively and qualitatively described and summarized the outcomes of MT and coronary revascularization interventions (i.e., PCI and CABAG). The Der-Simonian-Laird estimator in a random-effects model was used in the current meta-analysis of clinical trials[18] in the Stata software environment for calculating combined RR to identify the pooled RR and 95% confidence intervals (CIs), creating forest plots, and performing statistical calculations based on primary outcomes. The random-effects model provides a more conservative summary estimate, incorporating both within and between-trial variance.[19] Heterogeneity was analyzed using the I-squared statistic, which describes the proportion of variability due to heterogeneity between individual trials.[20]

Additional analyses: Two sensitivity analyses were conducted to determine the potential impact of uncertainty on the summary effect measures. In the first, the comparison of MT with CABG, the analysis was restricted to a subgroup of the largest sample size RCTs (CASS[21] and MASS-II[22]). In the second, the comparison of MT with PCI, trials with less than two years of follow-up (ACME[23] and EUROCTO[24]) were excluded.

Results

Study characteristics: A total of 9 RCTs involving 6705 patients with a mean follow-up of 54 months were included in the present systematic review. Among them, 5 trials had compared MT with PCI, 2 trials had compared MT with PCI and CABG, the TIME trial[25] had compared MT with intensive strategies (i.e., revascularization, PCI, or CABG), and the CASS trial[21] had compared MT with CABG. More than 80% of trial patients were men. The average age of patients was 63.8 years. Moreover, 8 trials had included post-MI patients. Based on the angina classification of the Canadian Cardiovascular Society,[26] most patients had minimal angina or no symptoms (class of 0 or 1) (Table 1).

Concerning baseline medication use in the included trials, aspirin was the most frequently used medication. The use of other medications varied widely among the trials. For example, ACE inhibitor use ranged from 9% to 65%, whereas beta-blockers were used in 30% to 89% of trials, and statin use ranged from 12% to almost 90%. Furthermore, calcium channel blockers were used for 30 to 71% of patients. Rates of medication use were similar in patients randomly assigned to MT with PCI or CABG within each trial (Table 2).

Table 1. Design characteristics of the included trials

Study name	Country	Citation	Recruitment year(s)	Sample size	Follow-up period (m)	Patients mean age at recruitment	Intervention	Comparison
CASS	USA	Rogers et al., 1990	1974-1979	780	132	51.2 (± 7.3)	MT	CABG
ACME	USA	Parisi et al., 1992	1987-1990	212	6	62.5 (± 8.4)	MT	PCI
MASS	Brazil	(Hueb et al., 1995	1988-1991	214	42	56 (± 8.0)	MT	PCI and CABG
RITA-2	UK and Ireland	Henderson et al., 2003	1992-1996	1018	84	58.1 (± 7.1)	MT	PCI
MASS II	Brazil	Hueb et al., 2010	1995-2000	611	120	60 (± 9.0)	MT	PCI and CABG
TIME	Switzerland	TIME Investigators, 2001	1996	301	12	80 (± 3.5)	MT	PCI or CABG
EUROCTO	France	Werner et al., 2018	1999-2004	396	12	65 (± 9.8)	MT	PCI
FAME2	Europe and North America	De Bruyne et al., 2014	2010-2012	888	24	63.7 (± 9.5)	MT	PCI
COURAGE	USA	Boden et al., 2007	2012-2015	2285	55.2	61.7 (± 9.9)	MT	PCI

ACME: Angioplasty Compared to Medicine; CABG: Coronary artery bypass grafting; CASS: The coronary artery surgery Study; COURAGE: Clinical Outcome Utilizing Revascularization and Aggressive Drug Evaluation; EUROCTO: Evaluate the Utilization of Revascularization or Optimal Medical Therapy for the Treatment of Chronic Total Coronary Occlusions; FAME2: Fractional Flow Reserve versus Angiography for Multi-vessel Evaluation 2; MASS II: The Second Medicine, Angioplasty, or Surgery Study; MASS: Medicine, Angioplasty, or Surgery Study; MT: Medical therapy; PCI: Percutaneous coronary intervention; RITA-2: The Second Randomized Intervention Treatment of Angina; TIME: Trial of invasive versus medical therapy in elderly patients

Table 2. Baseline medication use in the included trials

Trial name	Aspirin (%)			Beta-blockers (%)			ACEIS or ARBS			Statins/Lipid lowering agents (%)			Nitrates (%)			CCB		
	MT	PCI	CABG	MT	PCI	CABG	MT	PCI	CABG	MT	PCI	CABG	MT	PCI	CABG	MT	PCI	CABG
COURAGE	1077	1097	-	1008	975	-	734	737	-	1014	992	-	825	714	-	488	459	-
	(95)	(96)		(89)	(85)		(65)	(62)		(89)	(86)		(72)	(62)		(43)	(40)	
EUROCTO	130	252	-	112	197	-	75	143	-	134	235	-	44	59	-	37	64	-
	(94.9)	(97.3)		(81.8)	(76.1)		(54.7)	(55.2)		(91.2)	(90.7)		(32.1)	(22.8)		(27)	(24.7)	
FAME2	-	-	-	-	-		-	-		-	-		-	-	-	-	-	-
ACME	97	89	-	53	31	-	-	-	-	-	-	-	63	28	-	76	37	-
	(91)	(85)		(50)	(30)								(59)	(27)		(71)	(35)	
RITA-2	447	439	-	335	344	-	56	46	-	60	70	-	210	233	-	273	238	-
	(87)	(87)		(65)	(68.3)		(10.9)	(9.1)		(11.7)	(13.9)		(40.9)	(46.2)		(53.1)	(47.2)	
MASS-II	162	164	142	138	125	89	59	62	43	138	150	99	148	84	24	124	62	89
	(80)	(80)	(70)	(68)	(61)	(44)	(29)	(30)	(21)	(68)	(73)	(49)	(73)	(41)	(12)	(61)	(30)	(44)
TIME	122	128		106	124		52	34		33	37		112	115		73	77	
	(82)	(85)		(72)	(82)		(35)	(23)		(22)	(25)		(76)	(76)		(49)	(51)	
CASS	-	-	-	166	-	172	-	-	-	12	-	14	214	-	219	-	-	-
				(42.6)		(44)				(3.1)		(3.6)	(55)		(56.2)			
MASS	53	54		33	37	-	18	22	-	26	30	-	-	-		-	-	-
	(78)	(75)		(46)	(52)		(25)	(30)		(36)	(42)							

ACEIs: Angiotensin-converting enzyme inhibitors; ACME: Angioplasty Compared to Medicine; MASS: Medicine, Angioplasty, or Surgery Study; CABG: Coronary artery bypass grafting; CASS: The coronary artery surgery Study; COURAGE: Clinical Outcome Utilizing Revascularization and Aggressive Drug Evaluation; EUROCTO: Evaluate the Utilization of Revascularization or Optimal Medical Therapy for the Treatment of Chronic Total Coronary Occlusions; FAME2: Fractional Flow Reserve versus Angiography for Multi-vessel Evaluation 2; MASS II: The Second Medicine, Angioplasty, or Surgery Study; TIME: Trial of invasive versus medical therapy in elderly patients; MT: Medical therapy; PCI: Percutaneous coronary intervention; RITA-2: The Second Randomized Intervention Treatment of Angina

Regarding outcomes measured in each study, all studies reported all-cause mortality, 8 studies reported CV mortality, MI, and UR, 5 studies reported stroke, and only 4 studies reported freedom from angina at the end of follow-up (Table 3).

Risk of bias within studies: Based on the results of the Cochrane risk of bias tool, the majority (6 out of 9) of RCTs included in this systematic review had a fair quality, and the remaining 3 trials had a poor quality. The primary source of the problem was a lack of blinding (Table 4).

Synthesis of results

Results of individual studies: The pooled analysis of risk ratios of individual trials comparing CV mortality between MT and CABG showed no statistically significant difference in CV mortality among MT and CABG, as evidenced by risk ratio of CASS [1.13 (0.81, 1.58) [, MASS [0.97 (0.14, 6.71)], and MASS II [1.91 (1.18, 3.08)]. The overall risk ratio of CV mortality was 1.38 (0.92, 2.08) (P = 0.198) (Figure 2).

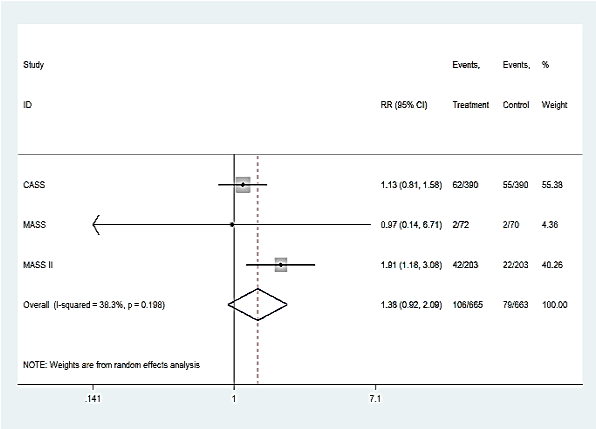

Figure 2. Pooled RR of CV mortality comparing MT with CABG

CABG: Coronary artery bypass grafting; CASS: The coronary artery surgery study; CI: Confidence Interval; CV: Cardiovascular; MASS: Medicine, Angioplasty, or Surgery Study; MT: Medical Therapy; RR: Risk Ratio; MASS II: The Second Medicine, Angioplasty, or Surgery Study

Figure 3 and 4 illustrate the forest plots of individual trials, and pooled analysis of risk ratios and 95% CIs comparing the outcomes of CV mortality, MI, UR, stroke, and freedom from angina for MT compared with PCI, respectively.

Comparison of the effect of MT and CABG on CV mortality: CV mortality was reported in 3 studies with 1328 patients. Only the MASS-II trial showed a significant statistical difference in favor of CABG.[22] The pooled analysis revealed 185 cases of CV mortality, with 106 deaths in the MT group and 79 deaths in the CABG group with a RR of 1.385 (95% CI: 0.915-2.094; P = 0.123). However, an I^2 statistic of 38.2% and P = 0.198 indicates no important heterogeneity in the estimates of CV mortality of MT versus CABG across studies.[27] Moreover, Tau-squared of 0.0513 was obtained for between-study variance (Figure 2).

Comparison of the effect of MT and PCI on clinical outcomes: Concerning CV mortality, 6 studies with 5316 patients reported CV mortality. None of the trials reported significant statistical differences between MT and PCI. The pooled analysis showed that there was a total of 177 cases of CV mortality, with 96 deaths in the MT group and 81 deaths in the PCI group with a RR of 1.22 (95% CI: 0.918-1.26; P = 0.170) (Figure 3, A). However, an I^2 statistic of 0% with P = 0.764 indicates an unimportant heterogeneity in the estimates of CV mortality of MT versus PCI across studies.[27]

Furthermore, the estimated between-study variance was Tau-squared = 0.0000. Concerning MI, 7 studies, with 5351 patients, reported MI. Only the MASS-II trial showed a significant statistical difference in favor of PCI.[22] The pooled analysis revealed 469 MI, with 229 MI in the MT group and 240 MI in the PCI group with a RR of 1.001 (95% CI: 0.763-1.313; P = 0.995) (Figure 3, B). However, an I^2 statistic of 33.6% with P = 0.172 indicates an unimportant heterogeneity in the estimates of MI of MT versus CABG across studies.[27] Moreover, the estimated between-study variance was Tau-squared = 0.0394.

Concerning unplanned revascularization, 7 studies, with 5351 patients, reported UR. At the end of the trial follow-up, 25.27% of MT patients experienced revascularization, compared with 18.51% of patients who received PCI. The pooled RR of UR associated with MT compared with PCI was 1.151 (95% CI: 0.847-1.562; P = 0.368) (Figure 4, C). However, an I^2 statistic of 82.2% with P < 0.001 indicates an important heterogeneity in the estimates of revascularization for MT versus PCI across studies.[27] In addition, the estimated between-study variance was Tau-squared = 0.1060.

Stroke was reported during follow-up in 5 studies with 3838 patients. None of the individual trials showed significant statistical differences between MT and PCI. At the end of the trial follow-up, 1.7% of MT patients experienced a stroke, compared with 2.16% of patients who had undergone PCI. The pooled RR of stroke associated with MT compared with PCI was 0.799 (95% CI: 0.510-1.253; P = 0.329) (Figure 4, D).

Table 3. Outcomes measured in each study

Trial	All-cause death			CV mortality			MI			Stroke			UR			Freedom from angina		
	MT	PCI	CABG	MT	PCI	CABG	MT	PCI	CABG	MT	PCI	CABG	MT	PCI	CABG	MT	PCI	CABG
ACME	1 (0.93)	0.00	-	-	-	-	3 (2.8)	5 (4.76)	-	-	-	-	11 (10)	23 (23)	-	102	96	-
RITA-2	43 (8.37)	43 (8.53)	-	24 (4.47)	20 (3.97)	-	23 (4.47)	32 (6.35)	-	-	-	-	182 (35.41)	137 (27.18)	-	360 (7)	383 (76)	-
COURAGE	74 (6.5)	68 (5.93)	-	25 (2.2)	23 (2)	-	128 (11.25)	143 (12.47)	-	14 (1.23)	22 (1.92)	-	348 (30.6)	228 (19.88)	-	-	-	-
EUROCTO	0	2 (0.8)	-	0	2 (0.8)	-	0	5 (1.9)	-	1 (0.7)	2 (0.8)	-	9 (6.7)	5 (2.0)	-	79 (58)	184 (71)	-
FAME2	8 (1.8)	6 (1.3)	-	3 (0.7)	3 (0.7)	-	30 (6.8)	26 (5.8)	-	4 (0.9)	7(1.6)	-	18 (4.0)	7 (1.6)	-	-	-	-
MASS-II	63 (31)	49 (24.1)	(25.1)	42 (20.7)	29 (14.3)	(10.8)	42 (20.7)	27 (13.3)	20 (10.3)	14 (6.9)	11 (5.4)	17 (8.40)	80 (39.4)	86 (41.9)	15 (7.40)	-	-	-
MASS	6 (6.9)	5 (6.94)	1 (1.4)	2 (2.78)	4 (5.71)	2 (2.86)	3 (4.17)	2 (2.86)	3 (4.29)	1 (1.39)	1 (1.43)	1 (1.43)	12 (16.67)	21 (30)	0	23 (32)	58 (82)	68 (98)
TIME	6 (4)	13 (8.5)		5 (3.38)	11 (7.2)		17 (11.5)	12 (7.8)		-	-	-	-	-	-	-	-	-
CASS	84 (21.54)	-	73 (19)	62 (15.89)	-	55 (14.10)	-	-	-	-	-	-	24 (6.15)	-	49 (12.56)	-	-	-

ACME: Angioplasty Compared to Medicine; CABG: Coronary artery bypass grafting; CASS: The coronary artery surgery Study; COURAGE: Clinical Outcome Utilizing Revascularization and Aggressive Drug Evaluation; CV: Cardiovascular; EUROCTO: Evaluate the Utilization of Revascularization or Optimal Medical Therapy for the Treatment of Chronic Total Coronary Occlusions; FAME2: Fractional Flow Reserve versus Angiography for Multi-vessel Evaluation 2; MASS II: The Second Medicine, Angioplasty, or Surgery Study; MASS: Medicine, Angioplasty, or Surgery Study; MI: Myocardial Infarction; MT: Medical therapy; PCI: Percutaneous coronary intervention; RITA-2: The Second Randomized Intervention Treatment of Angina; TIME: Trial of invasive versus medical therapy in elderly patients; UR: Unplanned Revascularization

Table 4. Risk of bias within studies based on the Cochrane risk of bias tool

Study, Year of Publication	Sample size	Selection bias	Performance bias (blinding)	Detection bias	Attrition bias	Other biases	Total
CASS, 1990	780	Unclear	High	Low	Low	Low	Poor quality
ACME, 1992	212	Low	High	Low	Low	Low	Fair quality
MASS, 1995	214	Unclear	High	Low	Low	Low	Poor quality
RITA-2, 2003	1018	Low	High	Low	Low	Low	Fair quality
MASS-II, 2010	611	Low	High	Low	Low	Low	Fair quality
TIME, 2001	301	Low	High	Low	Low	Low	Fair quality
COURAGE, 2007	2285	Low	High	Low	Low	Low	Fair quality
FAME2, 2014	888	Unclear	High	Low	Low	Low	Poor quality
EUROCTO, 2018	396	Low	High	Low	Low	Low	Fair quality

ACME: Angioplasty Compared to Medicine; CASS: The coronary artery surgery Study; COURAGE: Clinical Outcome Utilizing Revascularization and Aggressive Drug Evaluation; EUROCTO: Evaluate the Utilization of Revascularization or Optimal Medical Therapy for the Treatment of Chronic Total Coronary Occlusions; FAME2: Fractional Flow Reserve versus Angiography for Multi-vessel Evaluation 2; MASS-II: The Second Medicine, Angioplasty, or Surgery Study; MASS: Medicine, Angioplasty, or Surgery Study; RITA-2: The Second Randomized Intervention Treatment of Angina; TIME: Trial of invasive versus medical therapy in elderly patients

However, an I^2 statistic of 0.0% indicates no heterogeneity in the estimates of stroke of MT versus PCI across studies.[27] Moreover, the estimate of between-study variance was Tau-squared > 0.00001.

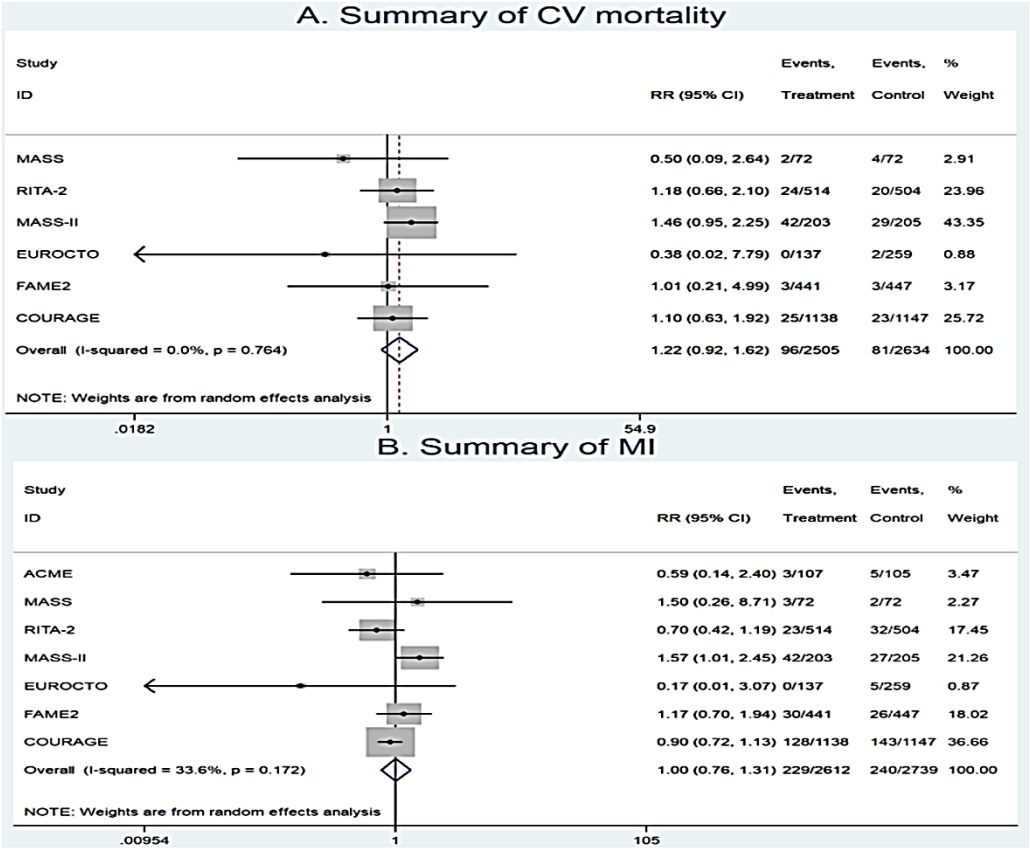

Figure 3. Pooled Risk Ratio of A. Cardiovascular mortality and B. MI comparing MT with PCI
ACME: Angioplasty compared to medicine; CABG: Coronary artery bypass grafting; CASS: The coronary artery surgery Study; COURAGE: Clinical Outcome Utilizing Revascularization and Aggressive Drug Evaluation; EUROCTO: Evaluate the Utilization of Revascularization or Optimal Medical Therapy for the Treatment of Chronic Total Coronary Occlusions; FAME2: Fractional Flow Reserve versus Angiography for Multi-vessel Evaluation 2; MASS II: The Second Medicine, Angioplasty, or Surgery Study; MASS: Medicine, Angioplasty, or Surgery Study; MT: medical therapy; PCI: Percutaneous coronary intervention; RITA-2: The Second Randomized Intervention Treatment of Angina; TIME: Trial of invasive versus medical therapy in elderly patients; RR: Risk Ratio

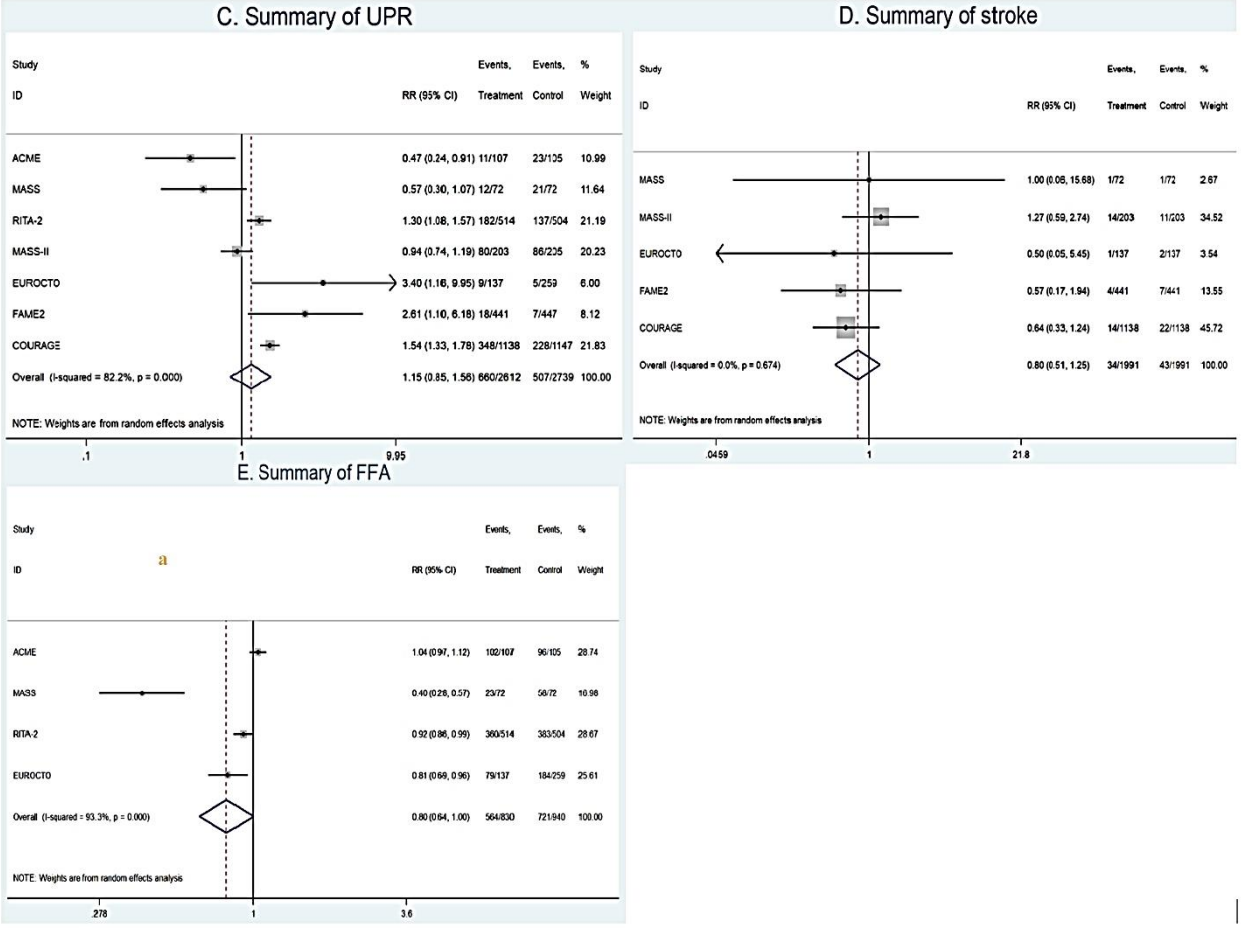

Figure 4. Pooled Risk Ratio of C. Unplanned revascularization, D. stroke, and E. Freedom from Angina comparing MT with PCI

ACME: Angioplasty Compared to Medicine; CABG: Coronary artery bypass grafting; CASS: The coronary artery surgery Study; COURAGE: Clinical Outcome Utilizing Revascularization and Aggressive Drug Evaluation; EUROCTO: Evaluate the Utilization of Revascularization or Optimal Medical Therapy for the Treatment of Chronic Total Coronary Occlusions; FAME2: Fractional Flow Reserve versus Angiography for Multi-vessel Evaluation 2; MASS II: The Second Medicine, Angioplasty, or Surgery Study; MASS: Medicine, Angioplasty, or Surgery Study; MT: Medical therapy; PCI: Percutaneous coronary intervention; RITA-2: The Second Randomized Intervention Treatment of Angina; TIME: Trial of invasive versus medical therapy in elderly patients; RR: Risk Ratio; UR: Unplanned Revascularization

Freedom from angina was reported at the end of follow-up in 4 studies with 1770 patients. Significant differences in favor of PCI were reported in 3 trials (MASS,[28] RITA-2,[29] and EUROCTO[24]). About 68% of MT patients showed freedom from angina at the end of follow-up, compared with 76.70% of patients who received PCI. Nevertheless, the pooled RR of freedom from angina associated with MT compared with PCI was 0.801 (95% CI: 0.640-1.003; P = 0.053) (Figure 4, E). An I^2 statistic of 93.3% with P < 0.001 indicates very important heterogeneity in the estimates of freedom from angina at the end of follow-up in MT versus PCI across studies.[27] Furthermore, the estimated between-study variance was Tau-squared = 0.0443.

Risk of bias across studies: Based on outcomes of interest, the funnel plot and Egger's linear regression test were conducted with the use of Stata software, and statistical significance was set at P < 0.05. The funnel plot for the comparison of CV mortality between MT and PCI was asymmetric, and Egger's test was significant, both of which suggest publication bias. The funnel plot for the comparison of freedom from angina at the end of follow-up between MT and PCI was asymmetric, and Egger's test was not significant. In this case, the asymmetrical funnel plot may be the result of variability in study design.[30]

Additional analysis: Sensitivity analysis showed that overall random-effects meta-analyses based on comparisons, PCI or CABG, were robust.

Discussion

In this systematic review and meta-analysis, we compared MT with PCI and CABG in terms of CV mortality, MI, UR, stroke, and freedom from angina in managing stable CAD.

An essential basis of a meta-analysis is that the same research question is being addressed on a comparable patient population across all included studies. We found that 3 earlier meta-analyses assessing the efficacy of PCI versus MT had included studies that recruited patients after recent MI or with a history of unstable angina.[31-33] Nevertheless, the inclusion criteria of our study were similar to that of the studies by Pursnani et al.[34] and Thomas et al.[14] from two aspects. The first is the use of stringent criteria to exclude trials that enrolled patients with recent MI. The second is the exclusion of trials that compared the unspecified type of revascularization with MT.[25] Recent acute coronary syndrome is defined as the exclusion criterion to minimize the heterogeneity between studies. Accordingly, we included more comparable patients in our analysis.

Moreover, 4 of the 8 included RCTs in this study had recruited patients after 2000 with the average follow-up of 4.4 (1 to 10) years. Thus, it is possible to capture advances in MT, PCI, and CABG. In this period of follow-up, it is possible to observe different health outcomes.

In the comparison of MT with CABG, because of the small number of included studies, only CV mortality was compared. However, there was no significant statistical difference in CV mortality between MT and CABG.

The main finding of this meta-analysis was that there is no statistically significant difference between MT and PCI in terms of the reduction of CV mortality, nonfatal MI, UR, stroke, and freedom from angina in patients with stable CAD. The pooled RR of CV mortality associated with MT compared with PCI and CABG was 1.22 and 1.385, respectively. The overall RR of MI, UR, stroke, and freedom from angina associated with MT was 1.001, 1.151, 0.799, and 0.801, respectively, compared with PCI.

Trials with newer patient recruitment showed a lower risk of CV mortality in MT compared with PCI. However, newer trials with patient recruitment after 2000 showed a lower risk of stroke with MT (from 6.9% in older trials to 0.73% in newer trials). However, this variation in newer studies could be due to the increasing use of CV risk factor modifying medicines. While the UR associated with MT was not significantly different from that associated with PCI, less UR was reported in patients who underwent PCI in RCTs with recruitment after 2000. This difference could also be due to advances in PCI practice over time from the early 1990s to the 2010s. Furthermore, there were differences in the methodology of the trials because of new achievements in PCI practice over time.

Notably, in comparison of MT with PCI, I2 statistics demonstrate low heterogeneity in pooling results from older (ACME23 and MASS28) and newer trials (COURAGE35 and FAME236) for MI, UR, and stroke outcomes. While we, like Stergiopoulos et al.,[33] did not find a significant statistical difference in freedom from angina between MT and PCI, newer trials claim PCI is more effective than MT in reducing angina. However, the results of both studies indicate high heterogeneity based on the I^2 statistical index.

The findings of this meta-analysis in terms of the outcomes of CV mortality, nonfatal MI, or UR compared between MT and PCI confirmed the finding of previous studies,[34,14,37] which also did not report a statistically significant difference between MT and PCI. This may be the reason why different guidelines emphasize optimal MT to start the treatment of stable CAD patients.[4,8,9]

Finally, we state that the absence of a statistically significant difference does not mean that MT, PCI, and CABG have the same clinical efficacy. It is the role of decision-makers in the field of stable CAD to decide between the different alternatives.

Conclusion

This meta-analysis showed no statistical difference between MT and CABG in terms of CV mortality. The findings also suggest that MT and PCI are not statistically different in terms of CV mortality and the incidence of MI, UR, stroke, and freedom from angina. Our results further strengthen the current guideline recommendations that treating patients with stable CAD should be initiated with OMT. Based on the results of this study, there was no significant statistical difference between MT and PCI; however, that does not mean that they have an equal clinical effect.

Limitations: There are some limitations to interpreting the results of the analysis at the outcome level. The first is that we included studies only written in the English language, and studies written in other languages could impact outcomes. The second limitation is the lack of blinding because of the nature of the different strategies (MT, PCI, and CABG).

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Conflict of Interests

Authors have no conflict of interests.

Authors' Contribution

All listed authors in this systematic review and meta-analysis have credit for authorship based on Uniform Requirements for Manuscripts Submitted to Biomedical Journals.

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