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Invasive therapy versus conservative therapy for patients with stable coronary artery disease: An updated meta-analysis

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Abstract

Background: Heart disease remains the leading cause of death in the United States. Although there are clear indications for revascularization in patients with acute coronary syndromes, there is debate regarding the benefits of revascularization in stable ischemic heart disease. We sought to perform a comprehensive meta-analysis to assess the role of revascularization compared to conservative medical therapy alone in patients with stable ischemic heart disease.

Hypothesis: There is no significant difference in all-cause mortality or cardiovascular mortality between invasive and medical arms.

Methods: We performed a systematic literature search from January 2000 to June 2020. Our literature search yielded seven randomized controlled trials. We analyzed a total of 12 013 patients (6109 in revascularization arm and 5904 in conservative medical therapy arm). Primary outcome was all-cause mortality. Secondary outcomes included major adverse cardiac events (MACE) (death, myocardial infarction [MI], or stroke), cardiovascular mortality, MI, and stroke. Additional subgroup analysis for all-cause mortality was performed comparing percutaneous coronary intervention (PCI) with bare metal stent versus conservative therapy; and PCI with drug eluting stent versus conservative therapy.

Results: There was no statistically significant difference in primary outcome of all-cause mortality between either arm (odds ratio [OR] = 0.95; 95% CI [confidence interval], 0.83 to 1.08; p = .84). There were statistically significant lower rates of MACE (death, MI or stroke) in the revascularization arm when compared to conservative arm.

Conclusions: Our analysis did not show any survival advantage of an initial invasive strategy over conservative medical therapy in patients with stable coronary artery disease (CAD).

KEYWORDS

coronary artery bypass grafting, medical therapy, percutaneous coronary intervention, stable coronary artery disease

1 | INTRODUCTION

Benefits of revascularization with percutaneous coronary intervention (PCI) or coronary artery bypass graft surgery (CABG) for patients presenting with acute coronary syndrome (ACS) have been clearly established. Multiple trials[1,2] have shown improved overall survival and reduction in recurrent myocardial infarction (MI) in patients with ACS. PCI leads to effective restoration of vessel patency, reduced re-occlusion, and improved residual left ventricular function. This evidence culminated in revascularization for ACS becoming a class I indication as per 2011 ACCF/AHA/SCAI Guidelines on PCI[3] and 2018 ESC/EACTS guidelines on myocardial revascularization.[4] On the contrary, benefits of revascularization in stable ischemic heart disease have remained a topic of debate and controversy. Several large clinical trials[5-8] have not shown any clear difference in mortality between revascularization and conservative therapy arms. New evidence from long term outcomes of FAME-2[9] trial has reported lower incidence of MI with PCI.[9] With publication of the results of the ISCHEMIA[10] trial and the 5 years follow-up results of FAME-2[9] trial, we sought to provide in this meta-analysis a comprehensive and updated assessment of the role of coronary revascularization coupled with medical therapy compared to conservative medical therapy alone (conservative therapy from here-on) in patients with stable ischemic heart disease.

2 | METHODS

We performed a systematic literature search on PubMed, Cochrane, Embase and Ovid MEDLINE database from January 2000 to June 2020. Search terms included (stable coronary artery disease OR stable angina OR angina) AND (medical therapy OR conservative management OR conservative strategy) AND (PCI OR expanded PCI OR revascularization OR CABG OR surgery). Inclusion criteria were randomized controlled trials (RCTs), trials in humans and English

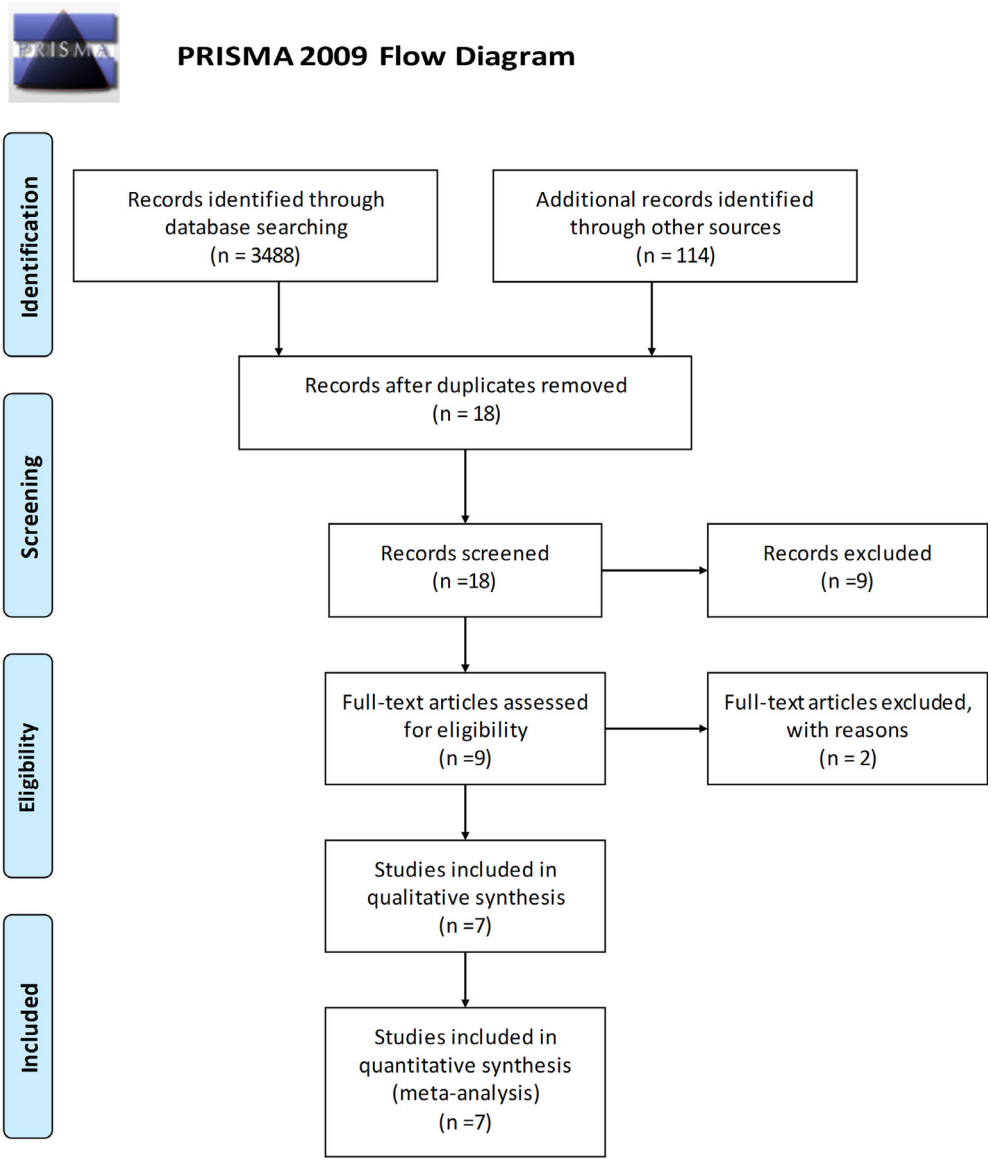

FIGURE 1 PRISMA flow diagram depicting summary of study selection process

language. Non-randomized trials, including observational studies, were excluded. Trials investigating treatment strategies other than directly comparing intervention to medical therapy were excluded. This led to exclusion of three major trials namely: ORBITA[11] trial where the outcomes analyzed were angina relief, rather than hard end points, and follow up period was very short; DEFER trial[12] which looked at outcomes of safety in deferring intervention in patients where fractional flow reserve (FFR) value was >0.75 (no conservative therapy alone arm) and[3] the trial by Hambrecht et al[13] which compared PCI with a 12 month exercise training program (no conservative therapy alone arm). There has been significant evolution in medical therapy for stable CAD. Pivotal trials looking at inhibitors of HMG-CoA reductase (statins) from 1990's[14,15] showed a significant improvement in mortality in patients with coronary artery disease. This has led to statins becoming the cornerstone of medical therapy in CAD. On the other hand, trials from 1990 to 2000's which looked at benefit of revascularization to medical therapy; had balloon angioplasty as the primary means of intervention. PCI with stents (preferably drug eluting over bare metal) is now standard practice for revascularization. Based on these significant paradigm shifts in therapies in both arms (revascularization and conservative), we excluded trials before 2000 as they did not reflect the current standard of care. This meta-analysis was

TABLE 1 Baseline characteristics of the included trials

Trials (year published)	N (no. of patients)	Age (years)	Male	HTN	DM	Smoking	Ejection fraction (%)	H/o CVA	Type of stent used
TIME (2004)[5,6]:									
MT	148	80	58%	58%	22%	32%	NA	7%	BMS (100%)
INV	153	80	58%	64%	20%	37%	NA	10%	
MASS II (2010)[8]:									
MT	203	60 ± 9	69%	55%	36%	33%	68 ± 7	N/A	BMS (100%)
PCI	205	60 ± 9	67%	61%	23%	27%	68 ± 8		
CABG	203	60 ± 9	72%	63%	29%	32%	68 ± 9		
COURAGE (2007)[7]:									
MT	1138	61.8 ± 9.7	968 (85%)	764 (67%)	399 (35%)	259 (23%)	60.9 ± 10.3	102(9%)	BMS (100%)
PCI	1149	61.5 ± 10.1	979 (85%)	757 (66%)	367 (32%)	260 (23%)	60.8 ± 11.2	100 (9%)	
JSAP (2008)[34]:									
MT	191	64.2 ± 7.6	144 (75%)	121 (63.4%)	76 (39.8%)	23.7%	65.8 ± 9.6	10 (5.4%)	BMS (100%)
PCI	188	64.5 ± 7.2	141 (75%)	119 (63.3%)	76 (40.4%)	13.1%	64.0 ± 9.7	13 (7.3%)	
BARI 2 D (2009)[21]:									
MT	1192	62.4	70.4%		100%	24.2%	57.3%	10.0%	BMS (56%) and
PCI and CABG	1176	62.3	70.3%		100%	22.9%	57.0%	9.5%	DES (34.7%)
FAME 2 (2018)[9]:									
MT	441	63.9	338 (76.6%)	343 (77.8%)	348 (78.9%)	90 (20.4%)		28 (6.3%)	DES (97%)
PCI	447	63.5	356 (79.6%)	347 (77.6%)	330 (73.8%)	89 (18.9%)		33 (7.45)	
ISCHEMIA (2020)[10]:									
MT	2591	64	2029	73.4%	42.2%	N/A	60%	2.6%	DES (98%)
INV	2588	64	1982	73.4%	41.4%		60%	3.4%	

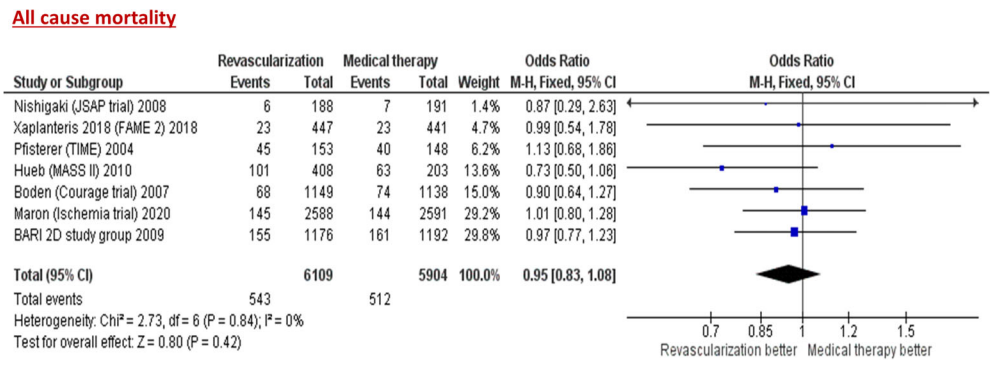

FIGURE 2 Forest plot of pooled odds ratio (OR) comparing revascularization versus medical therapy for primary outcome of all-cause mortality. The rectangle represents the point estimate (horizontal line indicates the 95% CI), with its size being proportional to the weight of the study in the meta-analysis. The diamond represents the pooled estimate (with its size representing the 95% CI)

performed using PRISMA statement guidelines,[16] (Figure 1). Two investigators (A. V., K. K.) independently extracted outcomes into a data collection form. Disagreements were resolved by discussions between the two authors or via reaching a consensus by involving a third investigator (H. C.). The definitions of outcomes were accepted as provided in the studies. In cases of multiple follow up publications in a trial, the longest available follow up was accepted. Ethical/Institutional review board approval was not applicable to our study.

Primary outcome was all-cause mortality. Secondary outcomes included MACE (death, MI or stroke), cardiovascular mortality, MI and stroke. Additional subgroup analysis for all-cause mortality was performed comparing[1] PCI with bare metal stent versus conservative therapy; and[2] PCI with drug eluting stent versus conservative therapy.

Data was extracted on an intention-to-treat basis. Measures of heterogeneity, including Cochran's Q-statistic and I^2 index tests were computed. Two-sided p value of $\leq .05$ was considered significant. Effect size estimates were presented using the calculated odds ratios and corresponding 95% confidence intervals (CI). Sensitivity analysis was also performed with sequential exclusion of individual

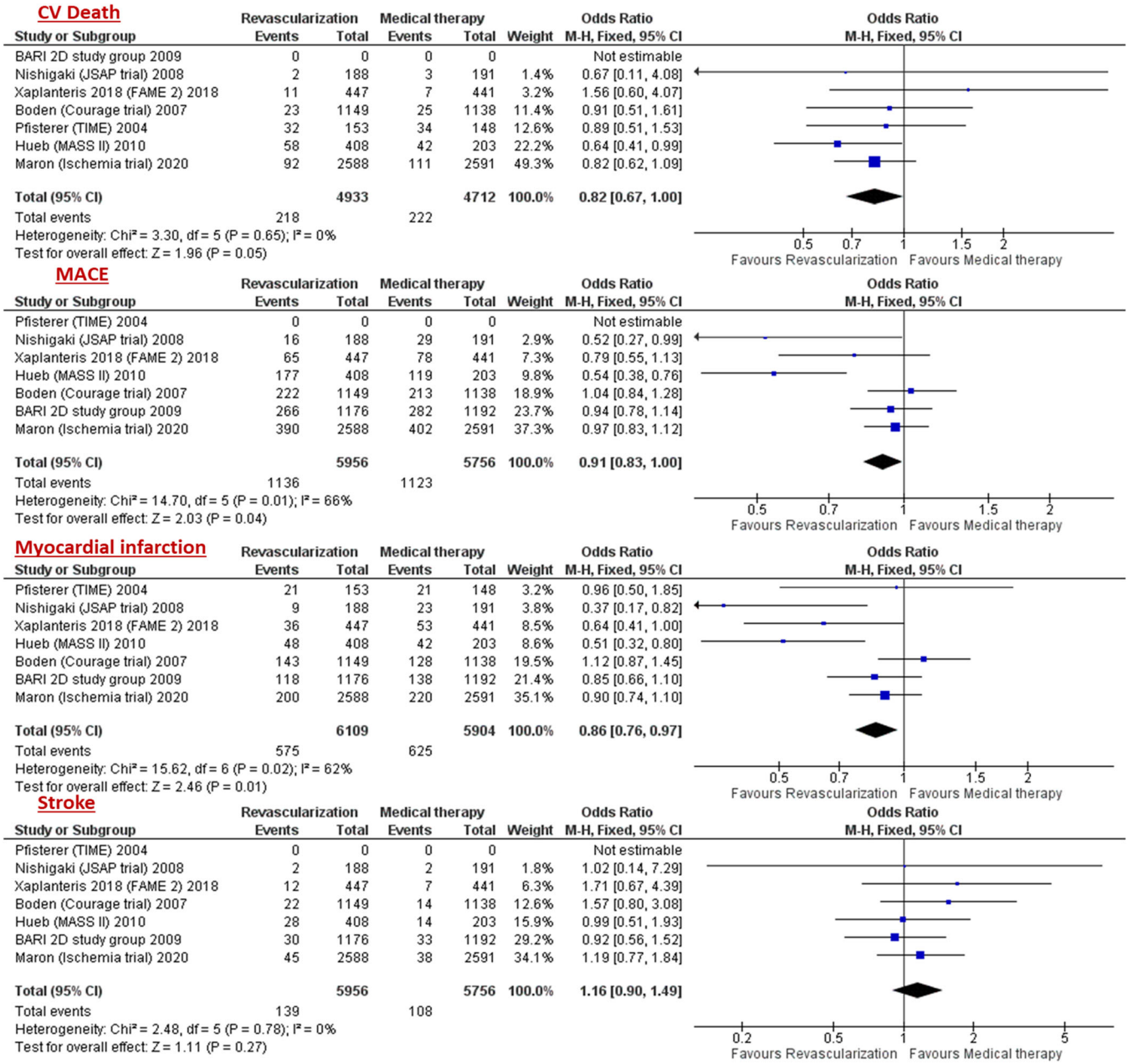

FIGURE 3 Forest plots of pooled odds ratio (OR) comparing revascularization versus medical therapy for secondary outcomes of cardiovascular death (CV death), MACE, myocardial infarction (MI), and stroke. The rectangle represents the point estimate (horizontal line indicates the 95% CI), with its size being proportional to the weight of the study in the meta-analysis. The diamond represents the pooled estimate (with its size representing the 95% CI)

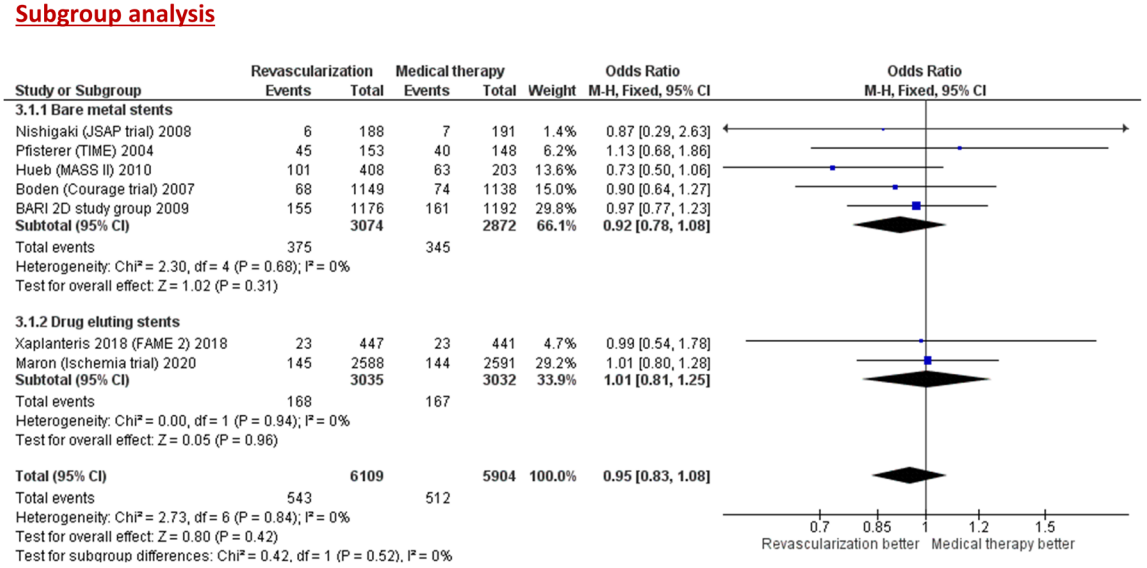

FIGURE 4 Forest plot of pooled odds ratio (OR) of subgroup analysis comparing revascularization versus medical therapy for primary outcome of all-cause mortality when stratified based on type of stents (bare metal vs. drug eluting stents). The rectangle represents the point estimate (horizontal line indicates the 95% CI), with its size being proportional to the weight of the study in the meta-analysis. The diamond represents the pooled estimate (with its size representing the 95% CI)

studies. We assessed the risk of bias for each study using criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions[17] and Forest plot was used for publication bias. All data was transferred into a Review Manager 5 file and statistical analysis was performed using Review Manager (RevMan), Version 5.3, Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014.

3 | RESULTS

Our literature search yielded seven RCTs. We analyzed a total of 12 013 patients (6109 in revascularization arm and 5904 in conservative medical therapy arm). The mean age was 65 years in both arms. The longest follow up available was 10 years. The baseline characteristics of the included patients in each trial are given in Table 1. Outcomes of interest from included trials are given in (Table S1).

3.1 | Primary pooled analysis

The results of this analysis show no statistically significant difference in primary outcome of all-cause mortality between revascularization and conservative therapy (odds ratio [OR] = 0.95; 95% CI (confidence interval), 0.83–1.08; p = .84) (Figure 2). There were statistically significant lower rates of MACE (death, MI, or stroke) (OR = 0.91; 95% CI, 0.83–1.00; p < .04), cardiovascular death (OR = 0.82; 95% CI, 0.67–1.00; p = .05) and MI (OR = 0.86, 95% CI, 0.76–0.97; p < .01) in the revascularization arm when compared to conservative arm. There was no statistically significant difference in stroke (OR = 1.16, 0.90–1.49; p = .27) between the two arms. (Figure 3).

3.2 | Subgroup analysis

Subgroup analyses (Figure 4) showed no significant difference in all-cause mortality when the included trials were stratified based on use of bare metal stents (OR = 0.92; 95% CI, 0.78–1.08; p = .31) or drug eluting stents (OR = 1.01; 95% CI, 0.81–1.25; p = .52).

4 | DISCUSSION

This meta-analysis of over 12 000 patients shows no difference in primary outcome of all-cause mortality between revascularization with medical therapy and conservative therapy for patients with symptomatic but stable CAD. However, secondary outcomes analyses showed that revascularization is associated with reduced incidence of MACE (death, MI, or stroke) which is driven by a nearly 14% reduction in MI and cardiovascular death when compared to conservative therapy alone.

Current ACC/AHA/AATS/PCNA/SCAI/STS guidelines on stable CAD support coronary revascularization if the patients continue to have ischemic symptoms on optimal medical therapy or in whom revascularization may alter prognosis, such as in patients with reduced EF, where revascularization has a mortality benefit over conservative therapy.[18] Therefore, current guidelines established PCI or CABG as more of a second line therapy in patients with stable CAD.[19,20] Although CABG and PCI are acceptable means of coronary revascularization, the trials included in our meta-analysis have PCI as the predominant means of revascularization, except for BARI-2D,[21] MASS-II[8] and ISCHEMIA[10] trial where a significant proportion (32%, 33%, and 26%, respectively) of patients underwent CABG.

Heart disease has remained the leading cause of death in the United States for more than four decades. However, there has been a

significant decline in mortality over the years. Aggressive risk factor modification for primary and secondary prevention in CAD has contributed to this remarkable decline in mortality. Previous to the year 2000, trials addressing treatment of stable CAD predominantly used plain old balloon angioplasty (POBA) as the interventional treatment strategy. The outcomes of patients undergoing POBA are marred by the significant rates of restenosis in up to 30%–50% of patients.[22,23] With the advent of bare metal stents, there was reduced incidence of rate of angiographic restenosis and repeat revascularization when compared to angioplasty alone,[24,25] although there was no difference in mortality or MI. Drug eluting stents, which were introduced for commercial use in April 2003, have had significant impact on reducing the rates of restenosis and repeat revascularization when compared to bare metal stents.[26,27] Additionally, intracardiac imaging by utilizing intravascular ultrasound (IVUS) or optical coherence tomography (OCT) in guiding PCI has consistently shown to reduce MACE (cardiac death, target lesion–related MI or ischemia-driven revascularization).[28] This benefit was due to a reduction in target lesion revascularization with the use of IVUS, which was sustained to 5 years of follow-up. Similar results were shown in a meta-analysis of 31 studies with 17 882 patients where the use of intravascular imaging techniques for PCI guidance reduces the risk of cardiovascular death and adverse events.[29]

Although the field of coronary interventions has come a long way in PCI techniques and equipment, multiple prior meta-analyses have either shown limited[30-34] or no difference in outcomes between PCI and conservative therapy.[35,36] There have been several postulations as to why that is. Despite the improvement in procedural, operator techniques and promising research in stent technology, patients with stable coronary disease have not shown a decrease in death or MI with revascularization. Exclusion of patients with high-risk anatomical features and enrollment of patients with milder levels of ischemia could have resulted in disproportionate number of patients with low ischemic burden to be enrolled, biasing the results to the null.

The International Study of Comparative Health Effectiveness with Medical and Invasive Approaches (ISCHEMIA)[10] was specifically designed to overcome the aforementioned limitations of prior data and to determine the effect of revascularization added to medical therapy in patients with stable coronary disease and moderate or severe ischemia. ISCHEMIA trial, failed to show any difference in mortality in either invasive or conservative arm. However, inclusion of patients with less severe CAD than initially proposed remains a major limitation of this trial. One of the major findings in ISCHEMIA was lower incidence of spontaneous MIs on long term follow up in the invasive strategy arm. Cumulatively, however, the increased peri-procedural MIs in the invasive group negated the effect of late onset MI's and there was no significant difference between both arms at 3 years.

Our analysis updates the current available literature and includes the 5 years follow-up data from the FAME 2[9] and ISCHEMIA[10] trial which compromise more than half of the patients included in the analysis. The emphasis in the analysis was on the longest follow up data available for each trial and the inclusion of trials which are predominantly reflective of contemporary medical practices in both the medical and the invasive arms. A similar meta-analysis has been published previously by Bangalore et al.[37] This meta-analysis included 14 randomized clinical trials with 14 877 patients and had a weighted mean follow up of 4.5 years. They reported no difference in mortality between medical therapy or revascularization. Revascularization was associated with a reduced nonprocedural MI, but also with increased procedural MI. A significant reduction in unstable angina and increase in freedom from angina was also observed with revascularization. Our meta-analysis differs from the analysis by Bangalore et al predominantly on the basis of inclusion criteria of trials. Older trials such as ACME I,[38] ACME II,[39] RITA-2,[40] and MASS I[41] did not have aggressive use of statins for lipid lowering and balloon angioplasty was the predominant means of intervention. We chose to exclude these trials as neither the medical therapy nor the interventions represented current standard of care.

The finding of no survival benefit between the two groups has been consistent among all of the included trials and prior analyses. One of the major findings in our analysis was higher incidence of MI in patients treated with conservative therapy alone. Those results are predominantly driven by ISCHEMIA[10] and MASS II[8] data. Our findings also differ from the only recent meta-analysis that has included the results of the ISCHEMIA trial[36] which showed no difference in MI rates between either arms in patients with stable CAD. This difference could be related to the fact that the above-mentioned meta-analysis included older studies where the use of balloon angioplasty was the predominant practice in the invasive strategy. Our choice to include primary definition of MI's in the ISCHEMIA trial could have also contributed to this difference.

Coronary artery disease should be considered under the category of chronic coronary syndrome to reflect this multi-faceted disease process that requires interventions on multiple frontiers for a desired response. Atherosclerotic plaque deposition begins in early years of childhood and adolescence as fatty streaks,[24,42] and takes decades before obstructive lesions impede coronary flow and lead to symptoms. Aggressive medical therapy including high intensity statins has shown favorable results in plaque stabilization and possibly even plaque regression.[43] This in conjunction with moderate to high intensity exercise training can increase collateral flow index[44] and help with symptom control. The role of revascularization with PCI or CABG where feasible largely applies to patients with persistent symptoms despite maximal medical therapy.

Our analysis, in alignment with prior individual trials and analyses, failed to show any survival advantage of an initial invasive strategy over conservative medical therapy in patients with stable CAD. The reduced incidence of spontaneous MIs in the revascularization arm is promising. Although numerically, the decrease in spontaneous MI are offset by an increase in peri-procedural MI, periprocedural MI and spontaneous MI do not carry the same weight in prognostic significance[45] and should not be considered equivalent as clinical event end points. Large peri-procedural MI have been shown to be independently associated with increased mortality, however the clinical significance of smaller biomarkers elevations is unclear.[45,46] Periprocedural MI appears to be more of a marker of baseline patient risk, atherosclerosis burden, and procedural complexity (calcifications, tortuosity).[47]The differences in the definitions and our inability to separate the procedural and spontaneous MIs in many of the analyzed trials can contribute to a decreased apparent clinical benefit of revascularization.

5 | CONCLUSION

The current meta-analysis of seven contemporary RCTs did not show any survival advantage of an initial invasive strategy over conservative medical therapy in patients with stable CAD. There was a significantly lower risk of MACE in the revascularization group, predominantly driven by reduced spontaneous M. Shared clinical decision making based on patient's symptoms should be pursued to determine further management options.

6 | LIMITATIONS

The results of our meta-analysis need to be interpreted with some inherent limitations. We did not have access to patient level data. Patients with stable ischemic heart disease and low left ventricular ejection fraction or left main disease were excluded from all trials and hence the results should not be applied in those disease states. Although, the aim of our meta-analysis was to assess the benefit of revascularization for stable CAD, the results predominantly reflect use of PCI, given small number of patients who underwent CABG. We were unable to stratify the results of revascularization based on CABG versus PCI. Choice of CABG over PCI may reflect higher burden of disease and ischemia and expectedly outcomes like stroke and periprocedural MI could be different. Additionally, the type of troponin assay used and definitions of periprocedural MI have been varied in different trials and has been mostly linked to biomarker elevation in the absence of addressable symptoms.

DATA AVAILABILITY STATEMENT

The authors declare that all data supporting the findings of this study are available within the article (and its supplementary information files).

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REFERENCES

1. Keeley EC, Boura JA, Grines CL. Primary angioplasty versus intravenous thrombolytic therapy for acute myocardial infarction: a quantitative review of 23 randomised trials. *Lancet*. 2003;361(9351):13-20.
2. Fox KA, Clayton TC, Damman P, et al. Long-term outcome of a routine versus selective invasive strategy in patients with non-ST-segment elevation acute coronary syndrome a meta-analysis of individual patient data. *J Am Coll Cardiol*. 2010;55(22):2435-2445.
3. Levine GN, Bates ER, Blankenship JC, et al. 2011 ACCF/AHA/SCAI guideline for percutaneous coronary intervention: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Society for Cardiovascular Angiography and Interventions. *Cath Cardiovas Inter*. 2013;82(4):266-355.
4. Neumann F-J, Sousa-Uva M, Ahlsson A, et al. 2018 ESC/EACTS guidelines on myocardial revascularization. *Eur Heart J*. 2018;40(2):87-165. https://doi.org/10.1093/eurheartj/ehy394.
5. Pfisterer M, Buser P, Osswald S, et al. Outcome of elderly patients with chronic symptomatic coronary artery disease with an invasive vs optimized medical treatment strategy one-year results of the randomized TIME trial. *JAMA*. 2003;289(9):1117-1123. https://doi.org/10.1001/jama.289.9.1117.
6. Pfisterer M. Long-term outcome in elderly patients with chronic angina managed invasively versus by optimized medical therapy: four-year follow-up of the randomized trial of invasive versus medical therapy in elderly patients (TIME). *Circulation*. 2004;110(10):1213-1218.
7. 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;356(15):1503-1516.
8. Hueb W, Lopes N, Gersh BJ, et al. Ten-year follow-up survival of the medicine, angioplasty, or surgery study (MASS II). *Circulation*. 2010;122(10):949-957.
9. Xaplanteris P, Fournier S, Pijls NHJ, et al. Five-year outcomes with PCI guided by fractional flow reserve. *N Engl J Med*. 2018;379(3):250-259.
10. Maron DJ, Hochman JS, Reynolds HR, et al. Initial invasive or conservative strategy for stable coronary disease. *N Engl J Med*. 2020;382(15):1395-1407.
11. Al-Lamee R, Thompson D, Dehbi H-M, et al. Percutaneous coronary intervention in stable angina (ORBITA): a double-blind, randomised controlled trial. *Lancet*. 2018;391(10115):31-40. https://doi.org/10.1016/S0140-6736(17)32714-9.
12. Bech GJW, Bruyne BD, Pijls NHJ, et al. Fractional flow reserve to determine the appropriateness of angioplasty in moderate coronary stenosis. *Circulation*. 2001;103(24):2928-2934. https://doi.org/10.1161/01.CIR.103.24.2928.
13. Hambrecht R, Walther C, Möbius-Winkler S, et al. Percutaneous coronary angioplasty compared with exercise training in patients with stable coronary artery disease: a randomized trial. *Circulation*. 2004;109(11):1371-1378.
14. Scandinavian Simvastatin Survival Study G. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian simvastatin survival study (4S). *Lancet*. 1994;344(8934):1383-1389.
15. Sacks FM, Pfeffer MA, Moye LA, et al. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. *N Engl J Med*. 1996;335(14):1001-1009. https://doi.org/10.1056/NEJM199610033351401.
16. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. *BMJ*. 2009;339:2700.
17. Cochrane Handbook for Systematic Reviews of Interventions | Cochrane Training.
18. Wolff G, Dimitroulis D, Andreotti F, et al. Survival benefits of invasive versus conservative strategies in heart failure in patients with reduced ejection fraction and coronary artery disease: a meta-analysis. *Circ Heart Fail*. 2017;10(1). https://doi.org/10.1161/circheartfailure.116.003255.
19. Fihn SD, Blankenship JC, Alexander KP, et al. 2014 ACC/AHA/AATS/PCNA/SCAI/STS focused update of the guideline for the diagnosis and management of patients with stable ischemic heart disease. A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines, and the American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. *J Am Coll Cardiol*. 2014;64(18):1929-1949.
20. Knuuti J, Wijns W, Saraste A, et al. 2019 ESC guidelines for the diagnosis and management of chronic coronary syndromes. *Eur Heart J*. 2020;41(3):407-477.
21. BARI 2D Study Group, Frye RL, August P, Brooks MM, et al. A randomized trial of therapies for type 2 diabetes and coronary artery disease. *N Engl J Med*. 2009;360(24):2503-2515.

22. Hirshfeld JW, Schwartz JS, Jugo R, et al. Restenosis after coronary angioplasty: a multilvariate statistical model to relate lesion and procedure variables to restenosis. *J Am Coll Cardiol*. 1991;18(3):647. https://doi.org/10.1016/0735-1097(91)90783-6.
23. Gruentzig AR, King SB, Schlumpf M, Siegenthaler W. Long-term follow-up after percutaneous transluminal coronary angioplasty. *N Engl J Med*. 1987;316(18):1127-1132. https://doi.org/10.1056/NEJM198704303161805.
24. Agostoni P, Biondi-Zoccai GGL, Gasparini GL, et al. Is bare-metal stenting superior to balloon angioplasty for small vessel coronary artery disease? Evidence from a meta-analysis of randomized trials. *Eur Heart J*. 2005;26(9):881-889. https://doi.org/10.1093/eurheartj/ehi116.
25. Fischman DL, Leon MB, Baim DS, et al. A randomized comparison of coronary-stent placement and balloon angioplasty in the treatment of coronary artery disease. *N Engl J Med*. 1994;331(8):496-501. https://doi.org/10.1056/NEJM199408253310802.
26. Bønaa KH, Mannsverk J, Wiseth R, et al. Drug-eluting or bare-metal stents for coronary artery disease. *N Engl J Med*. 2016;375(13):1242-1252.
27. Sabaté M, Brugaletta S, Cequier A, et al. Clinical outcomes in patients with ST-segment elevation myocardial infarction treated with everolimus-eluting stents versus bare-metal stents (EXAMINATION): 5-year results of a randomised trial. *Lancet*. 2016;387(10016):357-366.
28. Hong S-J, Mintz GS, Ahn C-M, et al. Effect of intravascular ultrasound–guided drug-eluting stent implantation. 5-year follow-up of the IVUS-XPL randomized. *Trial*. 2020;13(1):62-71. https://doi.org/10.1016/j.jcin.2019.09.033.
29. Buccheri S, Franchina G, Romano S, et al. Clinical outcomes following intravascular imaging-guided versus coronary angiography–guided percutaneous coronary intervention with stent implantation. A systematic review and Bayesian network meta-analysis of 31 studies and 17,882 patients. *JACC Cardiovasc Interv*. 2017;10(24):2488-2498. https://doi.org/10.1016/j.jcin.2017.08.051.
30. Schomig A, Mehilli J, Waha A, Seyfarth M, Pache J, Kastrati A. A meta-analysis of 17 randomized trials of a percutaneous coronary intervention-based strategy in patients with stable coronary artery disease. *J Am Coll Cardiol*. 2008;52(11):894-904.
31. Jeremias A, Kaul S, Rosengart TK, Gruberg L, Brown DL. The impact of revascularization on mortality in patients with nonacute coronary artery disease. *Am J Med*. 2009;122(2):152-161.
32. Bangalore S, Pursnani S, Kumar S, Bagos PG. Percutaneous coronary intervention versus optimal medical therapy for prevention of spontaneous myocardial infarction in subjects with stable ischemic heart disease. *Circulation*. 2013;127(7):769-781. https://doi.org/10.1161/CIRCULATIONAHA.112.131961.
33. Windecker S, Stortecky S, Stefanini GG, et al. Revascularisation versus medical treatment in patients with stable coronary artery disease: network meta-analysis. *BMJ*. 2014;348:3859. https://doi.org/10.1136/bmj.g3859.
34. Nishigaki K, Yamazaki T, Kitabatake A, et al. Percutaneous coronary intervention plus medical therapy reduces the incidence of acute coronary syndrome more effectively than initial medical therapy only among patients with low-risk coronary artery disease a randomized, comparative, multicenter study. *JACC Cardiovasc Interv*. 2008;1(5):469-479.
35. Khan SU, Singh M, Lone AN, et al. Meta-analysis of long-term outcomes of percutaneous coronary intervention versus medical therapy in stable coronary artery disease. *Eur J Prev Cardiol*. 2019;26(4):433-436.
36. Chacko L, J PH, Rajkumar C, et al. Effects of percutaneous coronary intervention on death and myocardial infarction stratified by stable and unstable coronary artery disease: a meta-analysis of randomized controlled trials. *Circ Cardiovasc Qual Outcomes*. 2020;13(2):e006363.
37. Bangalore S, Maron DJ, Stone GW, Hochman JS. Routine revascularization versus initial medical therapy for stable ischemic heart disease. *Circulation*. 2020;142(9):841-857. https://doi.org/10.1161/CIRCULATIONAHA.120.048194.
38. Parisi AF, Folland ED, Hartigan P. A comparison of angioplasty with medical therapy in the treatment of single-vessel coronary artery disease. Veterans affairs ACME investigators. *N Engl J Med*. 1992;326(1):10-16.
39. Folland ED, Hartigan PM, Parisi AF. Percutaneous transluminal coronary angioplasty versus medical therapy for stable angina pectoris: outcomes for patients with double-vessel versus single-vessel coronary artery disease in a veterans affairs cooperative randomized trial. Veterans affairs ACME Investigators. *J Am Coll Cardiol*. 1997;29(7):1505-1511.
40. Coronary angioplasty versus medical therapy for angina: the second Randomised Intervention Treatment of Angina (RITA-2) trial. RITA-2 trial participants. *Lancet*. 1997;350(9076):461-468.
41. Hueb WA, Bellotti G, de Oliveira SA, et al. The medicine, angioplasty or surgery study (MASS): a prospective, randomized trial of medical therapy, balloon angioplasty or bypass surgery for single proximal left anterior descending artery stenoses. *J Am Coll Cardiol*. 1995;26(7):1600-1605.
42. Insull W. The pathology of atherosclerosis: plaque development and plaque responses to medical treatment. *Am J Med*. 2009;122(1):3-14. https://doi.org/10.1016/j.amjmed.2008.10.013.
43. Nissen SE, Nicholls SJ, Sipahi I, et al. Effect of very high-intensity statin therapy on regression of coronary atherosclerosis: the ASTEROID trial. *JAMA*. 2006;295(13):1556-1565.
44. Möbius-Winkler S, Uhlemann M, Adams V, et al. Coronary collateral growth induced by physical exercise. *Circulation*. 2016;133(15):1438-1448. https://doi.org/10.1161/CIRCULATIONAHA.115.016442.
45. Lansky AJ, Stone GW. Periprocedural myocardial infarction. *Circ Cardiovasc Interv*. 2010;3(6):602-610. https://doi.org/10.1161/CIRCINTERVENTIONS.110.959080.
46. Ben-Yehuda O, Chen S, Redfors B, et al. Impact of large periprocedural myocardial infarction on mortality after percutaneous coronary intervention and coronary artery bypass grafting for left main disease: an analysis from the EXCEL trial. *Eur Heart J*. 2019;40(24):1930-1941. https://doi.org/10.1093/eurheartj/ehz113.
47. Prasad A, Gersh BJ, Bertrand ME, et al. Prognostic significance of periprocedural versus spontaneously occurring myocardial infarction after percutaneous coronary intervention in patients with acute coronary syndromes: an analysis from the ACUITY (acute catheterization and urgent intervention triage strategy) trial. *J Am Coll Cardiol*. 2009;54(5):477-486.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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