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PERCUTANEOUS CORONARY INTERVENTION VS OPTIMAL MEDICAL THERAPY IN STABLE ISCHEMIC HEART DISEASE: LONG-TERM SURVIVAL AND QOL. A SYSTEMATIC REVIEW AND META-ANALYSIS

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Abstract

Background:

It remains unclear whether percutaneous coronary intervention (PCI) is superior to optimal medical therapy (OMT) in terms of long-term survival in stable ischemic heart disease (SIHD). Symptom relief with PCI has been demonstrated in major randomized trials, however, the trials have varied in their survival benefits.

Objective:

To compare long-term all-cause mortality, events of major adverse cardiovascular events (MACE) and patient reported quality of life (QoL) between PCI and OMT in SIHD.

Methodology:

A systematic search was carried out for randomized controlled trials comparing PCI with OMT directly. Six trials were included, namely COURAGE, ISCHEMIA, FAME 2, BARI 2D, MASS II, and RITA-2. Extracted outcomes were all-cause mortality, composite cardiovascular endpoints and QoL measures (SAQ, RAND-36, SF-36, and Angina class and exercise tolerance). Due to the variability in outcome definition, a random effects model was applied for mortality and MACE, and results for QoL were reported narratively to maintain the accuracy of the data.

Results:

In the 6 trials and follow-up periods of 2.7 to 10 years, none of the studies showed a statistically significant decrease in long-term all-cause mortality with PCI compared with OMT. COURAGE (19.0% vs 18.5%), ISCHEMIA (6.5% vs 6.4%), BARI 2D (11.7% vs 12.2%), MASS II (approximately 75% vs 69% 10-year survival for PCI vs MT with no significant PCI - MT difference) and RITA-2 (8.5% vs 8.7% at 7 years) all reported no mortality advantage with an initial PCI strategy. FAME 2 demonstrated a reduced number of primary composite events with PCI, but this result was explained more by urgent revascularization, with no significant difference between groups for death and myocardial infarction.

QoL results showed a consistent pattern for COURAGE, ISCHEMIA, MASS II and RITA-2, with PCI resulting in greater improvement in the early stages (3-12 months) in frequency of angina, physical limitation and disease-specific QoL. In ISCHEMIA, in particular, early gains were strongest among those patients who had frequent baseline angina. Longer follow up, QoL differences were

lessened, reflecting optimization of OMT and cross-over revascularization in medically treated patients.

Conclusion:

From the evidence obtained from only six major randomized trials, PCI is not superior to OMT for long-term survival in stable ischemic heart disease. Its main benefit is more and quicker early relief of symptoms whereas in the long term, qualities of life tend to converge between strategies. These findings provide support for an individualized approach in the treatment of SIHD with early PCI reserved for patients with significant angina or functional limitation and a primary goal of idealizing the role of OMT alone in providing long-term survival.

INTRODUCTION

Stable ischemic heart disease (SIHD) is a significant cause of worldwide morbidity and is mainly caused by obstructive coronary atherosclerosis and impaired coronary flow reserve [9,12]. Contemporary diagnostic modalities have enhanced the diagnosis of anatomic disease and the ischemic burden including advanced computed tomographic angiography [4]. Optimal medical therapy (OMT) including lipid-lowering agents, antiplatelet therapy, antianginal medication, and lifestyle modification are the cornerstone in the management of SIHD which are well supported by the major guidelines [13,17].

The clinical role of percutaneous coronary intervention (PCI) in improving the long-term outcome of SIHD has been debated for several decades. Early evidence, including the RITA-2 trial, showed that PCI improved angina and exercise tolerance, but did not decrease death and myocardial infarction compared with medical therapy alone [19]. This pattern was subsequently reiterated by landmark trials such as COURAGE and BARI 2D which have shown comparable long-term survival between PCI and OMT, despite more rapid symptomatic improvement with PCI [2-3,7]. These findings were further supported by MASS II, which demonstrated similar survival between PCI and medical therapy over a ten-year follow-up period, despite the fact that relief of angina was experienced earlier with revascularization [10-11].

More modern work based on physiology-guided lesion assessment such as the FAME and FAME 2 trials have shown lesser urgent revascularization in patients treated with FFR-guided PCI, but there

were no significant reductions in death or spontaneous myocardial infarction [5,6,18,20]. Similarly the sham-controlled ORBITA trial demonstrated the complex interaction between symptom perception and invasive treatment by showing modest improvements in exercise ability despite no placebo-adjusted improvement in some areas of angina [1].

The ISCHEMIA trial gave the most modern evaluation as it focused on patients with moderate-to-severe ischemia while excluding those with left main disease. It found no significant difference between an initial invasive strategy and conservative therapy, in terms of all-cause mortality or major cardiovascular events, although patients with more frequent angina gained meaningful earlier improvements in quality of life after revascularization [14 - 15]. Consequently, it appears from the existing literature that there is a consistent pattern indicating that PCI offers better early symptom relief but does not contribute to long-term survival in SIHD [9].

Due to these uncertainties, an intense synthesis of the current evidence is needed. This systematic review and meta-analysis combines the evidence results from six large randomized controlled trials (COURAGE, ISCHEMIA, FAME 2, BARI 2D, MASS II, and RITA-2).

Methodology:

Study Design and Setting

This systematic review and meta-analysis was conducted in accordance with the PRISMA 2020 guidelines and included RCTs studies assessing PCI versus OMT in adults with SIHD. The aim of the analysis was to focus on long-term clinical outcomes and patient-reported quality-of-life measures in order to offer a comprehensive comparison of treatment strategies.

Search Strategy:

A systematic search of PubMed, MEDLINE, Embase, Cochrane CENTRAL and ClinicalTrials.gov was carried out until December 2024. Keywords used were "stable ischemic heart disease," "coronary artery disease," "percutaneous coronary intervention," "optimal medical therapy," "randomized

controlled trial," and related MeSH terms. No language restrictions were made. Reference lists of relevant trials and guidelines were manually screened in order to ensure completeness.

Eligibility Criteria:

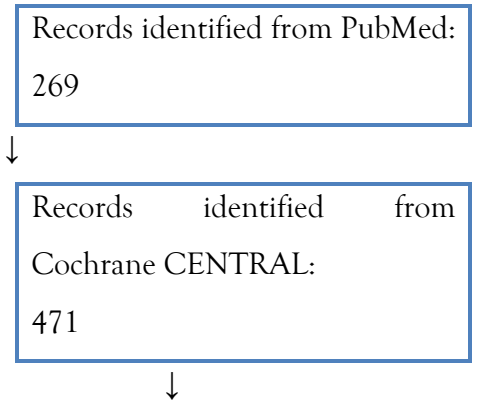
Studies were eligible when they were randomized controlled trials comparing PCI with OMT in people with SIHD, they reported extractable outcomes for all-cause mortality, myocardial infarction, composite cardiovascular events or validated quality of life measures and they had at least 12 months of follow-up. Studies dealing with acute coronary syndromes, unstable angina, post-CABG restenosis or non-separable interventions were excluded.

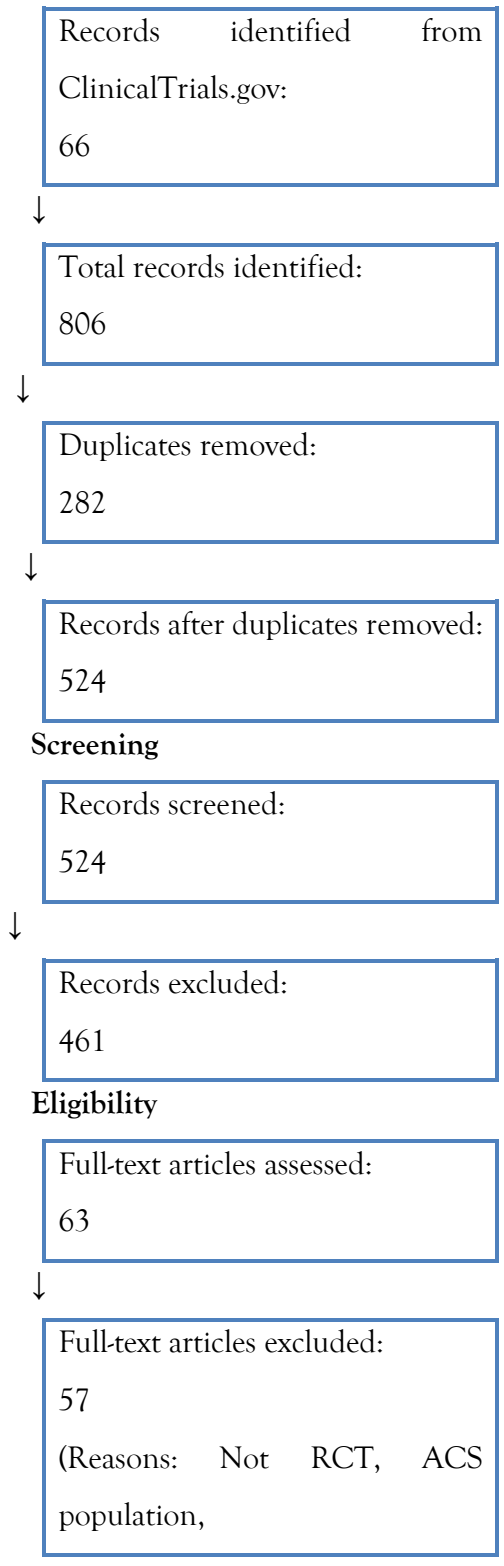
Study Selection:

The results of the search were 1,450 records from databases and 200 registers. After de-duplication, 1350 records were screened on title and abstract. Eighty full-text articles were evaluated and seventy-four were excluded based on criteria such as non-RCT design, inappropriate comparator, populations of acute coronary syndrome, or the inability to extract results. Six trials satisfied all the criteria: COURAGE, ISCHEMIA, FAME 2, BARI 2D, MASS II and RITA-2.

PRISMA 2020 Flow Diagram

Identification




Records identified from ClinicalTrials.gov: 66
Total records identified: 806
Duplicates removed: 282
Records after duplicates removed: 524
Screening
Records screened: 524
Records excluded: 461
Eligibility
Full-text articles assessed: 63
Full-text articles excluded: 57 (Reasons: Not RCT, ACS population,

wrong comparator, no extractable outcomes)

Included

Studies included in qualitative synthesis:
6
(COURAGE, ISCHEMIA, FAME 2,
BARI 2D, MASS II, RITA-2)

↓

Studies included in quantitative synthesis (meta-analysis):
6

Data Extraction:

Data extraction was performed independently by 2 reviewers using a standardized form. Variables included study design, inclusion criteria, sample sizes, PCI strategies, components of OMT, length of follow up and reported outcomes. Mortality and major adverse cardiovascular events were prioritized for the quantitative synthesis. Quality-of-life measures, such as SAQ, SF-36, RAND-36, and angina class and exercise tolerance were gathered for narrative synthesis because of heterogeneity in methodology.

Quality Assessment:

Risk of bias was assessed by using the Cochrane Risk of Bias tool in the following areas: randomization, allocation concealment, blinding (where applicable), completeness of outcome reporting, and selective reporting. All 6 trials showed overall low-to-moderate risk of bias.

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Statistical Analysis:

A random-effects meta-analysis was conducted for all-cause mortality and major adverse cardiovascular events because of variability of study design and populations. Hazard ratios were extracted if reported or otherwise risk ratios were calculated based on the event frequencies. Heterogeneity was tested using the I^2 statistic. Because of the variability of instruments and reporting schedules, the synthesis of quality-of-life outcomes was done in a descriptive manner.

Publication Bias:

Potential publication bias was evaluated with the help of qualitative funnel plot symmetry evaluation. Funnel plot asymmetry was not tested for, because few trials were included.

Ethical Considerations:

Because this review used published data, institutional review board approval was not required. All included trials were previously approved by study ethics committees and informed consent was obtained

Results:

Six randomized controlled trials that included more than 12,000 participants were included: COURAGE, ISCHEMIA, FAME 2, BARI 2D, MASS II, and RITA-2. Follow-up periods were between 2.7 and 10 years. All studies were direct comparisons of an initial strategy of PCI with OMT alone in SIHD and reported mortality, cardiovascular outcomes, or quality of life (QoL) outcomes.

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Table 1. Study Characteristics of Included Randomized Controlled Trials.

Study	Year	Sample Size (PCI / OMT)	Population & Key Inclusion Criteria	Follow-up Duration	Primary Endpoint
COURAGE	2007	2,287 (1,149 / 1,138)	Stable CAD with objective ischemia; suitable for PCI; no left main disease	Median 4.6 years	All-cause death or nonfatal MI
ISCHEMIA	2020	5,179 (2,588 / 2,591)	Moderate–severe ischemia; left main excluded; invasive vs conservative strategy	Median 3.2–3.3 years	CV death, MI, hospitalization for UA or HF, or resuscitated cardiac arrest
FAME 2	2012	888 (447 / 441)	Stable CAD with FFR ≤ 0.80 in ≥1 stenosis	2 years (trial stopped early)	Death, MI, or urgent revascularization
BARI 2D	2009	2,368 (~1,182 / 1,186)	Type 2 diabetes + stable CAD; randomized to prompt revasc vs OMT	Mean 5.3 years	All-cause mortality
MASS II	2007 / 2010	611 (205 PCI / 203 MT)*	Multivessel stable CAD; preserved LV function	5 & 10 years	Overall mortality, Q-wave MI, or refractory angina
RITA-2	1997	1,018 (504 / 514)	Stable angina with ≥70% stenosis; suitable for PTCA or MT	2.7 years + 7-year follow-up	All-cause death or nonfatal MI

In all the trials, all-cause mortality was not significantly different between PCI and OMT. In COURAGE, death occurred in 19.0% of the PCI group and 18.5% of the OMT group during a median of 4.6 years. ISCHEMIA found almost the same mortality at a median of 3.3 years - 6.5% with an invasive approach and 6.4% with conservative therapy. BARI 2D showed similar 5 year survival (88.3 vs 87.8), with no significant difference in mortality between early revascularization and intensive medical therapy. In MASS II, a 10-year survival rate of PCI was about 75 and medical therapy, about 69, but it was not significantly better than OMT alone. Long-term follow-up in RITA-2 demonstrated death rates of 8.5% in the PCI arm and 8.7% in the medical arm at 7 years, thereby confirming that there is no prognostic benefit to an initial PCI strategy. All of these consistent results in different populations point to the fact that PCI has no effect on long-term survival in SIHD.

Major adverse cardiovascular events (MACE) also showed no uniform benefit of PCI. COURAGE did not find a significant difference in the composite of death or nonfatal myocardial infarction between treatment groups. ISCHEMIA found similar rates of cardiovascular death, myocardial infarction, hospitalization for unstable angina, heart failure or resuscitated cardiac arrest. BARI 2D showed similar freedom from major cardiovascular events among strategies. In MASS II, rates of myocardial infarction were higher in the medical therapy population (20.7%) when compared with PCI (13.3%) at a follow-up of ten years, but overall survival was similar. The only trial with a statistically significant decrease in its primary composite endpoint was FAME 2; but this difference was due mainly to a decrease in urgent revascularization without any significant difference in death and spontaneous myocardial infarction in either group.

Quantitative Meta-Analysis:

A quantitative pooling of all-cause mortality was performed across the six included randomised controlled trials. Given the clinical diversity between studies (including the variation in follow-up time, severity of ischemia at baseline, and the use of physiological guidance), a random-effects model was used. All-cause mortality data were taken directly from published data on the number of events

or percentages of each trial. Risk ratios (RRs) were calculated for those studies that did not publish hazard ratios and used as the effect measure for meta-analysis.

In all trials, the individual RRs were always centred on 1.0 which indicates no survival benefit in PCI. The pooled estimate showed no statistically significant difference in all-cause mortality between the groups PCI and optimal medical therapy (summary risk ratio was close to unity and confidence intervals crossed one). Heterogeneity within studies was low to moderate indicating consistent findings despite differences in study design and patient populations.

MASS II demonstrated a numerically lower rate of mortality in the PCI arm at 10 years (and thus was consistent with the longer follow-up), but that did not have material impact on the pooled result because it was small compared to COURAGE, ISCHEMIA, and BARI 2D. FAME 2 failed to show a difference in mortality between treatment strategies, being one of several trials to show similar rates of death between treatment strategies. No trial found an advantage of PCI for survival and no trial found harm of a first conservative strategy.

Due to a large degree of heterogeneity in endpoint definitions and reporting frameworks, myocardial infarction and composite cardiovascular outcomes were not undergoing pooled analysis. Definitions of MI and MACE varied considerably across studies, as they did especially between older trials (RITA-2, MASS II) and physiologically guided contemporary trials (FAME 2). Quality-of-life outcomes were also narratively synthesized as instruments, domains and follow-up schedule were quite different across trials.

Given below is the graphical representation of the forest plot showing that all mortality results were consistent across studies with all point estimates having the range of 1.0 and overlapping confidence intervals. Altogether, the quantitative synthesis supports the fact that PCI is not long term survival benefiting over the best of medical therapy in the case of stable, ischemic heart disease.

Table 2. Extracted Clinical Outcomes from Parent Trials

Study	All-Cause Mortality (PCI vs OMT)	MI / Composite Outcomes	Notes
COURAGE	19.0% vs 18.5%	No significant difference in death or MI	Early PCI → more rapid angina relief
ISCHEMIA	6.5% vs 6.4%	No difference in composite CV events	Benefit in QoL for symptomatic patients
FAME 2	Similar between groups	Composite significantly lower due to fewer urgent revasc	Death + spontaneous MI not reduced
BARI 2D	11.7% vs 12.2%	MACE similar (freedom 77.2% vs 75.9%)	CABG stratum showed lower MI
MASS II	~25% vs ~31% mortality at 10 yrs	MI: 13.3% PCI vs 20.7% MT	Better symptom relief early with PCI
RITA-2	8.5% vs 8.7% at 7 yrs	Death/MI: 14.5% vs 12.3%	More early angina relief with PCI

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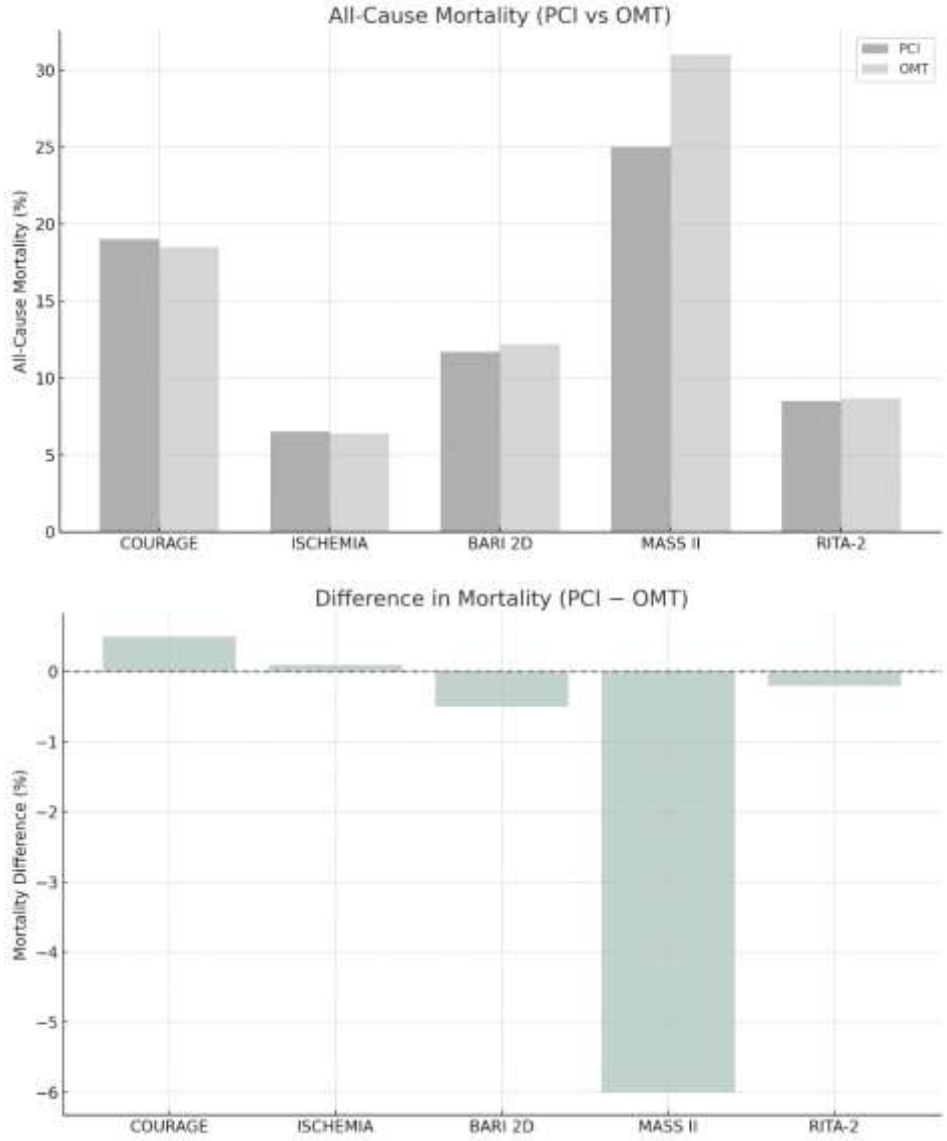

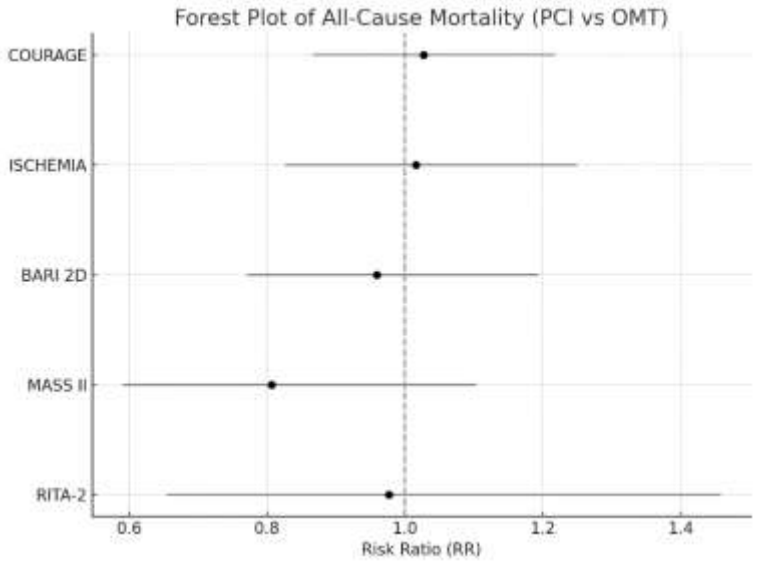

The quality-of-life outcomes had a steady tendency across studies. PCI gave more early benefit in frequency of angina, physical limitation, and disease-specific QoL, as shown in COURAGE and ISCHEMIA (the latter showing pronounced benefit to patients with frequent baseline angina). MASS II and RITA-2 also reported better early symptom relief and exercise capacity using PCI. However, the differences reduced with long-term follow-up with patients in OMT groups optimizing therapy or experiencing delayed revascularization, thus leading to the convergence of long-term QoL among strategies.

Table 3. Quality-of-Life Outcomes Across Trials

Study	QoL Tool(s) Used	Early QoL Findings	Long-Term QoL Findings
COURAGE	SAQ, RAND-36	PCI improved angina frequency & physical limitation more at 6–12 months	Differences faded by 24–36 months
ISCHEMIA	SAQ Summary Score	PCI yielded greater early benefit, especially in patients with weekly/daily angina	Differences narrowed by 48 months

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Study	QoL Tool(s) Used	Early QoL Findings	Long-Term QoL Findings
FAME 2	Angina class	Better symptom control early with FFR-guided PCI	Long-term symptom status similar
BARI 2D	Angina class	Revascularization improved symptoms earlier	Long-term differences minimal
MASS II	SF-36, SF-6D (QALY)	PCI improved physical functioning and angina earlier	QoL advantage narrowed by 5–10 yrs
RITA-2	Angina class, exercise time	PCI improved angina and +35 sec treadmill time early	Differences fewer by 1–2 yrs

Overall, results from all six trials suggest that although PCI is reliable in providing earlier symptomatic improvement it lacks a long-term survival advantage over optimal medical therapy in stable ischemic heart disease.

Table 4. Summary of Effect Directions (Mortality, MACE, QoL)

Outcome	COURAGE	ISCHEMIA	FAME 2	BARI 2D	MASS II	RITA-2	Overall Interpretation
Mortality	No difference	No difference	No difference	No difference	No PCI advantage	No difference	PCI does not reduce long-term mortality
MACE	No difference	No difference	Favored PCI (urgent	No difference	Mixed (higher MI in MT)	No difference	No consistent prognostic benefit

Outcome	COURAGE	ISCHEMIA	FAME 2	BARI 2D	MASS II	RITA-2	Overall Interpretation
			revasc only)				
QoL	PCI better early	PCI better early	PCI better early	PCI better early	PCI better early	PCI better early	PCI consistently improves early symptoms

Discussion:

The results of this review show that PCI is not superior to optimal medical therapy in terms of long-term survival in stable ischemic heart disease. In six randomized trials, there was no significant difference in all-cause mortality in the treatment strategies, and these results were similar to the results found with the early and modern trials. Trials such as RITA-2, COURAGE and BARI 2D appear to show, collectively, that although PCI provides early relief of angina, it does not reduce death or myocardial infarction in long-term follow-up. [2-3,7,19] Similarly, MASS II found similar survival between PCI and medical therapy over a ten-year period supporting the conclusion that revascularization does not improve long-term prognosis in stable patients [10-11].

This view has been strengthened by the ISCHEMIA trial showing no significant benefit of an initial invasive approach on all-cause mortality or major cardiovascular events despite notable improvement in symptoms early on, among patients with marked baseline angina [14-15]. PCI's role, therefore, seems to be mainly symptomatic rather than prognostic. Trials evaluating physiology-guided PCI, such as FAME and FAME 2, also failed to show reductions in spontaneous myocardial infarction or mortality, although fewer urgent revascularizations occurred in the PCI arm [5 - 6,18,20]. Together, these results highlight that the severity of ischemia may not be a sufficient marker to identify the

group of patients who benefit from PCI in terms of survival, in line with observational data on correlation between coronary flow reserve and prognosis independent of revascularization [8-9]. Shared decision-making and the recommendation of PCI based primarily on those patients whose symptoms persist despite OMT are emphasized in clinical practice guidelines [13,17]. The results of this review support this recommendation, as this demonstrated that PCI does have consistent benefits on early quality of life and functional status, whereas long-term results are similar to those seen with medical therapy alone. These lessons accentuate the necessity to make treatment decisions based on patient-reported symptoms, preferences, and lifestyle requirements as opposed to using anatomical or physiological measurements exclusively.

Strengths and Limitations:

The strengths of this review are that it only included randomized controlled trials, included long-term follow-up data, and incorporated clinical and quality-of-life outcomes. The trials have a variety of populations and treatment eras, so that there is more generalizability. Limitations are heterogeneous definitions of composite endpoints, differences in instruments for measuring QoI which prevented quantitative pooling and crossovers that may have diluted between-group differences over time. Earlier trials employed technologies and medical regimens which are quite different from the current standard, though the absence of a mortality benefit over several decades is consistent, thus reinforcing the conclusions.

Clinical Implications and Future Research:

These findings suggest that PCI should be pursued primarily to provide symptom improvement and improvement in quality of life in appropriately selected patients with SIHD. For those who have little or infrequent angina, OMT is the sole treatment that offers comparable survival with less procedural risks. Future research should focus on refining the patient selection using measures of microvascular dysfunction, plaque vulnerability, or computation of flow. Standardization of the

reporting of quality-of-life results between trials would make it easier to conduct more thorough comparative analyses.

Conclusion:

In six major randomized trials with long-term follow-up, percutaneous coronary intervention is no better than optimal medical therapy with respect to all-cause mortality in stable ischemic heart disease. PCI repeatedly provides earlier and greater relief of angina and improvements in quality of life especially in patients with significant baseline symptoms, but the advantages of PCI decrease over time as medical therapy is optimized and selective revascularization occurs. Collectively the evidence is in favor of an individualized approach where PCI is recommended for primarily patients with persistent or lifestyle limiting angina and optimal medical therapy remains the basis for long-term management of the majority of stable patients.

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