class II B, level B evidence for the treatment of femoropopliteal ISR with DCB, while the 2016 American College of Cardiology/American Heart Association guidelines for the management of lower extremity peripheral artery disease issues no recommendations. Contrary to our results, a previous meta-analysis of 3 studies concluded DCB provides better clinical performances as compared to standard balloon angioplasty at 1-year follow-up. However, the study had limitations, as it included studies with follow up between 6 and 12 months, and lacked long-term follow-up. The present meta-analysis included studies with a 3-year follow-up. Additional the previous analysis reported no benefit in Rutherford classification or ankle-brachial index at 1-year follow-up. The present meta-analysis also has a few limitations. First, it is a study-level meta-analysis. Second, both RCTs and observational studies were included in the present meta-analysis, though the majority was constituted by RCTs. In conclusion, the present meta-analysis found no difference in the risk of all-cause mortality or target vessel revascularization between DCB compared with standard balloon angioplasty in femoropopliteal ISR patients.

## Disclosures

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Rajkumar Doshi, MD MPH[a,*]
Ashish Kumar, MBBS[b]
Devina Adalja, MBBS[c]
Igor Vaz, MD[d]
Mariam Shariff, MBBS[b]

[a] Department of Internal Medicine, University of Nevada Reno School of Medicine, Reno, Nevada
[b] Department of Critical Care, St John's Medical college hospital, Bengaluru, Karnataka, India
[c] Department of Medicine, GMERS Gotri Medical College and Hospital, Vadodara, Gujarat, India
[d] Department of Internal Medicine, Jackson Memorial Hospital/University of Miami, Florida

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14 July 2020

1. Liao C Jun, Song S Han, Tan LI, Zhang Y, Zhang W de. Randomized controlled trial of orchid drug-coated balloon versus standard percutaneous transluminal angioplasty for treatment of femoropopliteal artery in-stent restenosis. *Int Angiol* 2019;38:365–371.
2. Kinstner CM, Lammer J, Willfort-Ehringer A, Matzek W, Gschwandtner M, Javor D, Funovics M, Schoder M, Koppensteiner R, Loewe C, Ristl R, Wolf F. Paclitaxel-Eluting balloon versus standard balloon angioplasty in in-stent restenosis of the superficial femoral and proximal popliteal artery: 1-year results of the PACUBA trial. *JACC Cardiovasc Interv* 2016;9:1386–1392. [Internet] Available from: http://www.sciencedirect.com/science/article/pii/S1936879816304253.
3. Ott I, Cassese S, Groha P, Steppich B, Voll F, Hadamitzky M, Ibrahim T, Kufner S, Dewitz K, Wittmann T, Kasel AM, Laugwitz K-L, Schunkert H, Kastrati A, Fusaro M. ISAR-PEBIS (Paclitaxel-Eluting Balloon Versus Conventional Balloon Angioplasty for In-Stent Restenosis of Superficial Femoral Artery): a randomized trial. *J Am Heart Assoc* 2017;6:e006321. [Internet] Available from: https://pubmed.ncbi.nlm.nih.gov/28743787.
4. Grotti S, Liistro F, Angioli P, Ducci K, Falsini G, Porto I, Ricci L, Ventoruzzo G, Turini F, Bellandi G, Bolognese L. Paclitaxel-Eluting balloon vs standard angioplasty to reduce restenosis in diabetic patients with in-stent restenosis of the superficial femoral and proximal popliteal arteries: three-year results of the DEBATE-ISR study. *J Endovasc Ther* 2015;23:52–57. [Internet] Available from: https://doi.org/10.1177/1526602815614555.
5. Hans K, Thilo T, Maja I, Michael S, Dierk S, Erwin B, Sebastian S, Arne K, Ulrich B, Thomas Z. Drug-Coated balloon versus standard balloon for superficial femoral artery in-stent restenosis. *Circulation* 2015;132:2230–2236. [Internet] Available from: https://doi.org/10.1161/CIRCULATIONAHA.115.017364.

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## Meta-Analysis of the Effect of Percutaneous Coronary Intervention on Death and Myocardial Infarction in Patients With Stable Coronary Artery Disease and Inducible Myocardial Ischemia


**Background. There has been a continuous debate about the survival benefit of percutaneous coronary intervention (PCI) for the management of patients with stable ischemic heart disease (SIHD) and moderate to severe ischemia. In this study we aimed to summarize the currently available evidence from randomized controlled trials (RCTs) on PCI versus medical therapy (MT) for patients with SIHD.**

**Methods. An electronic database search was conducted for RCTs that compared PCI on top of MT versus MT alone. A random effects model was used to calculate relative risk (RR) and 95% confidence intervals (CIs).**

**Results. A total of 7 RCTs with 10,043 patients with a mean age of 62.54 ± 1.56 years and a median follow up of 3.9 years were identified. Among patients with SIHD and moderate to severe ischemia by stress testing, PCI didn't show any benefit for the primary outcome of all-cause mortality compared to MT(RR = 0.85; 95% CI 0.646−1.12; p = 0.639). There was also no benefit in cardiovascular (CV) death (RR = 0.88 ; 95% CI 0.71−1.09; p = 0.18) or myocardial infarction (MI) (RR = 0.271; 95% CI 0.782−1.087; P = 0.327) in the PCI group as compared to MT.**

**Conclusion. Among patients with SIHD and evidence of moderate to severe ischemia by stress testing, PCI on top of MT appears to add no mortality benefit as compared to with MT alone.** **© 2020 Elsevier Inc. All rights reserved.** **(Am J Cardiol 2020;133:168−185)**

Whether percutaneous coronary intervention (PCI) reduces death or myocardial infarction in patients with stable coronary artery disease remains controversial. Although data from large observational studies have shown that the presence of moderate or severe myocardial ischemia[1] increases the risk of death and myocardial infarction and that PCI reduces this risk in patients with stable coronary artery disease as compared with medical therapy (MT) alone, randomized controlled trials, including the Clinical Outcomes Utilizing Revascularization and Aggressive

DruG Evaluation trial[2] and the recently published International Study of Comparative Health Effectiveness with Medical and Invasive Approaches (ISCHEMIA) trial[3] showed no mortality benefit with an invasive approach compared to MT alone among those with moderate to severe ischemia at baseline. ISCHEMIA, however, was not powered for mortality as it was a secondary outcome. To address this, we performed a meta-analysis of randomized controlled trials comparing PCI plus MT versus MT alone in stable coronary artery disease patients to evaluate end points of all-cause mortality, cardiovascular mortality, and myocardial infarction in a larger cohort of patients with objective evidence of myocardial ischemia.

We searched electronic databases including PubMed, EMBASE, Cochrane library for randomized controlled trials comparing PCI + MT to MT alone. We included only randomized controlled trials utilizing contemporary guideline-directed MT and documented objective evidence of ischemia by either treadmill exercise, myocardial imaging (stress perfusion scintigraphy), or by fractional flow reserve.[2–8] The primary end point for our meta-analysis was all-cause mortality reported at maximum follow-up. Secondary outcomes included cardiovascular mortality and myocardial infarction. All outcomes are reported as relative risks. Analyses were performed using the random-effects model, heterogeneity was assessed using the $I^2$ statistic test, and all statistical analyses were performed using the R studio software.

A total of 10,043 patients with median follow-up of 3.9 years (range: 3.25 to 5) from 7 randomized controlled trials (Table 1) were included in the current analysis.[2–8] Mean age was 62.5 ± 1.6 years and 80% were men. Compared with MT alone, PCI plus MT showed no benefit for all-cause mortality (relative risk = 0.96; 95% confidence interval [CI] 0.83, 1.11; p = 0.639, $I^2$ 0%), cardiovascular death (relative risk = 0.88; 95% CI 0.71 to 1.09; p = 0.18, $I^2$ 0%) or myocardial infarction (relative risk = 0.27; 95% CI 0.78 to 1.08; p = 0.33, $I^2$ 26%; Figure 1). Sensitivity analyses showed no difference in final estimates for each outcome. Meta-regression assessing the effect of mean ejection fraction and age showed no effect on outcomes.

In this study-level meta-analysis of stable coronary artery disease patients with documented evidence of ischemia at baseline, we observed no benefit of PCI plus MT versus MT alone in reducing all-cause mortality, cardiovascular mortality, or myocardial infarction. Our results contrast with earlier meta-analyses which did not include results from ISCHEMIA and were limited to only three studies with short-term follow-up.[9]

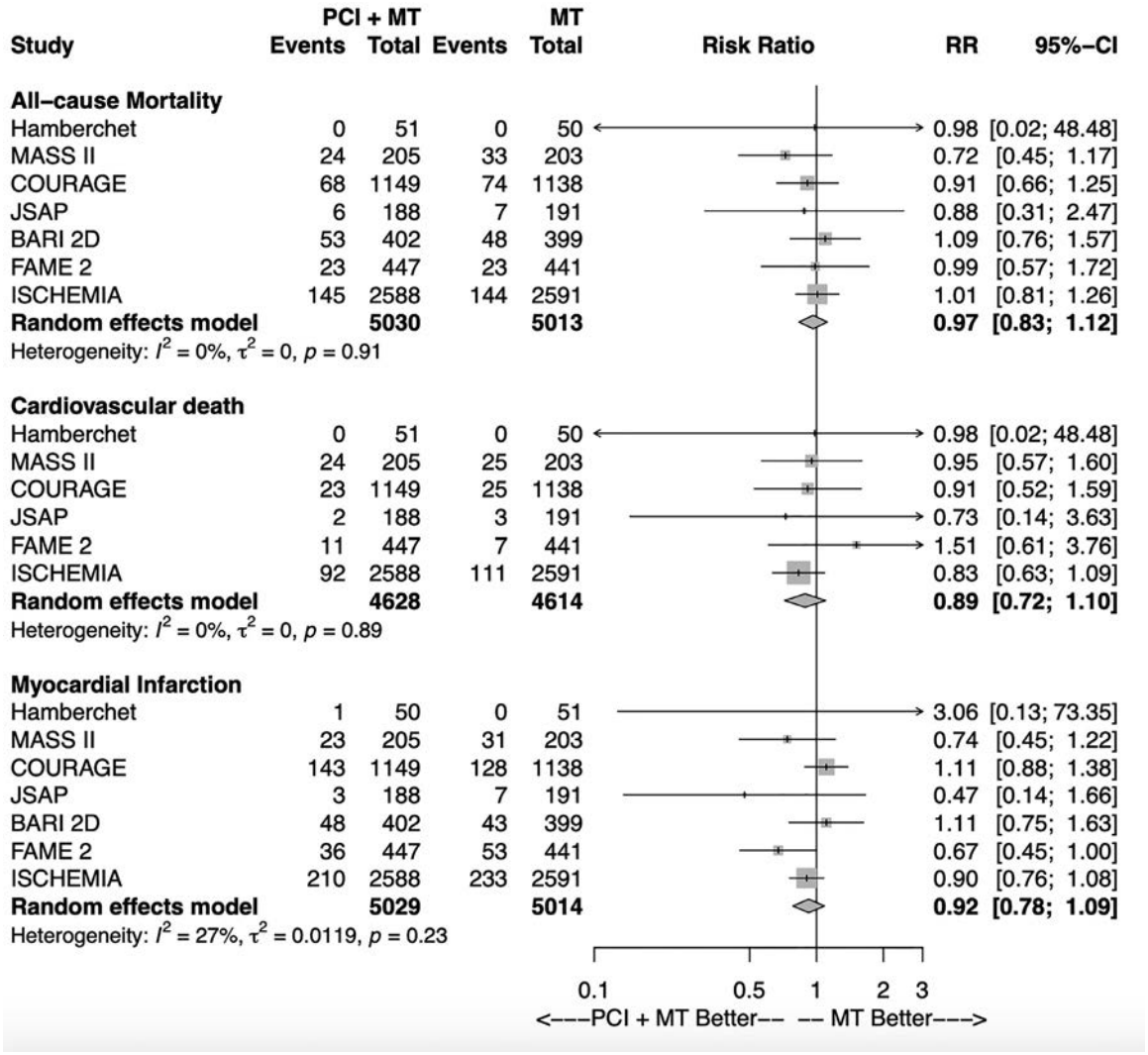
Our analysis has certain limitations. In some trials, revascularization was not coronary lesion specific, was guided by stress imaging, and was based on interventionalist discretion, which might have contributed to a lack of efficacy in PCI-treated patients. The use of fractional flow reserve, an invasive physiologic measure, was limited only to the Fractional Flow Reserve versus Angiography for Multivessel Evaluation trial[8] and a proportion of patients in ISCHEMIA. Furthermore, the number of narrowed coronary arteries and lesion severity may have differed across studies. Finally, this analysis applies only to stable coronary artery disease patients with normal ejection fraction and without left main disease.

In conclusion, in this meta-analysis of stable coronary artery disease patients with objective evidence of moderate to severe ischemia at baseline, including the recent ISCHEMIA trial, PCI when added to medical therapy did not reduce all-cause death, cardiovascular mortality, or myocardial infarction when compared with guideline-directed medical therapy alone.

Table 1
Characteristics of included trials.

| Study | Hambrecht et al[6] 2004 | | MASS II[5] 2007 | | COURAGE[2] 2007 | | JSAP[7] 2008 | | BARI 2D[4] 2009 | | FAME 2[8] 2018 | | ISCHEMIA[3] 2020 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | PCI + MT | MT | PCI + MT | MT | PCI + MT | MT | PCI + MT | MT | PCI + MT | MT | PCI + MT | MT | PCI + MT | MT |
| Number of participants | 50 | 51 | 205 | 203 | 1149 | 1138 | 192 | 192 | 402 | 399 | 447 | 441 | 2588 | 2591 |
| Age, mean (years) | 61 | 62 | 60 | 60 | 62 | 62 | 64 | 64 | 62 | 62 | 64 | 64 | 64 | 64 |
| Men | 100% | 100% | 67% | 69% | 85% | 85% | 75% | 75% | 70% | 70% | 80% | 77% | 77% | 78% |
| Diabetes Mellitus | 22% | 24% | 23% | 36% | 32% | 35% | 40% | 40% | 100% | 100% | 28% | 27% | 41% | 42% |
| Myocardial Infarction | 40% | 51% | 52% | 39% | 38% | 39% | 14% | 15% | 32% | 32% | 37% | 37% | 19% | 19% |
| Ejection Fraction | 62% | 64% | 67% | 68% | 61% | 61% | 64% | 65% | 57% | 57% | NA | NA | 60% | 60% |
| Mean number of coronary arteries narrowed >50% in diameter | 1.52 | 1.6 | 2 | 2 | 1.98 | 2.0 | 1.32 | 1.3 | 1.94 | 1.94 | 1.87 | 1.73 | 2.22 | 2.2 |
| Follow-up (years) | 1 | | 5 | | 4.6 | | 3.3 | | 5.3 | | 5 | | 3.2 | |
| PCI with Stents | 100% | NA | NA | NA | 94% | NA | 76% | NA | 91% | NA | 97% | NA | 93% | NA |
| Drug eluting stent | 0 | NA | 0 | NA | 3% | NA | 0 | 0 | 35% | NA | 95% | NA | 98% | NA |
| Medications at baseline | | | | | | | | | | | | | | |
| Aspirin | 98% | 98% | 80% | 80% | 96% | 95% | 98% | 92% | 93% | 94% | 87% | 90% | 100% | 100% |
| Beta-blocker | 86% | 88% | 61% | 68% | 85% | 89% | 44% | 52% | 83% | 87% | 76% | 78% | NA | NA |
| ACEI or ARB | 88% | 75% | 30% | 29% | 62% | 65% | 42% | 39% | 91% | 92% | 69% | 70% | 65% | 67% |
| Statin | 80% | 71% | 73% | 68% | 86% | 89% | 60% | 45% | 94% | 95% | 83% | 82% | 40% | 41% |

ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; PCI = percutaneous coronary intervention; MT = medical therapy; NA = not applicable.


Study
PCI + MT Events Total
MT Events Total
Risk Ratio
RR 95%–CI
All–cause Mortality
Hamberchet 0 51 0 50 0.98 [0.02; 48.48]
MASS II 24 205 33 203 0.72 [0.45; 1.17]
COURAGE 68 1149 74 1138 0.91 [0.66; 1.25]
JSAP 6 188 7 191 0.88 [0.31; 2.47]
BARI 2D 53 402 48 399 1.09 [0.76; 1.57]
FAME 2 23 447 23 441 0.99 [0.57; 1.72]
ISCHEMIA 145 2588 144 2591 1.01 [0.81; 1.26]
Random effects model 5030 5013 0.97 [0.83; 1.12]
Heterogeneity: $I^2$ = 0%, $\tau^2$ = 0, $p$ = 0.91
Cardiovascular death
Hamberchet 0 51 0 50 0.98 [0.02; 48.48]
MASS II 24 205 25 203 0.95 [0.57; 1.60]
COURAGE 23 1149 25 1138 0.91 [0.52; 1.59]
JSAP 2 188 3 191 0.73 [0.14; 3.63]
FAME 2 11 447 7 441 1.51 [0.61; 3.76]
ISCHEMIA 92 2588 111 2591 0.83 [0.63; 1.09]
Random effects model 4628 4614 0.89 [0.72; 1.10]
Heterogeneity: $I^2$ = 0%, $\tau^2$ = 0, $p$ = 0.89
Myocardial Infarction
Hamberchet 1 50 0 51 3.06 [0.13; 73.35]
MASS II 23 205 31 203 0.74 [0.45; 1.22]
COURAGE 143 1149 128 1138 1.11 [0.88; 1.38]
JSAP 3 188 7 191 0.47 [0.14; 1.66]
BARI 2D 48 402 43 399 1.11 [0.75; 1.63]
FAME 2 36 447 53 441 0.67 [0.45; 1.00]
ISCHEMIA 210 2588 233 2591 0.90 [0.76; 1.08]
Random effects model 5029 5014 0.92 [0.78; 1.09]
Heterogeneity: $I^2$ = 27%, $\tau^2$ = 0.0119, $p$ = 0.23
0.1
0.5
1
2
3
<---PCI + MT Better-- -- MT Better--->
Figure 1. Forest plot of included studies, for all-cause mortality cardiovascular death and myocardial infarction.
Hambrecht et al; Percutaneous Coronary Angioplasty Compared With Exercise Training in Patients With Stable Coronary Artery Disease.
BARI 2D; Bypass Angioplasty Revascularization Investigation 2 Diabetes
MASS II; Medicine Angioplasty Surgery Study.
COURAGE; Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation
JSAP; Japanese Stable Angina Pectoris.
FAME 5-year follow-up;Fractional Flow Reserve versus Angiogra-phy for Multivessel Evaluation trial.
ISCHEMIA; International Study of Comparative Health Effectiveness with Medical and Invasive Approaches.

## Disclosures

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Qais Radaideh, MD, MS[a,g,*]
Mohammed Osman, MD[b]
Babikir Kheiri, MD, MRCP, PGDip[c]
Ahmad Al-Abdouh, MD[d]
Mahmoud Barbarawi, MD[e]
Ghassan Bachuwa, MD, MS[e]
Jacqueline E. Tamis-Holland, MD[f]
Nicolas W Shammas, MD, MS[g]
William E Boden, MD[h]

[a] Division of Internal Medicine, University of Iowa Hospitals and Clinics, Iowa City, Iowa
[b] Division of Cardiology, West Virginia University School of Medicine, Morgantown, West Virginia
[c] Knight Cardiovascular Institute, Oregon Health & Science University, Portland, Oregon
[d] Department of Medicine, Saint Agnes Hospital, Baltimore, Maryland
[e] Department of Internal Medicine, Hurley Medical Center/Michigan State University, Flint, Michigan
[f] Division of Cardiology, Department of Medicine, Mount Sinai Saint Luke's Hospital, New York, New York
[g] Midwest Cardiovascular Research Foundation, Davenport, Iowa
[h] VA New England Health Care System, Boston University School of Medicine, Boston, Massachusetts

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15 July 2020

1. Hachamovitch R, Hayes SW, Friedman JD, Cohen I, Berman DS. Comparison of the short-term survival benefit associated with revascularization compared with medical therapy in patients with no prior coronary artery disease undergoing stress myocardial perfusion single photon emission computed tomography'. *Circulation* 2003;107:2900–2907.
2. Boden WE, O'Rourke RA, Teo KK, Hartigan PM, Maron DJ, Kostuk WJ, Knudtson M, Dada M, Casperson P, Harris CL, Chaitman BR, Shaw L, Gosselin G, Nawaz S, Title LM, Gau G, Blaustein AS, Booth DC, Bates ER, Spertus JA, Berman DS, Mancini GB, Weintraub WS, Courage Trial Research Group. Optimal medical therapy with or without PCI for stable coronary disease. *N Engl J Med* 2007;356:1503–1516.

3. Maron DJ, Hochman JS, Reynolds HR, Bangalore S, O'Brien SM, Boden WE, Chaitman BR, Senior R, Lopez-Sendon J, Alexander KP, Lopes RD, Shaw LJ, Berger JS, Newman JD, Sidhu MS, Goodman SG, Ruzyllo W, Gosselin G, Maggioni AP, White HD, Bhargava B, Min JK, Mancini GBJ, Berman DS, Picard MH, Kwong RY, Ali ZA, Mark DB, Spertus JA, Krishnan MN, Elghamaz A, Moorthy N, Hueb WA, Demkow M, Mavromatis K, Bockeria O, Peteiro J, Miller TD, Szwed H, Doerr R, Keltai M, Selvanayagam JB, Steg PG, Held C, Kohsaka S, Mavromichalis S, Kirby R, Jeffries NO, Harrell FE Jr., Rockhold FW, Broderick S, Ferguson TB Jr., Williams DO, Harrington RA, Stone GW, Rosenberg Y, Ischemia Research Group. Initial invasive or conservative strategy for stable coronary disease. *N Engl J Med* 2020;382:1395–1407.
4. Group, BARI 2D Study. A randomized trial of therapies for type 2 diabetes and coronary artery disease. *N Eng J Med* 2009;360:2503–2515.
5. Hueb W, Lopes NH, Gersh BJ, Soares P, Machado LA, Jatene FB, Oliveira SA, Ramires JA. Five-year follow-up of the Medicine, Angioplasty, or Surgery Study (MASS II): a randomized controlled clinical trial of 3 therapeutic strategies for multivessel coronary artery disease. *Circulation* 2007;115:1082–1089.
6. Hambrecht R, Walther C, Mobius-Winkler S, Gielen S, Linke A, Conradi K, Erbs S, Kluge R, Kendziorra K, Sabri O, Sick P, Schuler G. Percutaneous coronary angioplasty compared with exercise training in patients with stable coronary artery disease: a randomized trial. *Circulation* 2004;109:1371–1380.
7. Nishigaki K, Yamazaki T, Kitabatake A, Yamaguchi T, Kanmatsuse K, Kodama I, Takekoshi N, Tomoike H, Hori M, Matsuzaki M, Takeshita A, Shimbo T, Fujiwara H, Investigators Japanese Stable Angina Pectoris Study. 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;1:469–479.
8. Xaplanteris P, Fournier S, Pijls NHJ, Fearon WF, Barbato E, Tonino PAL, Engstrom T, Kaab S, Dambrink JH, Rioufol G, Toth GG, Piroth Z, Witt N, Frobert O, Kala P, Linke A, Jagic N, Mates M, Mavromatis K, Samady H, Irimpen A, Oldroyd K, Campo G, Rothenbuhler M, Juni P, De Bruyne B, Fame Investigators. Five-year outcomes with PCI guided by fractional flow reserve. *N Engl J Med* 2018;379:250–259.
9. Gada H, Kirtane AJ, Kereiakes DJ, Bangalore S, Moses JW, Genereux P, Mehran R, Dangas GD, Leon MB, Stone GW. Meta-analysis of trials on mortality after percutaneous coronary intervention compared with medical therapy in patients with stable coronary heart disease and objective evidence of myocardial ischemia. *Am J Cardiol* 2015;115. 1194-1190.

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## Drug-Coated Balloons Versus Drug-Eluting Stents in ST Elevation Myocardial Infarction: A Meta-analysis

The current drug-coated balloons (DCBs) are semicompliant and use an excipient to retain the drug. Upon inflation, there is rapid and homogenous delivery of the drug into the vessel wall.[1] DCBs can allow for a "leave nothing behind" strategy. Drug-eluting stents (DESs) leave behind a metallic implant and may contribute to late stent thrombosis, restenosis, and impaired vasomotor function.[2] An immediate, reliable, safe, and stable result is important in ST elevation myocardial infarction (STEMI). It needs to be determined if DCBs can provide such a result.[3] The goal of this meta-analysis is to compare the efficacy of DCBs versus the benchmark therapy of DES in STEMI.

We searched multiple databases for studies comparing the efficacy and safety of DCBs versus DES in STEMI. We used the odds ratio (OR) and corresponding 95% confidence interval (CI) for measuring outcomes.

Three studies were included (2 randomized controlled trials [RCTs], 1 post hoc analysis of an RCT).[2–4] Follow-up varied between 6 and 12 months. A total of 284 patients (138 DCB, 146 DES), with 21% women (24% DCB, 18% DES) were included. Hypertension was seen in 32% (32% DCB, 32% DES), diabetes 9% (11% DCB, 7% DES), hyperlipidemia 18% (15% DCB, 21% DES), and smoking in

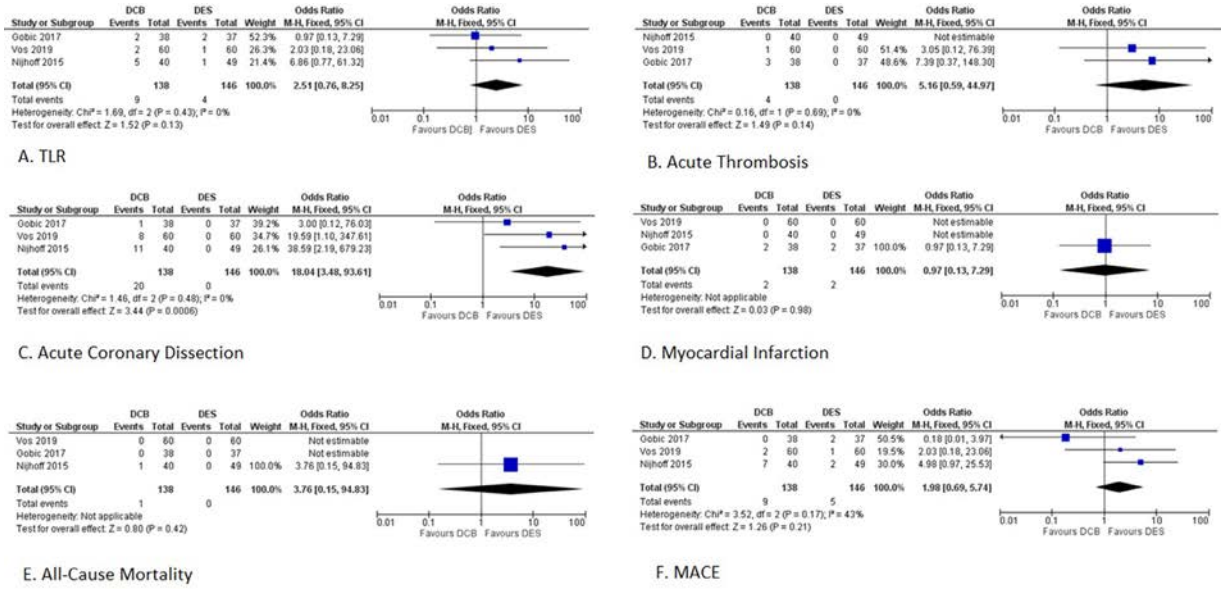


Figure 1. Forrest plots for comparison of different clinical outcomes between drug coated balloon and drug eluting stent in STEMI. Horizontal lines represent 95% confidence intervals (CI). The rectangles represent the point estimate, and the size of the rectangle is proportional to the weight given to each study in the meta-analysis. The diamond represents the summary estimate (size of the diamond = 95% CI). The vertical line represents the reference of no increased risk. Acute coronary dissection here includes type D-F only. MACE was defined as cardiac death, recurrent myocardial infarction, target lesion revascularization in Vos et al, cardiac death, recurrent MI, TLR, stent thrombosis in Gobic et al; death, MI and TLR by Nijhoff et al. MACE = major adverse cardiac events, MI-myocardial infarction; TLR = target lesion revascularization.