Meta-analysis of long-term outcomes of percutaneous coronary intervention versus medical therapy in stable coronary artery disease

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Percutaneous coronary intervention (PCI) improves survival and reduces the risk of recurrent myocardial ischemia in patients with acute coronary syndrome.[1] Conversely, the role of PCI in patients with stable coronary artery disease (CAD) remains controversial.[2] In the ORBITA trial, PCI was not associated with significant improvement in exercise time or angina frequency compared with a sham procedure,[2] whereas long-term outcomes of the FAME 2 trial showed that a fractional flow reserve (FFR)-guided PCI strategy was superior to medical therapy (MT) in terms of cardiovascular outcomes.[3] To address this controversy, we have performed an updated meta-analysis comparing the efficacy of PCI versus MT at a mean follow-up duration of 5 years.

A comprehensive search strategy was devised using MEDLINE, EMBASE and CENTRAL (inception to 30 May 2018) to identify randomized controlled trials (RCTs) with a sample size greater than 400 patients (to avoid small study effects)[4] and over 4 years follow-up duration. We included trials reporting PCI with stent implantation in 70% or more of the patients and statin therapy in 50% or more patients in the study population. The outcomes of interest were all-cause mortality, myocardial infarction (MI), stroke, cardiovascular mortality, revascularization and angina relief. Quality assessment of each trial was

performed using the Cochrane risk of bias tool. The literature search, data extraction and bias risk assessment was done by authors ANL, MSK and UF independently. Estimates were pooled using the DerSimonian and Laird random effects model and reported as risk ratio (RR) with 95% confidence interval (CI). Heterogeneity was quantified by I^2 with values greater than 75% consistent with high grade heterogeneity. Publication bias was assessed using Egger's regression test. Analyses were conducted at 5% significance. Comprehensive Meta-Analysis (version 3) was used for meta-analysis.

Five RCTs (8117 patients)[3,5–8] were finalized in this meta-analysis (Table 1). At a mean follow-up duration of 5 years, there were no significant differences between PCI and MT in terms of all-cause mortality (RR 0.99, 95% CI 0.86–1.15, $P = 95\%$, $I^2 = 0\%$), MI (RR 1.00, 0.95% CI 0.80–1.25, $P = 0.99$, $I^2 = 54\%$), stroke (RR 1.14, 95% CI 0.83–1.57, $P = 0.43$, $I^2 = 0\%$), revascularization 0.61, 95% CI 0.28–1.31, $P = 0.21$, $I^2 = 97\%$), cardiovascular mortality (RR 1.06, 95% CI 0.82–1.36, $P = 0.67$, $I^2 = 0\%$) or angina relief (RR 1.03, 95% CI 0.93–1.15, $P = 0.54$, $I^2 = 66\%$) (Figure 1). Egger's regression test did not detect publication bias (P (two-tailed) = 0.19).

This meta-analysis suggests that in patients with stable CAD, PCI was not associated with a reduction in cardiovascular outcomes, angina relief or survival benefit compared with MT at 5 years mean follow-up duration. The former meta-analyses included studies with shorter follow-ups with the lesser use of stents, which is contrary to the current standard of care.[9,10] The current study is unique because of the inclusion of more contemporary trials with longer follow-up durations and studies in which the use of stents ranged from 72% to 97% in the PCI arm. Therefore, these results should be considered more robust and reliable in view of current practice.

This study revalidates the beneficial role of optimal MT in patients with stable CAD. A recent meta-analysis of 10 studies (106,002 patients) confirmed that evidence-based medication regimens (beta-blockers, angiotensin-converting enzyme inhibitors, antiplatelet therapy and statins) were associated with a reduced risk of cardiovascular events and mortality.[11] However, it is important to mention that intensive MT should be coupled with aggressive risk modification to generate favorable cardiovascular outcomes. For instance, in a *post hoc* analysis of the BARI-2D trial, current or former smoking was associated with greater than twice the risk of all-cause mortality in patient with diabetes and stable CAD receiving MT or PCI.[12] Therefore, it is critical that physicians should enforce the importance of risk modification while prescribing guideline-directed MT.

This meta-analysis has limitations which are mainly related to the limitations inherent in the included RCTs. As drug-eluting stents were approved only after 2004, PCI was performed using bare-metal stents in the majority of the RCTs with the exception of the FAME 2 trial,[3] in which second generation drug-eluting stents were used as part of the study protocol. In some trials, balloon angioplasty alone without stenting was performed in more than 25% of the patients.[7] Also, there were a significant number of patients who crossed over from the MT to the PCI arm in these trials, which is not factored in in this meta-analysis. Another limitation is the heterogeneity in inclusion criteria and eligibility for PCI in these RCTs. In the OAT trial, patients with stable CAD were included who had persistent total occlusion of

the infarct-related coronary artery 3–28 days after MI.[7] Only the FAME 2 trial included an objective criterion, FFR for inclusion in the study.[3] In other trials, FFR was not mandatory to assess the significance of the coronary lesion. The majority of the patients probably represented a low-risk cohort, as evident from an average left ventricular ejection fraction of over 45% in all these trials. Furthermore, only a small proportion of patients with multivessel disease were included in these trials. Only one third of patients in the COURAGE and BARI-2D trials had three-vessel disease,[5,6] while the FAME 2 trial included only 9% of patients with three-vessel disease.[3]

In conclusion, in patients with stable CAD, PCI was not associated with a reduction in cardiovascular outcomes, angina relief or improved survival compared with MT at a mean follow-up duration of 5 years.

Funding

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Outcome	Study name	Events / Total		Statistics for each study					Risk ratio and 95% CI
		PCI	MT	Risk ratio	Lower limit	Upper limit	Z-Value	p-Value	
All cause mortality	FAME 2	23 / 447	23 / 441	0.99	0.56	1.73	−0.05	0.96	
	MASS II	32 / 205	33 / 203	0.96	0.61	1.50	−0.18	0.86	
	COURAGE	85 / 1149	95 / 1138	0.89	0.67	1.17	−0.84	0.40	
	OAT	87 / 1082	84 / 1084	1.04	0.78	1.38	−0.25	0.80	
	BARI 2D	102 / 798	96 / 807	1.07	0.83	1.39	−0.54	0.59	
				0.99	0.86	1.15	−0.08	0.94	
MI	FAME 2	36 / 447	53 / 441	0.67	0.45	1.00	−1.95	0.05	
	MASS II	23 / 205	31 / 203	0.73	0.44	1.22	−1.20	0.23	
	COURAGE	143 / 1149	128 / 1138	1.11	0.88	1.38	0.89	0.38	
	OAT	59 / 1082	44 / 1084	1.34	0.92	1.97	1.52	0.13	
	BARI 2D	90 / 798	82 / 807	1.11	0.84	1.47	0.72	0.47	
				1.00	0.80	1.25	−0.02	0.99	
Stroke	FAME 2	12 / 447	7 / 441	1.69	0.67	4.26	1.12	0.26	
	MASS II	7 / 205	7 / 203	0.99	0.35	2.77	−0.02	0.99	
	COURAGE	22 / 1149	14 / 1138	1.56	0.80	3.03	1.30	0.19	
	OAT	16 / 1082	19 / 1084	0.84	0.44	1.63	−0.51	0.61	
	BARI 2D	23 / 798	23 / 807	1.01	0.57	1.79	0.04	0.97	
				1.14	0.83	1.57	0.79	0.43	
Revascularization	FAME 2	60 / 447	225 / 441	0.26	0.20	0.34	−10.36	0.00	
	MASS II	66 / 205	49 / 203	1.33	0.97	1.83	1.79	0.07	
	COURAGE	228 / 1149	348 / 1138	0.65	0.56	0.75	−5.83	0.00	
				0.61	0.28	1.31	−1.27	0.21	
CV mortality	FAME 2	11 / 447	7 / 441	1.55	0.61	3.96	−0.92	0.36	
	MASS II	24 / 205	25 / 203	0.95	0.56	1.61	−0.19	0.85	
	COURAGE	23 / 1149	25 / 1138	0.91	0.52	1.60	−0.33	0.74	
	OAT	58 / 1082	52 / 1084	1.12	0.78	1.61	0.60	0.55	
				1.06	0.82	1.36	0.43	0.67	
Angina relief	FAME 2	26 / 352	35 / 343	0.72	0.45	1.18	−1.31	0.19	
	MASS II	119 / 205	92 / 203	1.28	1.06	1.55	2.54	0.01	
	COURAGE	316 / 423	296 / 406	1.02	0.94	1.11	0.59	0.56	
	OAT	234 / 263	233 / 257	0.98	0.93	1.04	−0.64	0.52	
				1.03	0.93	1.15	0.62	0.54	

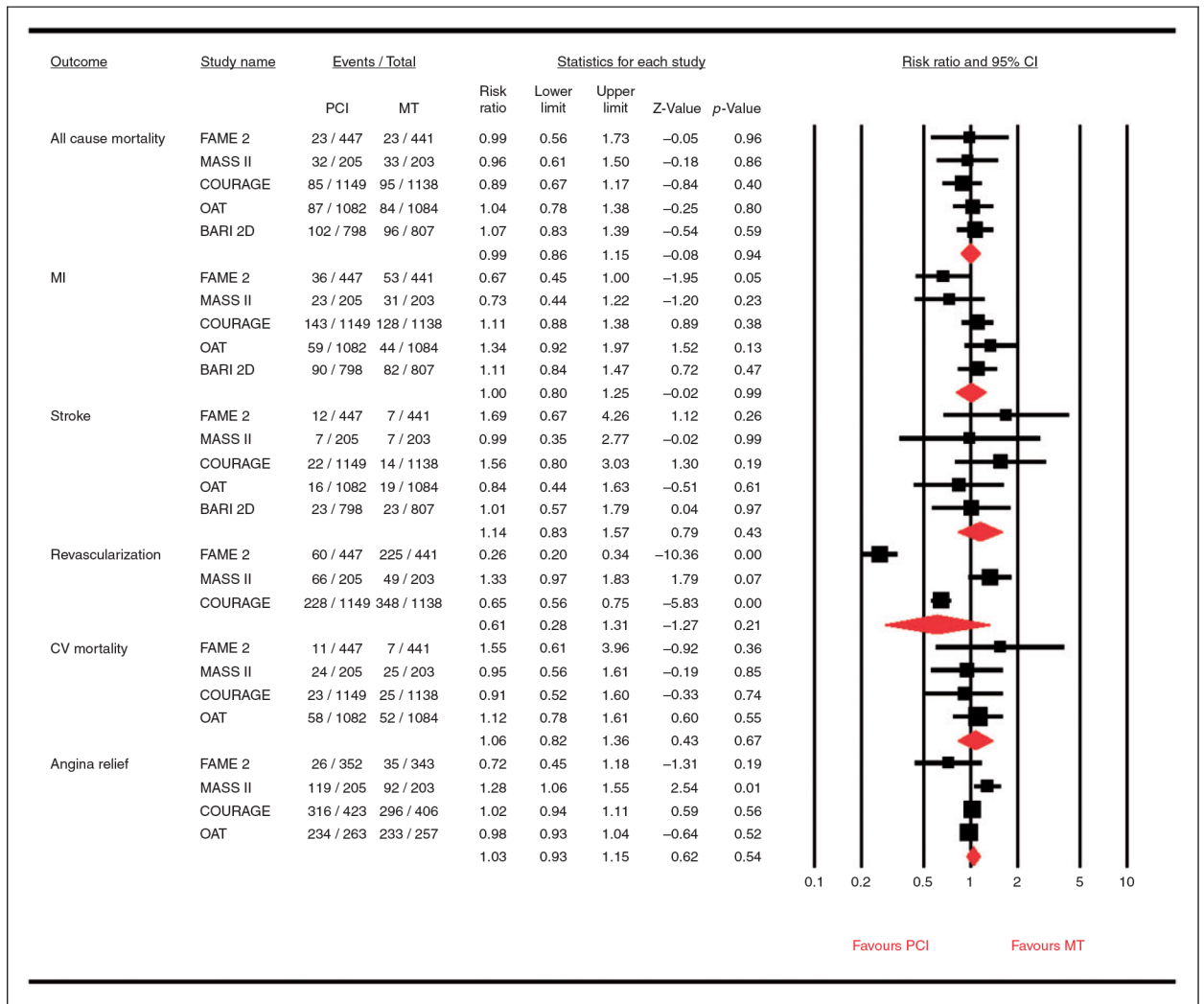0.1   0.2   0.5   1   2   5   10

Favours PCI   Favours MT

Figure I.
Forest plot comparing percutaneous coronary intervention (PCI) versus medical therapy (MT) in stable coronary artery disease patients.
MI: myocardial infarction; CV: cardiovascular; CI: confidence interval.

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Table 1.

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Baseline characteristics of the studies.

Studies (year)	Groups	n	Age (years)	Men (%)	DM (%)	Prior MI (%)	LVEF (%)	Aspirin (%)	β-blockers (%)	Statins (%)	CCB (%)	ACEI/ARB (%)	Stenotic vessels >50% (mean)	Stent (%)	DES (%)	Follow-up (months)	CRoB[a]
BARI-2D (2005)[7]	PCI	1176	62.3	70.4	100.0	31.7	57.0	93.5	83.9	94.6	-	91.2	-	90.0	35.0	5	*****
	MT	1192	62.4	70.3	100.0	32.4	57.3	94.2	87.9	95.4	-	92.0	-				
OAT (2006)[7]	PCI	1082	58.6	78.0	18.0	12.0	47.4	94.0	86.0	80.0	65.0	80.0	-	87.0	8.0	4	*****
	MT	1084	58.7	78.0	23.0	11.0	48.0	97.0	89.0	82.0	61.0	80.0	-				
MASS II (2006)[8]	PCI	205	60.0	67.0	23.0	52.0	67.0	100.0	85.0	74.0	-	28.0	2.35	72.0	0.0	5	*****
	MT	203	60.0	69.0	36.0	39.0	68.0	97.0	85.0	59.0	-	28.0	3.37				
COURAGE (2007)[5,9]	PCI	1149	61.5	85.0	32.0	38.0	60.8	95.0	85.0	93.0	42.0	62.0	1.9	94.0	3.0	4.6	******
	MT	1138	61.8	85.0	35.0	39.0	60.9	94.0	86.0	93.0	52.0	65.0	2.0				
FAME-2 (2018)[3]	PCI	447	63.5	79.6	27.5	37.1	-	90.2	68.3	90.2	29.3	78.0	93.9	97.0	95.0	5	******
	MT	441	63.8	76.6	26.5	37.8	-	91.9	83.8	100.0	29.7	86.5	93.7				

ACEI: angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blocker; BARI-2D: Bypass Angioplasty Revascularization 2 Diabetes; COURAGE: Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation; CCB: calcium channel blockers; CRoB: Cochrane risk of bias; DES: drug-eluting stent; DM: diabetes mellitus; FAME: Fractional Flow Reserve versus Angiography for Multivessel Evaluation; LVEF: left ventricular ejection fraction; MASS: Medicine, Angioplasty or Surgery Study; MI: myocardial infarction; OAT: Occluded Artery Trial.

[a] Scale constitutes of seven domains: random sequence generation (selection bias); allocation concealment (selection bias); blinding of participants and personnel (performance bias); blinding of outcome assessment (detection bias); incomplete data reporting (attrition bias); selective reporting (reporting bias) and other bias. Each domain carries one star and five or more stars represents good quality.