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ORIGINAL RESEARCH

Drug-Eluting or Bare-Metal Stents for Left Anterior Descending or Left Main Coronary Artery Revascularization

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BACKGROUND: New-generation drug-eluting stents (DES) reduce target-vessel revascularization compared with bare-metal stents (BMS), and recent data suggest that DES have the potential to decrease the risk of myocardial infarction and cardiovascular mortality. We evaluated the treatment effect of DES versus BMS according to the target artery (left anterior descending [LAD] and/or left main [LM] versus other territories [no-LAD/LM]).

METHODS AND RESULTS: The Coronary Stent Trialist (CST) Collaboration gathered individual patient data of randomized trials of DES versus BMS for the treatment of coronary artery disease. The primary outcome was the composite of cardiac death or myocardial infarction. Hazard ratios (HRs) with 95% CIs were derived from a 1-stage individual patient data meta-analysis. We included 26 024 patients across 19 trials: 13 650 (52.4%) in the LAD/LM and 12 373 (47.6%) in the no-LAD/LM group. At 6-year follow-up, there was strong evidence that the treatment effect of DES versus BMS depended on the target vessel (*P*-interaction=0.024). Compared with BMS, DES reduced the risk of cardiac death or myocardial infarction to a greater extent in the LAD/LM (HR, 0.76; 95% CI, 0.68–0.85) than in the no-LAD/LM territories (HR, 0.93; 95% CI, 0.83–1.05). This benefit was driven by a lower risk of cardiac death (HR, 0.83; 95% CI, 0.70–0.98) and myocardial infarction (HR, 0.74; 95% CI, 0.65–0.85) in patients with LAD/LM disease randomized to DES. An interaction (*P*=0.004) was also found for all-cause mortality with patients with LAD/LM disease deriving benefit from DES (HR, 0.86; 95% CI, 0.76–0.97).

CONCLUSIONS: As compared with BMS, new-generation DES were associated with sustained reduction in the composite of cardiac death or myocardial infarction if used for the treatment of LAD or left main coronary stenoses.

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Key Words: bare-metal stents ■ drug-eluting stent ■ left anterior descending artery ■ left main disease ■ percutaneous coronary intervention

Myocardial revascularization by means of percutaneous coronary intervention (PCI) has a central role in the management of patients with coronary artery disease.[1] Among patients undergoing PCI, lumen narrowing at the left anterior descending (LAD) coronary artery is reported to be as frequent as

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CLINICAL PERSPECTIVE

What Is New?

- Patients undergoing percutaneous coronary intervention in the territory of the left main or left anterior descending artery are at increased risk of cardiac death or myocardial infarction.

What Are the Clinical Implications?

- In about 26 000 patients randomized to new-generation drug-eluting stents or bare-metal stents, randomization to drug-eluting stents was associated with a stronger reduction in the risk of cardiac death or myocardial infarction when stents were implanted in the territory of the left main or left anterior descending artery compared with other territories.

Nonstandard Abbreviations and Acronyms

BMS	bare-metal stent
DES	drug-eluting stent
IPD	individual patient data
LM	left main
TVR	target-vessel revascularization

40%, rendering the LAD artery the most common target vessel requiring coronary stenting. While left main (LM) coronary stenoses were traditionally regarded as an indication for surgical revascularization, more recent studies using first- or newer-generation drug-eluting stents (DES) showed similar outcomes on hard end points compared with coronary artery bypass grafting in patients with mild to moderate complexity/extension of coronary artery disease.[2,3]

The extent of myocardium subtended to the LAD, and even more for LM systems, amounts to as much as 50% to 60% of the left ventricle and, as a result, significant LAD/LM disease is associated with impaired prognosis compared with coronary disease in other territories.[4,5] Contemporary, new-generation DES are recommended over bare-metal stents (BMS) in patients undergoing PCI for all lesions and patient subsets.[6] In an individual patient data (IDP) analysis including all available randomized trials, we found that new-generation DES reduced the risk of cardiac death or myocardial infarction (MI) compared with BMS mainly if used to treated the LAD territory.[7] In the present analysis, we leveraged the data from the Coronary Stent Trialists (CST) Collaboration to thoroughly investigate the efficacy and safety of new-generation DES in patients undergoing PCI in the LAD and/or LM artery compared with other territories.

METHODS

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Study Design and Patient Population

Methodological aspects of the present individual patient data (IPD) analysis were reported elsewhere,[7] and the study was registered online in the PROSPERO (International Prospective Register of Systematic Reviews; http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42017060520). Briefly, the CST Collaboration includes all randomized clinical trials comparing new-generation DES versus BMS in patients undergoing PCI. The search algorithm of the study is provided in Data S1. All principal investigators provided IPD using an anonymized electronic data set (Data S1). Data were checked for completeness and consistency, and were compared with the results of original publications. New-generation DES were identified as any DES subsequent to the Cypher sirolimus-eluting stent (Cordis, Miami Lakes, FL) and the Taxus paclitaxel-eluting stent (Boston Scientific, Natick, MA).

The present study was designed to evaluate the outcomes associated with DES versus BMS among patients undergoing PCI in the LAD/LM arteries compared with the target vessels. For the purpose of this analysis, we excluded patients with missing information on the intervened vessel as well as studies contributing only to 1 group (LAD/LM versus non-LAD/LM) aiming to compare the risks of events within each trial and minimize the risk of heterogeneity across studies influencing the results (ecological bias).

All trials complied with the provisions of the Declaration of Helsinki, and the ethics committees at each study center approved the study protocols. All patients provided written informed consent for participation in the individual studies.

Outcomes

The prespecified primary outcome in this analysis was the time to first occurrence of composite of cardiac death or MI. Secondary outcomes included the time to first occurrence of all-cause death, cardiac death, MI, target-vessel revascularization (TVR), and definite stent thrombosis. Outcomes were analyzed at the longest available follow-up in the primary analysis, as well as at 5- and 1-year follow-up and with a 30-day and 1-year landmark. End point definitions in each trial are reported in Data S1.

Statistical Analysis

Continuous variables were summarized by their means and SD across all included patients. Categorical variables were summarized by the corresponding counts and percentages.

The risk of adverse events among patients undergoing PCI in the LAD/LM versus no-LAD/LM was evaluated by using a multivariable Cox regression model adjusted for clinically relevant variables, including age, sex, smoking, hypertension, hyperlipidemia, diabetes, previous MI, previous PCI, previous coronary artery bypass grafting, clinical presentation, and multivessel disease. All outcomes were analyzed using time-to-event analysis and according to the intention-to-treat principle (ie, patients were analyzed according to the allocated treatment to DES or BMS). We first summarized the data using unadjusted Kaplan-Meier estimates at the longest available follow-up. We then performed a series of IPD meta-analyses. For all analyses, the pooled risk estimates were expressed as hazard ratios (HRs) with 95% CIs. We used a 1-stage fixed-effect model by using Cox regression analyses stratified by trial with robust estimator of variance.[7] Heterogeneity was calculated with the I^2 statistics from a 2-stage meta-analysis. As a guide, I^2 values <25% indicated low, 25% to 50% indicated moderate, and >50% indicated high heterogeneity. Two landmark analyses were performed: (1) an analysis with 1 landmark time point, calculating HRs between 0 and 365 days versus HRs >365 days; and (2) an analysis with 2 landmark time points, calculating HRs between 0 and 30 days versus HRs between 31 and 365 days versus HRs >365 days. As sensitivity analysis, we evaluated the treatment effect of DES versus BMS in LAD and LM groups, separately, as well as in patients receiving a new-generation DES (ie, after the exclusion of early-generation DES). Finally, we performed a 2-stage meta-analysis using the DerSimonian-Laird random-effects model.

All *P* values we calculated were based on 2-sided tests. We used Stata Statistical Software, release 14 (StataCorp LP, College Station, TX).

RESULTS

From the initial 26 616 participants, we excluded 408 patients from one trial because PCI was exclusively performed in saphenous vein grafts[8] and 185 patients across 12 trials because of missing information on the target vessel. Therefore, the final population consists of 26 023 patients enrolled across 19 trials, of whom 13 650 (52.4%) belonged to the LAD/LM group and 12 373 (47.6%) to the no-LAD/LM group.[9–27] In the LAD/LM group, 12 037 (46.3%) patients received stenting in the LAD, 1369 (5.3%) patients underwent stenting in the LM and 244 (0.9%) in both coronary territories. Data S1 describes study characteristics, patient populations, and the definitions used for outcomes (Tables S1 through S3). In the LAD/LM group, 7346 (53.8%) were randomized to DES and 6304 (46.2%) were randomized to BMS; in the no-LAD/LM group, 6521 (52.7%) were randomized to DES and 5852 (47.3%) were randomized to BMS. Baseline clinical characteristics were largely balanced between the 2 study groups (Table 1). Mean age between groups varied between 64.9 and 66.6 years. About 74% of patients were men, and about 19% had diabetes. Approximately 50% of patients had MI with or without ST-segment elevation at the time of the index PCI. Types of implanted devices are listed in Table S4. In both groups, patients randomized to BMS tended to receive stents with larger diameters and shorter lengths. The majority of patients received thin-strut stents (<100 μm); yet DES-treated patients more frequently received thick-strut stents (≥100 μm) as compared with those allocated to BMS irrespective of lesion location. Duration of dual antiplatelet therapy was longer (on average 45–55 days) in patients randomized to DES in both LAD/LM and no-LAD/LM groups. The mean (±SD) follow-up time was 3.1±1.8 years (median, 2.1; interquartile range, 1.9–4.9). Table S5 provides details on the risk of bias assessment. Overall, trials were judged at low risk of bias, although blinding of patients and performing physicians was done only in 2 trials.

Outcomes in Patients Undergoing PCI on LAD/LM Versus No-LAD/LM Artery

As depicted in Figure 1 and Figure S1, the multivariable regression model showed that patients undergoing PCI in the LAD/LM artery had a higher risk of the primary outcome of cardiac death or MI compared with those undergoing PCI in other vessels (16.11% versus 14.67%; adjusted HR, 1.18; 95% CI, 1.06–1.32; *P*=0.003). This risk increase emerged at 1 year and remained significant throughout the follow-up period. The risks of cardiac death, MI, TVR, and definite stent thrombosis were all higher in patients undergoing PCI in the LAD/LM artery. However, there was no evidence of a difference between the LAD/LM versus the no-LAD/LM group in terms of all-cause mortality.

Treatment Effect of DES Versus BMS by Target-Vessel Location

There was evidence for interaction (*P*=0.024) between randomized treatment (DES versus BMS) and the intervened artery (LAD/LM versus no-LAD/LM) with respect to the primary outcome of cardiac death or MI (Figures 2, 3 Panels A-B). At longest follow-up, DES, as compared with BMS, were associated with a greater reduction in the risk of cardiac death or MI in the LAD/LM (HR, 0.76; 95% CI, 0.68–0.85; *P*<0.001) than the

Table 1. Clinical and Procedural Characteristics Stratified by Type of Presentation and Randomization

	Patients with LAD/LM (n=13 650)		Patients without LAD/LM (n=12 373)	
	DES (n=7346)	BMS (n=6304)	DES (n=6521)	BMS (n=5852)
Age, y	n=7344, 66.1±12.5	n=6302, 66.6±12.7	n=6521, 64.9±11.9	n=5852, 65.5±12.0
Male, n (%)	n=7346, 5481 (74.6)	n=6304, 4633 (73.5)	n=6521, 4897 (75.1)	n=5852, 4317 (73.8)
Smokers, n (%)	n=7154, 1939 (27.1)	n=6098, 1703 (27.9)	n=6298, 2315 (36.8)	n=5664, 2078 (36.7)
Hypertension, n (%)	n=7326, 4331 (59.1)	n=6285, 3681 (58.6)	n=6502, 3784 (58.2)	n=5828, 3362 (57.7)
Hyperlipidemi, n (%)a	n=7198, 4029 (56.0)	n=6167, 3436 (55.7)	n=6349, 3741 (58.9)	n=5676, 3236 (57.0)
Diabetes, n (%)	n=7332, 1401 (19.1)	n=6295, 1159 (18.4)	n=6512, 1265 (19.4)	n=5844, 1055 (18.1)
Insulin-treated	n=1383, 226 (16.3)	n=1134, 191 (16.8)	n=1231, 198 (16.1)	n=1067, 151 (14.2)
Previous MI, n (%)	n=7324, 968 (13.2)	n=6289, 859 (13.7)	n=6500, 1077 (16.6)	n=5829, 954 (16.4)
Previous PCI, n (%)	n=5328, 849 (15.9)	n=4295, 738 (17.2)	n=4420, 954 (21.6)	n=3825, 867 (22.7)
Previous CABG, n (%)	n=7339, 247 (3.4)	n=6302, 221 (3.5)	n=6519, 514 (7.9)	n=5852, 446 (7.6)
Indication to PCI, n (%)				
Stable CAD	n=7257, 2165 (29.8)	n=6235, 1857 (29.8)	n=6469, 1794 (27.7)	n=5786, 1586 (27.4)
Unstable angina	n=7320, 1068 (14.6)	n=6272, 995 (15.9)	n=6491, 849 (13.1)	n=5819, 782 (13.4)
Non–ST-elevation MI	n=7277, 1858 (25.5)	n=6260, 1601 (25.6)	n=6495, 1566 (24.1)	n=5812, 1485 (25.6)
ST-elevation MI	n=7255, 1994 (27.5)	n=6235, 1620 (26.0)	n=6466, 2095 (32.4)	n=5784, 1793 (31.0)
Glycoprotein IIb/IIIa receptor inhibitors, n (%)	n=6454, 1367 (21.2)	n=5530, 1132 (20.5)	n=5705, 1392 (24.4)	n=5118, 1189 (23.2)
Multivessel disease	n=7127, 3271 (45.9)	n=6091, 2633 (43.2)	n=6190, 2398 (38.7)	n=5517, 2003 (36.3)
Number of implanted stents	n=7341, 1.7±1.1	n=6295, 1.7±1.1	n=6512, 1.5±0.9	n=5842, 1.5±0.8
Total stent length, mm	n=7310, 29.8±21.5	n=6259, 27.7±19.3	n=6468, 26.9±17.1	n=5802, 25.9±16.8
Mean stent diameter, mm	n=7311, 3.2±0.5	n=6257, 3.2±0.5	n=6467, 3.3±0.6	n=5801, 3.3±0.7
Overlapping stent	n=6982, 1284 (18.4)	n=5963, 1109 (18.6)	n=6238, 1090 (17.5)	n=5542, 1010 (18.2)
Number of stented segments, n (%)	n=7345	n=6301	n=6518	n=5850
0	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)
1	4936 (67.2)	4271 (67.8)	5211 (79.9)	4661 (79.7)
2	1684 (22.9)	1432 (22.7)	1047 (16.1)	988 (16.9)
3	537 (7.3)	433 (6.9)	208 (3.2)	165 (2.8)
4	140 (1.9)	114 (1.8)	47 (0.7)	27 (0.5)
5	37 (0.5)	44 (0.7)	3 (0.0)	8 (0.1)
6	9 (0.1)	6 (0.1)	1 (0.0)	0 (0.0)
7	2 (0.0)	1 (0.0)	1 (0.0)	0 (0.0)
Target-vessel location, n (%)				
Left main artery	n=7346, 1022 (13.9)	n=6304, 591 (9.4)	n=6521, 0 (0.0)	n=5852, 0 (0.0)
Left anterior descending artery	n=7346, 6476 (88.2)	n=6304, 5805 (92.1)	n=6521, 0 (0.0)	n=5852, 0 (0.0)
Left circumflex artery	n=7346, 1117 (15.2)	n=6304, 907 (14.4)	n=6521, 2930 (44.9)	n=5852, 2526 (43.2)
Right coronary artery	n=7346, 1127 (15.3)	n=6303, 897 (14.2)	n=6521, 4133 (63.4)	n=5852, 3777 (64.5)
Type of DES, n (%)				
Everolimus-eluting stent	n=7335, 3925 (53.5)	…	n=6508, 3536 (54.4)	…
Biolimus-eluting stent	n=7335, 1463 (20.0)	…	n=6508, 1178 (18.1)	…
Zotarolimus-eluting stent	n=7335, 1207 (16.5)	…	n=6508, 1169 (17.9)	…

(*Continued*)

Table 1. Continued

	Patients with LAD/LM (n=13 650)		Patients without LAD/LM (n=12 373)	
	DES (n=7346)	BMS (n=6304)	DES (n=6521)	BMS (n=5852)
Sirolimus-eluting stent	n=7335, 339 (4.6)	…	n=6508, 325 (5.0)	…
Other	n=7335, 394 (5.4)	…	n=6508, 305 (4.6)	…
Type of polymer, n (%)	n=7180	…	n=6375	…
Permanent-polymer DES	5188 (72.3)	…	4765 (74.7)	…
Biodegradable-polymer DES	1305 (18.2)	…	1076 (16.9)	…
Polymer-free DES	687 (9.6)	…	534 (8.4)	…
Thin-strut stent (<100 µm), n (%)	n=7335, 5772 (78.7)	n=6298, 5339 (84.8)	n=6508, 5223 (80.3)	n=5838, 4953 (84.8)
Type of $P2Y_{12}$ receptor inhibitor, n (%)	n=6719	n=5750	n=5761	n=5247
None	0 (0.0)	2 (0.0)	1 (0.0)	1 (0.0)
Clopidogrel	5475 (81.5)	5060 (88.0)	5081 (88.2)	4804 (91.6)
Ticagrelor	53 (0.8)	32 (0.6)	36 (0.6)	30 (0.6)
Prasugrel	1191 (17.7)	656 (11.4)	643 (11.2)	412 (7.9)
Duration of DAPT, d	n=6492, 290±185	n=5477, 235±181	n=5519, 292±177	n=4950, 248±173

BMS indicates bare-metal stent; CABG, coronary artery bypass grafting; CAD, coronary artery disease; DAPT, dual antiplatelet therapy; DES, drug-eluting stent; LAD, left anterior descending artery; LM, left main artery; MI, myocardial infarction; and PCI, percutaneous coronary intervention.

no-LAD/LM territory (HR, 0.93; 95% CI, 0.83–1.05; *P*=0.241). For the individual components of the primary outcome (Figures 2 and 3 Panels C-F), although interaction testing was not significant, DES were associated with a lower risk of cardiac death (HR, 0.83; 95% CI, 0.70–0.98; *P*=0.030; *P*-interaction=0.135) and MI (HR, 0.74; 95% CI, 0.65–0.85; *P*<0.001; *P*-interaction=0.077) in the LAD/LM group. Heterogeneity in the treatment effect of DES versus BMS was more evident at 1-year follow-up, resulting in a significant interaction for both cardiac death (HR, 0.72; 95% CI, 0.58–0.88 in LAD/LM versus HR, 1.09; 95% CI, 0.83–1.42 in no-LAD/LM; *P*-interaction=0.022) and MI (HR, 0.55; 95% CI, 0.46–0.66 in LAD/LM versus HR, 0.74; 95% CI, 0.60–0.91 in no-LAD/LM; *P*-interaction=0.041).

At maximum follow-up, we found also strong evidence for an interaction (*P*=0.004) with respect to all-cause mortality (Figures 2 and 4 Panels A-B), which was significantly reduced with DES among patients undergoing PCI in the LAD/LM artery (HR, 0.86; 95% CI, 0.76–0.97; *P*=0.013) but not among patients undergoing PCI in other vessels (HR, 1.12; 95% CI, 0.98–1.28; *P*=0.086). The interaction effect for all-cause mortality was stronger at 1-year follow-up (*P*-interaction=0.001) with a signal of benefit (HR, 0.77; 95% CI, 0.65–0.91) and harm (HR, 1.24; 95% CI, 1.01–1.53) with DES instead of BMS in the LAD/LM versus no-LAD/LM arteries, respectively.

As shown in Figures 2 and 4, a consistently beneficial effect of DES, as compared with BMS, with regard to target-vessel revascularization (*P*-interaction=0.329) was found in both LAD/LM (HR, 0.53; 95% CI, 0.47–0.59) and no-LAD/LM group (HR, 0.56; 95% CI, 0.49–0.64). The risk of definite stent thrombosis was also similarly reduced by DES (*P*-interaction=0.721) in the LAD/LM (HR, 0.61; 95% CI, 0.44–0.83) and no-LAD/LM artery (HR, 0.64; 95% CI, 0.44–0.93).

Landmark Analyses

In the landmark analyses (Table 2), analyzing the HRs from 0 to 365 days and from 365 days to the end of follow-up, we found that the heterogeneity by vessel location was mainly attributable to stronger effects of DES in the LAD/LM group within the first year after PCI. In a sensitivity analysis with 2 landmark points, the time window of greatest benefit from DES instead of BMS for the LAD/LM vessels was observed from 1 to 12 months after PCI (Table S6).

Sensitivity Analysis and Heterogeneity

We did not find clinically relevant heterogeneity between trials in both study groups (Table S7). When appraised separately (Figure 5), the treatment effect of DESs versus BMSs was homogenous for both LAD and LM subgroups. Results remained similar after excluding patients receiving early-generation DES (Table S8). A 2-stage meta-analysis yielded similar results to the 1-stage model (Figures S2 and S3).

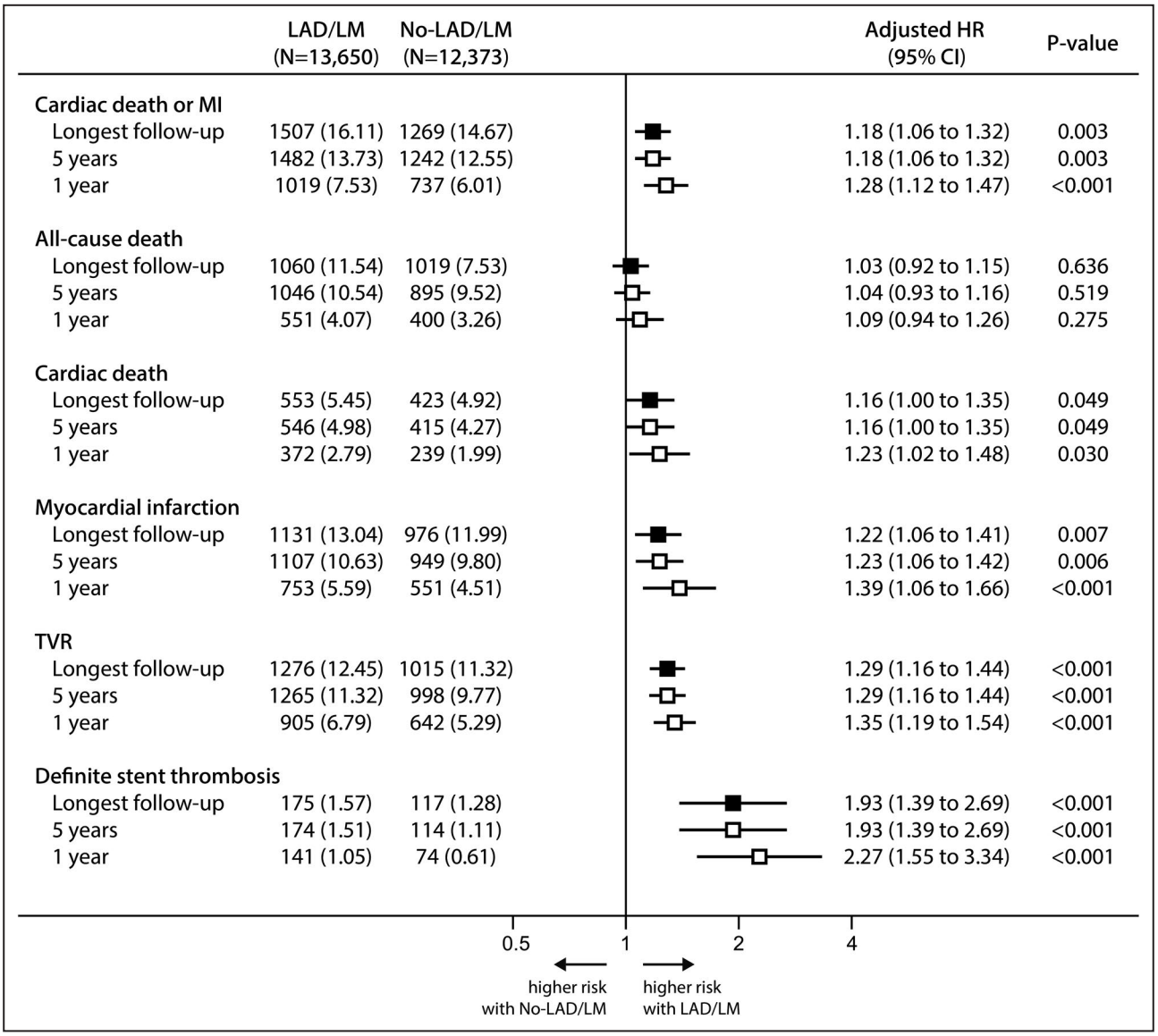

Figure 1. Clinical outcomes in patients undergoing percutaneous coronary intervention in the LAD/LM vs no-LAD/LM territory.

Squares indicate the HR (black for the longest follow-up, white for 5- and 1-year follow-up) and bars indicate 95% CI. HR indicates hazard ratio; LAD, left anterior descending artery; LM, left main artery; MI, myocardial infarction; and TVR, target-vessel revascularization.

DISCUSSION

The main findings of this IPD analysis that included the totality of randomized trials comparing new-generation DES versus BMS are that (1) DES were associated with a greater reduction in the risk of the primary outcome of cardiac death or MI as compared with BMS, when PCI was performed in the LAD or LM artery in comparison with other vessels; (2) patients receiving DES instead of BMS in the LAD/LM territory had also a lower risk of all-cause mortality; (3) irrespective of the intervened artery, DES were safer and more effective than BMS by reducing the risk of MI, target-vessel revascularization, and definite stent thrombosis; and (4) among patients undergoing PCI in the LAD/LM, we found a consistently beneficial effect of DES versus BMS for both LAD and LM subgroups with respect to primary and secondary outcomes.

Although new-generation DES have replaced BMS in contemporary practice, the evidence from individual randomized trials in supporting their use is essentially based on a lower risk of repeat revascularization procedures and stent thrombosis or MI. This latter effect has been demonstrated only in a minority of studies.[21,22] The CST Collaboration was developed to comprehensively evaluate the efficacy and safety of new-generation DES compared with BMS. By including 26 616 patients in 20 randomized trials, we found

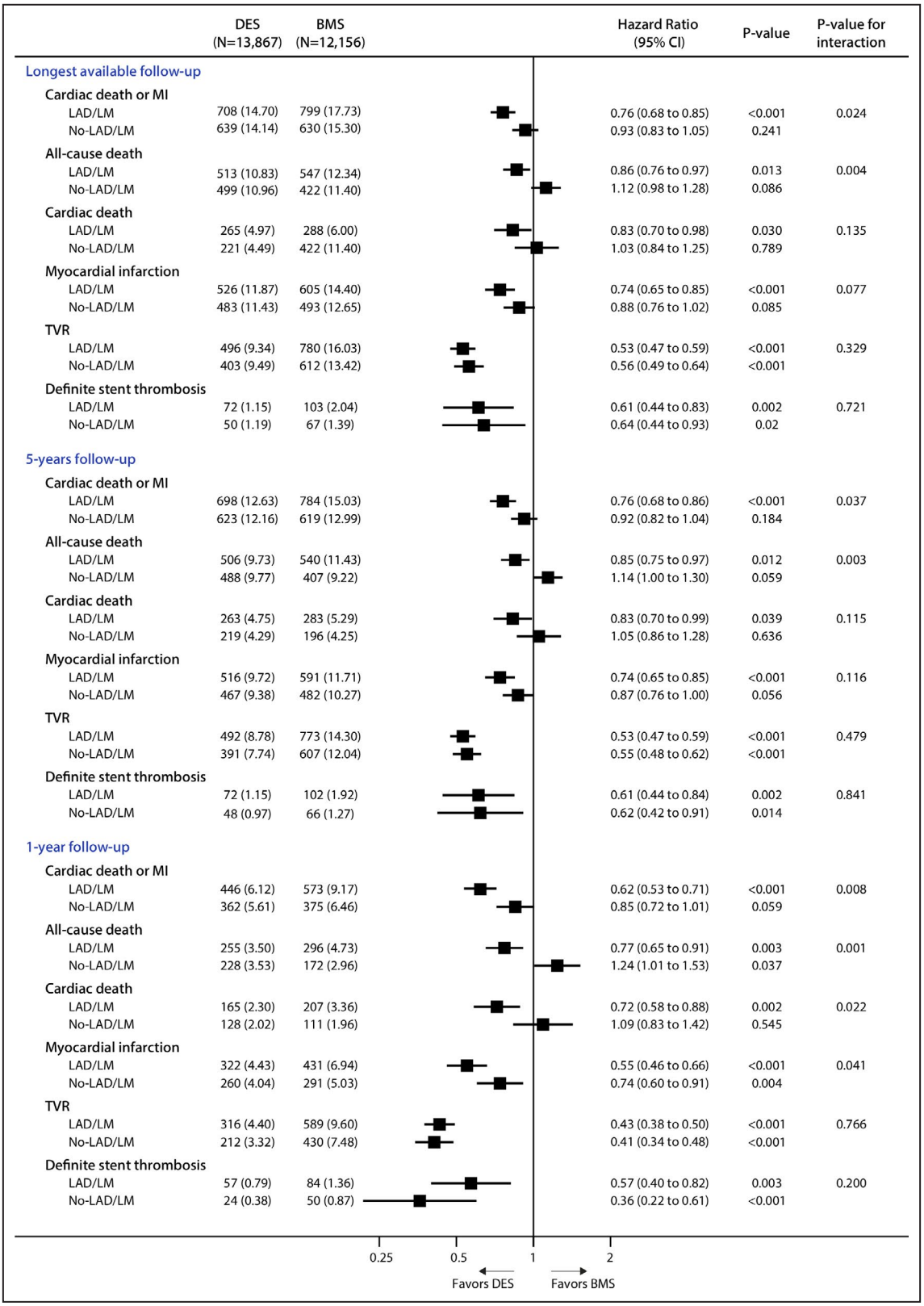

Figure 2. Effect of drug-eluting stents (DES) vs bare-metal stents (BMS) in patients undergoing percutaneous coronary intervention in the LAD/LM vs no-LAD/LM territory.

Data are shown at maximum, 5-y, and 1-y follow-up. HR indicates hazard ratio; LAD, left anterior descending artery; LM, left main artery; MI, myocardial infarction; and TVR, target-vessel revascularization.

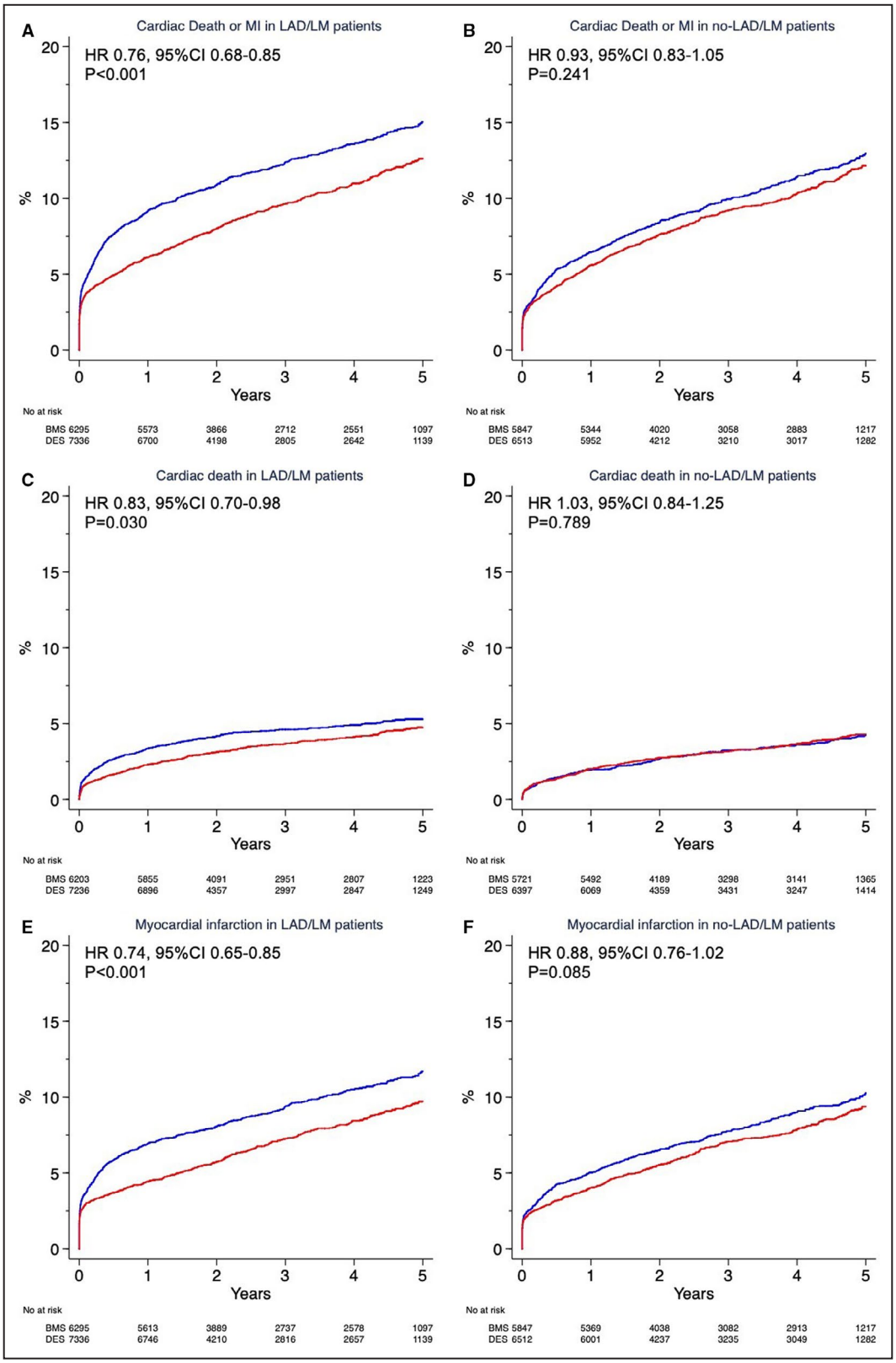

Figure 3. Kaplan-Meier curves for the primary outcome of cardiac death or myocardial infarction and its components in patients undergoing percutaneous coronary intervention in the LAD/LM vs no-LAD/LM territory and randomized to new-generation drug-eluting stents (red line) or bare-metal stents (blue line).

BMS indicates bare-metal stents; DES, drug-eluting stents; HR, hazard ratio; LAD, left anterior descending artery; and LM, left main artery.

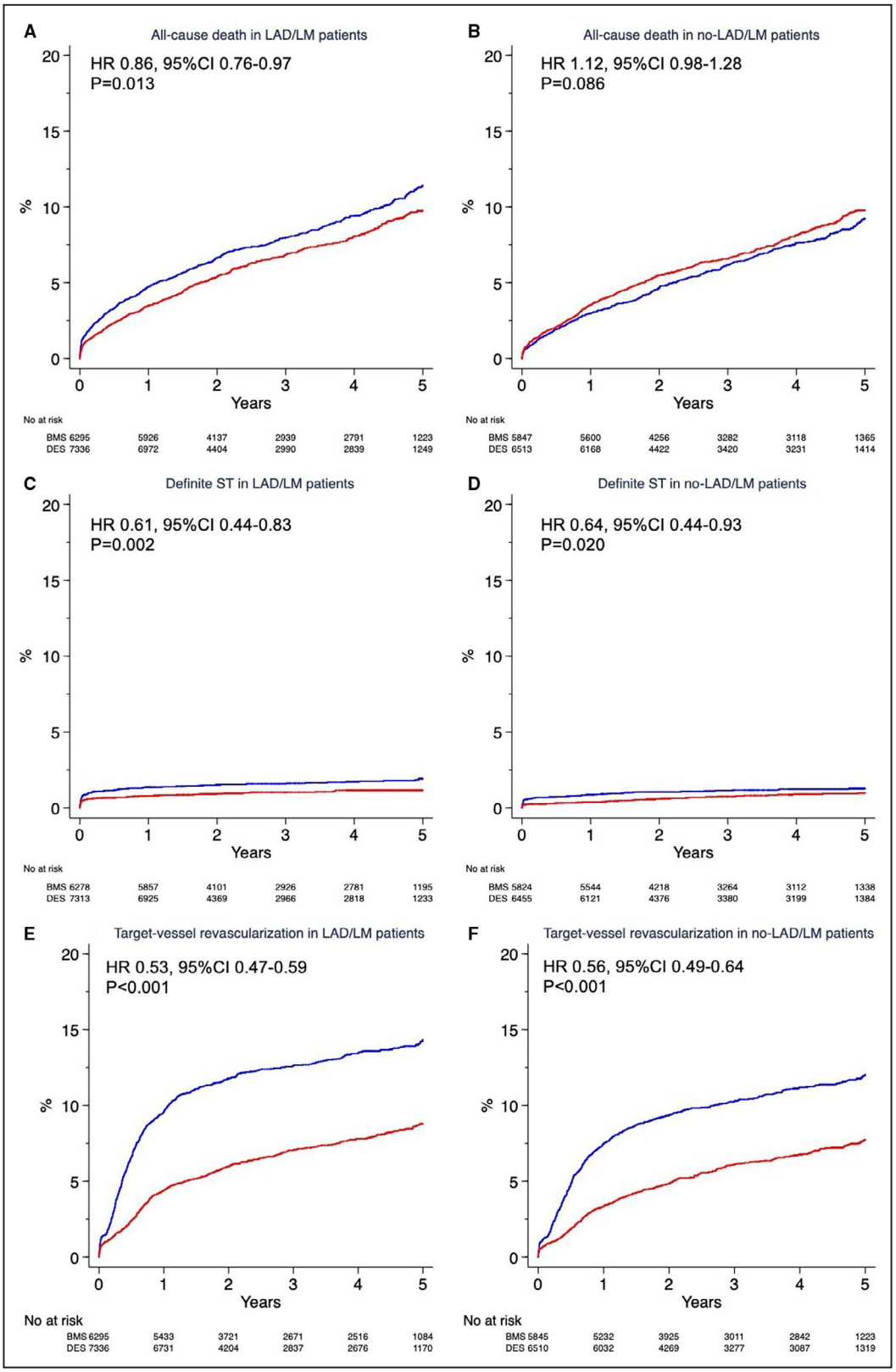

Figure 4. Kaplan-Meier curves for the secondary outcomes in patients undergoing percutaneous coronary intervention in the LAD/LM vs no-LAD/LM territory and randomized to new-generation drug-eluting stents (red line) or bare-metal stents (blue line).
BMS indicates bare-metal stent; DES, drug-eluting stents; HR, hazard ratio; LAD, left anterior descending artery; LM, left main artery; and ST, stent thrombosis.

Table 2. Landmark Analysis at 1-Year Follow-Up

	Patients with LAD/LM (n=13 650)				Patients without LAD/LM (n=12 373)				
	DES (n=7346)	BMS (n=6304)	HR (95% CI)	*P* value	DES (n=6521)	BMS (n=5852)	HR (95% CI)	*P* value	*P*-interaction between subgroups
Cardiac death or MI									
0–365 d	446 (6.12)	573 (9.17)	0.62 (0.53–0.71)	<0.001	362 (5.61)	375 (6.46)	0.85 (0.72–1.01)	0.059	0.008
>365 d	262 (9.14)	226 (9.42)	1.06 (0.89–1.27)	0.503	277 (9.04)	255 (9.44)	1.02 (0.86–1.22)	0.788	0.823
All-cause death									
0–365 d	255 (3.50)	296 (4.73)	0.77 (0.65–0.91)	0.003	228 (3.53)	172 (2.96)	1.24 (1.01–1.53)	0.037	0.001
>365 d	258 (7.60)	251 (7.98)	0.96 (0.80–1.14)	0.62	271 (7.70)	250 (8.69)	1.04 (0.88–1.24)	0.644	0.533
Cardiac death									
From 0–365 d	165 (2.30)	207 (3.36)	0.72 (0.58–0.88)	0.002	128 (2.02)	111 (1.96)	1.09 (0.83–1.42)	0.545	0.022
>365 d	100 (2.73)	81 (2.73)	1.10 (0.82–1.47)	0.546	93 (2.52)	91 (3.48)	0.96 (0.72–1.29)	0.781	0.512
MI									
0–365 d	322 (4.43)	431 (6.94)	0.55 (0.46–0.66)	<0.001	260 (4.04)	291 (5.03)	0.74 (0.60–0.91)	0.004	0.041
>365 d	204 (7.78)	174 (8.01)	1.09 (0.89–1.34)	0.391	223 (7.70)	202 (8.02)	1.04 (0.86–1.26)	0.684	0.760
TVR									
0–365 d	316 (4.40)	589 (9.60)	0.43 (0.38–0.50)	<0.001	212 (3.32)	430 (7.48)	0.41 (0.34–0.48)	<0.001	0.766
>365 d	180 (5.17)	191 (7.11)	0.81 (0.66–0.99)	0.044	191 (6.38)	182 (6.42)	0.93 (0.76–1.14)	0.472	0.349
Definite stent thrombosis									
0–365 d	57 (0.79)	84 (1.36)	0.57 (0.40–0.82)	0.003	24 (0.38)	50 (0.87)	0.36 (0.22–0.61)	<0.001	0.200
>365 d	15 (0.37)	19 (0.68)	0.74 (0.38–1.43)	0.364	26 (0.81)	17 (0.53)	1.40 (0.76–2.59)	0.286	0.128

BMS indicates bare-metal stent; CAD, coronary artery disease; DES, drug-eluting stent; HR, hazard ratio; LAD, left anterior descending artery; LM, left main artery; MI, myocardial infarction; and TVR, target-vessel revascularization.

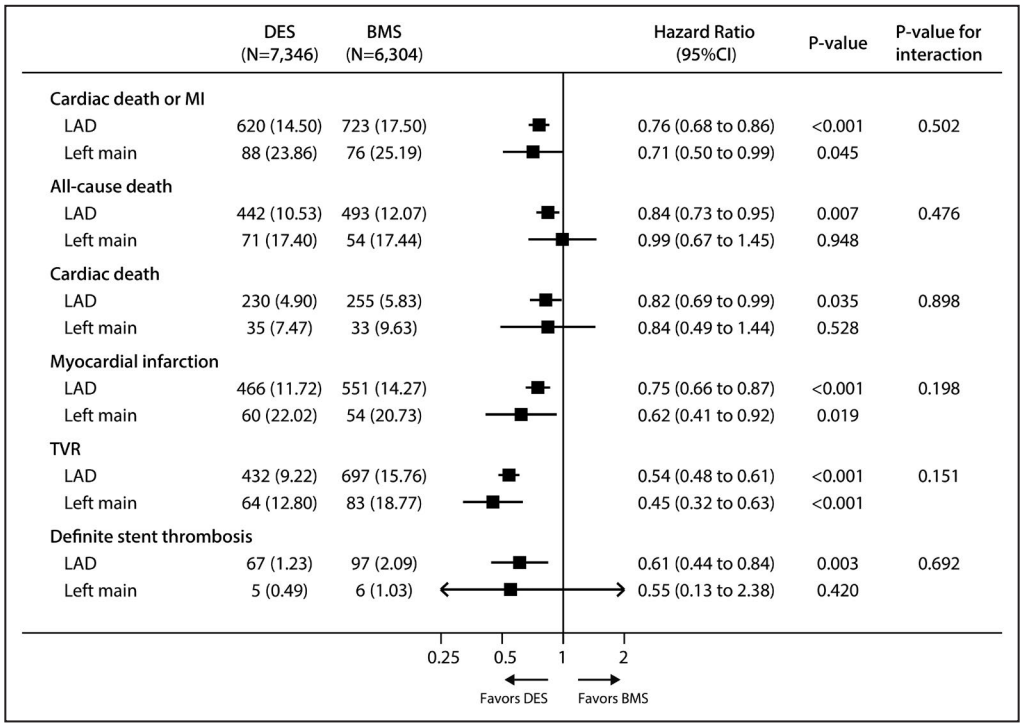

Figure 5. Effect of drug-eluting stents (DES) vs bare-metal stents (BMS) in patients undergoing percutaneous coronary intervention in the LAD vs LM artery.
HR indicates hazard ratio; LAD, left anterior descending artery; LM, left main artery; MI, myocardial infarction; and TVR, target-vessel revascularization.

a 26% relative reduction in the risk of cardiac death or MI in favor of DES because of a reduced risk of MI and to a lesser extent cardiac death.[7] The present analysis extends earlier results showing that new-generation DES provide differential benefits among patients undergoing PCI of coronary segments with a larger area at risk, such as the LAD or LM arteries. We found that LAD- and/or LM-treated patients experienced a 24% relative reduction in the hazard of cardiac death or MI at maximum follow-up when treated with DES, whereas a nonsignificant 7% relative risk reduction was observed in the no-LAD/LM group. At 1-year follow-up, the relative reduction in the risk of cardiac death or MI attested to 38% and 15% in the LAD/LM and no-LAD/LM groups, respectively. The superiority of new-generation DES over BMS for LAD/LM was driven by a decreased risk of both cardiac death (17% relative reduction) and MI (26% relative reduction). Conversely, only the MI component of the primary composite outcome was borderline reduced by 12% in the no-LAD/LM group at the time of longest follow-up. All-cause mortality was also reduced among patients in the LAD/LM group but not in the no-LAD/LM group, in whom all-cause mortality was apparently higher with DES (HR at 1-year follow-up, 1.24; P=0.037). We do not have a mechanistically plausible explanation for this finding, which might simply be a chance finding.

Cardiac fatalities and MIs were robustly decreased by DES allocation solely in LAD/LM recipients, even though the magnitude of treatment response associated with DESs versus BMSs was comparable for both LAD/LM and no-LAD/LM groups in terms of efficacy (HRs for TVR, 0.53 versus 0.56) and safety outcomes (HRs for stent thrombosis, 0.61 versus 0.64). This might be explained by more prognostically relevant implications of stent-related failures in LAD or LM arteries in view of larger myocardium at risk. Patients in the LAD/LM group had also a higher risk of all study outcomes, excepting all-cause death, suggesting a greater ischemic burden and thus benefit from safer and more effective coronary devices. In keeping with this, untreated LM stenosis as well as incomplete revascularization involving the LAD, especially in its proximal segment, are conditions associated with a higher risk of mortality.[28,29]

Serial assessments of outcomes at 1-year, 5-year, and longest follow-up as well as landmark analyses allowed for the evaluation of interactions between device type and lesion location over time. In line with prior findings,[7] we saw that the beneficial effects of DES on efficacy and safety end points accrued principally within the first year after PCI, even within 30 days, with no further incremental benefit or loss thereafter. Consistently, there was a stronger evidence of a difference between LAD/LM and no-LAD/

LM groups at 1-year follow-up with the heterogeneity in treatment response among the 2 groups reaching the strongest effect at 1 year. This again suggests that the observation of a larger benefit in the LAD/LM group with DES instead of BMS could be explained by the potentially more detrimental sequelae of TVR and stent thrombosis in these coronary tree segments, notwithstanding the comparable treatment effect of device type in LAD/LM and no-LAD/LM groups with respect to both TVR and stent thrombosis.

Limitations

Our study has a number of caveats and limitations. First, as an important limitation to the study, we did not collect lesion location in our IPD and therefore were unable to disentangle the treatment effect between proximal versus nonproximal LAD. Second, the study has limitations inherent in patient-level, pooled analyses reflecting the shortcomings of the original studies. Third, a mixture of new-generation DESs was used in the experimental arm, despite the fact that a limited number of DESs were implanted as previously described.[7] Fourth, although outcomes were assessed at the maximum follow-up of 6 years, the mean follow-up of the study was about 3 years. Whether differences between DES and BMS exist in the late follow-up and, importantly, whether the benefit of DES in the LAD/LM segments in terms of mortality is eroded in the long-term remain unaddressed by this study. However, other trials comparing new-generation DES with BMS are unlikely. Finally, we did not adjust or account for postrandomization covariates, such as actual duration of dual antiplatelet therapy, to avoid violating the principle of randomization.

In conclusion, our collaborative meta-analysis based on the totality of available randomized data showed that the use of new-generation DES rather than BMS in patients requiring PCI in the left anterior descending artery or in the left main system conferred additional benefits, with larger reductions in the risk of the composite outcome of cardiac death or MI, attributable to a reduction of both cardiac death and MI within the first year after intervention, without trade-off between efficacy and safety thereafter. The use of new-generation DES in the LAD artery and/or in the LM coronary artery was associated with a sustained decrease in the risk of all-cause mortality at long-term follow-up.

ARTICLE INFORMATION

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Supplementary Material

Data S1
Tables S1–S8
Figures S1–S3

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SUPPLEMENTAL MATERIAL

Data S1.

Supplemental Methods

Assembled Dataset

IPD were provided for the following variables, where available: demographic data and risk factors (age, sex, smoking status, hypertension, dyslipidemia, diabetes, insulin-treated diabetes), history of coronary artery disease (previous myocardial infarction, previous PCI, previous coronary artery bypass grafting), clinical presentation at the time of the index procedure (chronic coronary syndrome, unstable angina, non-ST-segment elevation acute coronary syndrome, ST-segment elevation myocardial infarction), pharmacological therapy during the index procedure (glycoprotein IIb/IIIa receptor inhibitors), angiographic and procedural data (number of implanted stents, mean stent length, mean stent diameter, overlapping stent, multivessel disease, intervened coronary vessel [left main coronary artery, left anterior descending artery, left circumflex artery, right coronary artery]), clinical outcomes (all-cause death, cardiac death, myocardial infarction, target-vessel revascularization, stent thrombosis [definite, probable, possible]).

Search Strategy

MEDLINE			EMBASE		
#	Searches	Results	#	Searches	Results
1	exp Coronary Artery Disease/	53764	1	exp coronary artery disease/	295369
2	exp Coronary Angiography/ or exp Percutaneous Coronary Intervention/ or exp Myocardial Infarction/ or exp Angioplasty, Balloon/ or exp Angioplasty, Balloon, Coronary/	245133	2	exp transluminal coronary angioplasty/ or exp percutaneous coronary intervention/ or exp heart infarction/	390579
3	exp Drug-Eluting Stents/	9443	3	exp drug eluting stent/	29291
4	exp Stents/	68340	4	exp bare metal stent/ or exp stent/	151736
5	coronar*.mp.	466007	5	coronar*.mp.	657251
6	myocard*.mp.	527091	6	myocard*.mp.	519513
7	PCI.mp.	22057	7	PCI.mp.	49674
8	coronary intervention*.mp.	35318	8	stent*.mp.	182836
9	stent*.mp.	102058	9	sirolimus*.mp.	14292
10	sirolimus*.mp.	18842	10	everolimus*.mp.	25372
11	everolimus*.mp.	6158	11	zotarolimus*.mp.	2972
12	zotarolimus*.mp.	674	12	biolimus*.mp.	1271
13	biolimus*.mp.	279	13	tacrolimus*.mp.	72081
14	tacrolimus*.mp.	22521	14	pimecrolimus*.mp.	3123
15	pimecrolimus*.mp.	873	15	rapamycin*.mp.	84597
16	rapamycin*.mp.	25218	16	1 or 5 or 6	957890
17	1 or 5 or 6	807736	17	2 or 7 or 8	533938
18	2 or 7 or 8 or 9	328216	18	3 or 4 or 9 or 10 or 11 or 12 or 13 or 14 or 15	295520
19	3 or 4	68340	19	16 and 17 and 18	62972
20	10 or 11 or 12 or 13 or 14 or 15 or 16 or 19	120856	20	trial*.mp. or exp "randomized controlled trial (topic)"/ or exp controlled clinical trial/ or exp "clinical trial (topic)"/ or exp "controlled clinical trial (topic)"/	2180244

21	17 and 18 and 20	28357	21	19 and 20	16711
22	exp RANDOM ALLOCATION/	94708			
23	random*.mp.	1201558			
24	exp RANDOMIZED CONTROLLED TRIAL/ or exp CLINICAL TRIAL/ or trial*.mp.	1522432			
25	22 or 23 or 24	1986524			
26	21 and 25	8036			

Table S1. **Main characteristics of randomized trials included in the pooled analysis.**

Study	N	FU (yrs)	Multi-centre	Type of DES	Type of BMS	Primary Endpoint	DAPT duration	Industry sponsor study
SPIRIT I	56	2	Yes	Xience EES	Multi-link Vision	6-month in-stent late loss	3 months both DES and BMS	Yes
STEALTH	120	5	Yes	BioMatrix BES	S-Stent	6-month in-stent late loss	3 months both DES and BMS	Yes
ENDEAVOR II	1,197	5	Yes	Endeavor ZES	Driver	cardiac death, MI, TVR	3 months both DES and BMS	Yes
PAINT	274	5	Yes	Infinnium PES Supralimus SES	Millenium Matrix	cardiac death, MI, TVR	12 months DES and 1 BMS	Yes
BASKET PROVE	1,540	3	Yes	Xience EES	Vision	cardiac death, MI	12 months both DES and BMS	No
CORACTO	66	1	Yes	Trinity SES	Constant	6-month in-stent late loss	6 months both DES and BMS	Yes
EUCATAX	423	3	Yes	STS Flex DE PES	STS Flex DE	cardiac death, MI, TVR	6 months DES and 3 BMS	Yes
COMFORTABLE	1,157	5	Yes	BioMatrix BES	Gazelle	cardiac death, MI, TVR	12 months both DES and BMS	No
EXAMINATION	1,498	5	Yes	Xience EES	Multi-link Vision	death, MI, Any Re-vascularization	12 months both DES and BMS	Yes
PRODIGY	1,502	2	Yes	Xience EES Endeavor ZES	Any < 100 μm	death, MI, CVA	6 or 24 months both DES and BMS	No
INSPIRON	61	4	Yes	Inspiron SES	Cronus	6-month in-stent late loss	9 or 12 months DES and 6 or 9 BMS	Yes
XIMA	800	1	Yes	Xience EES	Vision	death, MI, CVA	12 months DES and 3 BMS	No
BASKET PROVE II	2,291	3	Yes	Nobori BES Xience EES	ProKinetik	cardiac death, MI, TVR	12 months DES and 1 or 12 BMS	No
LEADERS-FREE	2,432	2	Yes	Biofreedom BES	Gazelle	cardiac death, MI, TVR, ST	1 month both DES and BMS	Yes
ZEUS	1,606	1	Yes	Endeavor ZES	Any BMS <100 μm	death, MI, TVR	1, 6 or 12 months both DES and BMS	No

ELISA-3	474	2	Yes	Xience EES	Vision	9-month in-stent late loss	12 months both DES and BMS	No
NORSTENT	8,745	6	Yes	Promus EES Resolute ZES Endeavor ZES Resolute ZES Cypher SES Taxus PES	Driver Integrity Liberte Multi-link Vision Multi-link 8 Carbostent Chrono Graftmaster Coroflex Multi-link Zeta	death, MI	9 months both DES and BMS	No
MASTER	500	1	Yes	Ultimaster	Kaname	cardiac death, MI, TVR	12 months both DES and BMS	Yes
SENIOR	1,200	1	Yes	Synergy	Omega or Rebel	death, MI, TLR, stroke	1 or 6 months both DES and BMS	No

BASKET PROVE: Basel Stent Kosten-Effektivitäts Trial Prospective Validation Examination, BES: biolimus-eluting stent, BMS: bare-metal stent, COMFORTABLE: Comparison of Biolimus Eluted From an Erodible Stent Coating With Bare Metal Stents in Acute ST-Elevation Myocardial Infarction, CORACTO: The Coracto™ Rapamycin-Eluting Stent in chronic coronary occlusions, DAPT: Dual Anti-Platelet Therapy, DES: drug-eluting stent, EES: everolimus-eluting stent, ELISA-3: Early or late intervention in high-risk non-ST-elevation acute coronary syndromes, ENDEAVOR II: The Medtronic Endeavor Drug Eluting Coronary Stent System in Coronary Artery Lesions, EUCATAX: comparison of a paclitaxel eluting stent with biodegradable polymer and glycolix coating versus bare metal stent design, EXAMINATION: clinical evaluation of the Xience-V stent in Acute Myocardial INfArcTION, INSPIRON: comparison of a novel sirolimus-eluting stent with abluminal biodegradable polymer and thin-strut cobalt-chromium alloy, LEADERS FREE: A Randomized Clinical Evaluation of the BioFreedom™ Stent, MASTER: Safety and Efficacy of Ultimaster Drug-eluting Stent in STEMI Patients, NORSTENT: Norwegian Coronary Stent Trial, PAINT: PercutAneous INTervention with biodegradable-polymer based paclitaxel-eluting or sirolimus-eluting versus bare stents for de novo coronary lesions, PRODIGY: Prolonging Dual Antiplatelet Treatment After Grading Stent-Induced Intimal Hyperplasia Study, SENIOR: The SYNERGY II Everolimus elutiNg stent In patients Older than 75 years undergoing coronary Revascularization associated with a short dual antiplatelet therapy, SPIRIT I: A randomized comparison of a durable polymer Everolimus-eluting stent with a bare metal coronary stent, STEALTH: STent Eluting A9 BioLimus Trial in Humans, TLR: target-lesion revascularization, TVR: Target-vessel revascularization, XIMA: Xience or Vision Stents for the Management of Angina in the Elderly, ZES: zotarolimus-eluting stent, ZEUS: Zotarolimus-eluting Endeavor sprint stent in Uncertain DES candidates.

Table S2. **Main inclusion and exclusion criteria in pooled randomized trials.**

Study	Major inclusion criteria	Major exclusion criteria
SPIRIT I	stable or unstable angina or silent ischaemia and a single primary de novo coronary lesion 3 mm in diameter, that could be covered by an 18 mm stent, with TIMI flow grade more than 0	AMI, LVEF<30%, LMA stenosis, ostial or bifurcation lesions, moderate to heavy calcification, presence of thrombus
STEALTH	symptoms of angina or ischemia and a lesion ≤ 24 mm in native vessel ≥ 2.75 mm and ≤ 4.0 mm	AMI/stroke/TIA within the prior 7 days, LVEF<30%, LMA stenosis, bifurcation lesion, need for more than 2 stent, prior stenting of target lesion, presence of thrombus
ENDEAVOUR II	evidence of myocardial ischemia and a single, untreated lesion (>14 but ≤27mm) in native vessel (≥2.25 but ≤3.5mm)	AMI, PCI within the prior 30 days, LVEF<30%, S-Cr>2 mg/dL, LMA, ostial or bifurcation lesion, severe calcification
PAINT	evidence of myocardial ischemia and a single, untreated lesion≤29mm in native vessel (≥2·5 but ≤3·5mm)	AMI, PCI of the target vessel within the prior 6 months, LVEF<30%, S-Cr>2 mg/dL, LMA stenosis, ostial or bifurcation lesions, severe calcification, presence of thrombus
BASKET PROVE	chronic or acute coronary disease, native vessel>3 but ≤4 mm	Cardiogenic shock, restenosis or thrombosis of prior stent, LMA or bypass graft lesion, need of oral anticoagulant, high risk of bleeding
CORACTO	CTO eligible to PCI	High risk of bleeding, native vessel <2·5 or >4·5 mm
EUCATAX	evidence of myocardial ischemia and a de novo stenosis ≥70% in a major coronary vessel	AMI, LVEF<30%, in-stent restenosis
COMFORTABLE	STEMI within 24 hours from symptom onset	mechanical complication of AMI, need of oral anticoagulant, high risk of bleeding

EXAMINATION	STEMI within 48 hours from symptom onset and native vessel ≥2·5 but ≤4mm	need of oral anticoagulant, stent thrombosis
PRODIGY	Stable angina or acute coronary syndrome including STEMI with at least 1 lesion in native coronary vessel≥2·25 mm in diameter	Planned surgery within 24 months, history of bleeding, concomitant need of oral anticoagulant therapy
INSPIRON	evidence of myocardial ischemia and a de novo lesion <20mm in vessel≥2·25 but ≤3·5mm	Cardiogenic shock, LVEF<30%, requiring of 3 stents, LMA, ostial or bifurcation lesion, presence of thrombus
XIMA	≥80 years old pts with stable angina or ACS and a lesion ≥15mm long or <3mm wide	STEMI, cardiogenic shock, history of gastrointestinal or intracerebral bleeding
BASKET PROVE II	chronic or acute coronary disease, native vessel>3 but ≤4 mm	Cardiogenic shock, restenosis or thrombosis of prior stent, LMA or bypass graft lesion, need of oral anticoagulant, high risk of bleeding
LEADERS-FREE	chronic or acute coronary disease and a high bleeding risk	Cardiogenic shock, active bleeding, vessel <2·25 - >4·0mm
ZEUS	chronic or acute coronary disease and a high bleeding risk or high thrombosis risk or low restenosis risk	Pregnancy
ELISA-3	unstable angina or NSTEMI	STEMI, cardiogenic shock, active bleeding, acute posterior infarction
NORSTENT	chronic or acute coronary disease and lesion of native vessel or bypass graft	Prior PCI, bifurcation lesion, need of anticoagulant
MASTER	STEMI within 24 hours from symptom onset and a lesion of native vessel >2·5 but <4mm	mechanical complication of AMI, need of oral anticoagulant, high risk of bleeding

SENIOR	chronic or acute coronary disease in patients aged 75 years or older	Planned cardiac or non-cardiac surgery, history of haemorrhagic stroke, inability or contraindication to DAPT, life expectancy < 1year

AMI: acute myocardial infarction, CTO: Chronic Total Occlusion, DAPT: Dual anti-platelet therapy, LMA: Left Main Artery, LVEF: Left Ventricle Ejection Fraction, NSTEMI: Non-ST-segment Elevation Myocardial Infarction, PCI: Percutaneous Coronary Intervention, S-Cr: Serum Creatinine, STEMI: ST-segment Elevation Myocardial Infarction, TIA: Transient Ischemic Attack, TIMI: Thrombolysis In Myocardial Infarction.

Table S3. **Definition of clinical endpoints in randomized trials included in the IPD meta-analysis.**

Endpoint	SPIRIT I	STEALTH	ENDEAVOUR II	PAINT	BASKET PROVE	CORACTO	EUCATAX
Cardiac death	All deaths that could not be clearly attributed to another cause were considered cardiac deaths.	Not reported	All cardiac death cannot be clearly attributed to a vessel other than the target vessel	All deaths that could not be unequivocally attributed to non-cardiac cause were considered cardiac deaths.	any death without a clear extracardiac cause	Not reported	Not reported
Myocardial infarction	A Q-wave MI or non-Q-wave MI, defined as an increase in CK level to more than twice the upper limit of the normal range, and an increased level of CK-MB	Not reported	Q waves in at least 2 contiguous leads, or an elevation in CK levels to greater than twice the upper limit of normal in the presence of an elevated CK-MB level	New Q waves or ST-segment depression/elevation and rising of CK, CK-MB or cTn in the setting of clinical ischemia	a clinical event with typical electrocardiographic (Q waves or ST-segment elevation/depression) or enzymatic changes (cTn or CK-MB exceeding the 99th percentile of a reference control group)	Not reported	typical chest pain combined with either new pathological Q waves or an increase in CK>3 the upper limit of normal, with a concomitant increase in the myocardial band isoenzyme

Target vessel revascularization	Not reported	Not reported	revascularization for ischemia owing to stenosis>50%, or without signs of ischemia to stenosis>70% anywhere within the target vessel,	revascularization for ischemia owing to stenosis>50%, or without signs of ischemia to stenosis>70% anywhere within the target vessel	Not reported	Not reported	revascularization for symptoms or signs of ischemia, or without signs of ischemia to stenosis>70% anywhere within the target vessel

Endpdoint	COMFORTABLE	EXAMINATION	PRODIGY	INSPIRON	XIMA	BASKET PROVE II
Cardiac death	All deaths are considered cardiac unless an unequivocal non-cardiac cause can be established.	any death due to proximate cardiac cause, unwitnessed death and death of unknown cause, and all procedure-related deaths, including those related to concomitant treatment	Any death unless a definite non-cardiovascular cause could be established.	Not reported	Nor reported	any death without a clear extracardiac cause

Myocardial infarction	Q waves with elevated biomarkers or chest pain; CK-MB/cTn>1 ULN and chest pain or ECG changes	Q waves with elevated biomarkers or chest pain; CK-MB/cTn>1 ULN and chest pain or ECG changes	Rise and/or fall of cardiac biomarker values with at least one value above the 99th percentile ULN with at least one of the followings: - Symptoms of ischemia. - Typical EKG changes. -New pathological Q waves. - Evidence of new loss of viable myocardium	Not reported	cTn or CK-MB>99th percentile ULN and symptoms or ECG/imaging changes	a clinical event with typical electrocardiographic (Q waves or ST-segment elevation/depression) or enzymatic changes (cTn or CK-MB exceeding the 99th percentile of a reference control group)
Target vessel revascularization	revascularization for symptoms or signs of ischemia owing to stenosis>50%, or without signs of ischemia to stenosis>70% anywhere within the target vessel	revascularization for symptoms or signs of ischemia owing to stenosis>50%, or without signs of ischemia to stenosis>70% anywhere within the target vessel	Defined as repeat PCI or CABG of the target vessel.	Not reported	stented vessel requiring revascularization with balloon angioplasty, stenting, or coronary artery bypass grafting within 1 year of the original procedure	Not reported

Endpdoint	LEADERS-FREE	ZEUS	ELISA-3	NORSTENT	MASTER	SENIOR

Cardiac death	any death in which a cardiac cause cannot be excluded, due to AMI, cardiac perforarion, arrhythmia, stroke within 30 days, procedural complication,	Any death due to immediate cardiac cause, unwitnessed or unknown cause	Not reported	death within 28 days from onset symptoms of AMI, or UA, sudden death when there's no other clear reason.	Not reported	Not reported
Myocardial infarction	cTn or CK-MB>99th percentile ULN and symptoms or ECG/imaging changes	cTn or CK-MB>99th percentile ULN and symptoms or ECG/imaging changes	New Q waves or creatine kinase level or MB fraction at least twice ULN	cTn or CK-MB>99th percentile ULN and symptoms or ECG/imaging changes	Not reported	myocardial necrosis in a clinical setting consistent with AMI according to 3rd universal definition MI

Target vessel revascularization	PCI or surgery in the treated vessel with symptom and/or documented ischemia or for a stenosis > 70%	revascularization for symptoms or signs of ischemia owing to stenosis>50%, or without signs of ischemia to stenosis>70% anywhere within the target vessel	Not reported	Clinically driven repeat PCI of the target vessel	Not reported	Not reported

AMI: Acute myocardial infarction, CABG: coronary artery bypass grafting, CK: creatine kinase, CK-MB: creatine kinase myocardial band, cTn: cardiac Troponin, ECG: electrocardiography, MI: myocardial infarction, UA: Unstable Angina, ULN: upper limit of normal.

Table S4. **Type of implanted stents.**

Type of stent	No. of patients	Percent	Strut thickness (μm)
Drug-eluting stents (n=13,867)			
Xience EES	4,005	28.9	81
Promus EES	2,866	20.7	81
Endeavor ZES	1,901	13.7	91
Biofreedom BES	1,221	8.8	112
Nobori BES	765	5.5	120
Biomatrix BES	655	4.7	112
Synergy EES	593	4.3	74
Resolute ZES	475	3.4	91
Ultimaster SES	368	2.7	80
Eucatax PES	209	1.5	85
Cypher SES	115	0.8	140
Infinnium PES	111	0.8	60
Supralimus SES	106	0.8	60
Taxus PES	90	0.7	132
Inspiron SES	41	0.3	75
Coracto SE	34	0.3	80
Bare-metal stents (n=12,156)			
Driver BMS	2,976	24.5	91
Vision BMS	2,529	20.8	81
Gazelle BMS	1,792	14.7	112
Integrity BMS	914	7.5	91
Liberté BMS	778	6.4	97
Pro-kinetic BMS	760	6.3	60
Omega/Rebel BMS	599	4.9	81
Eucatech BMS	211	1.7	85
Kaname BMS	120	1.0	81
Multi-Link 8 BMS	92	0.8	81
Chrono Carbostent BMS	81	0.7	80
Milennium Matrix BMS	57	0.5	60
Multi-Link Flexmaster BMS	56	0.5	81
S-Stent	40	0.3	112
Constant BMS	32	0.3	80
Cronus BMS	20	0.2	75
Coroflex Blue BMS	3	0.02	60

Graftmaster BMS	2	0.02	520
Multi-Link Zeta BMS	2	0.02	102

Among patients randomized to new-generation DES, BMS were implanted in 22 (0.16%) patients and information was missing in 24 (0.17%) patients. Among patients randomized to BMS, DES were implanted in 25 (0.2%) patients and information was missing in 812 (6.7%) patients. Mixed stents were used in 266 (1.9%) patients randomized to new-generation DES and 255 (2.0%) patients randomized to BMS. Early-generation DES were implanted in 205 (1.5%) patients randomized to DES. BMS: bare-metal stents. BES: Biolimus-eluting stent. DES: drug-eluting stents. EES: Everolimus-eluting stent. PES: Paclitaxel-eluting stent. SES: Sirolimus-eluting stent. ZES: Zotarolimus-eluting stent. Abbott Vascular (Santa Clara, CA, USA) make Xience, Vision, Multi-link 8, Multi-Link Flexmaster, Multi-Link Zeta and Graftmaster. Alvimedica (Istanbul Turkey) make Constant, Coracto and Chrono Carbostent. AMG (Winsen, Germany) make AMG. B Braun (Melsungen, Germany) make Coroflex. Biosensors International (Jalan Tukang, Singapore) make BioMatrix, BioFredoom, Gazelle and S-Stent. Biotronik (Berlin, Germany) make Pro-kinetic. Boston Scientific (Marlborough, MA, USA) make Taxus, Promus and Liberté. Cordis (Eastbridgewater, NJ, USA) make Cypher. Eucatech (Reinhelfeden, Germany) make Eucatax and Eucatech. Medtronic (Minneapolis, MN, USA) make Endeavor, Resolute, Driver and Integrity. Sahajanand Medical Technologies (Surat, India) make Infinnium, Supralimus and Millenium Matrix. Scitech Medical (Goiàs, Brasil) make Inspiron and Cronus. Terumo (Tokyo, Japan) make Nobori, Ultimaster and Kaname.

Table S5. Risk of bias in the included trials as assessed by the Cochrane risk of bias assessment tool.

Study	Sequence generation	Allocation concealment	Blinding of participants and personnel	Blind outcome assessment	Incomplete outcome data	Selective outcome reporting
SPIRIT I	Low risk	Low risk	High-risk	Low risk	Low risk	Low risk
STEALTH	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
ENDEAVOUR II	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
PAINT	Low risk	Low risk	High-risk	Low risk	Low risk	Low risk
BASKET PROVE	Low risk	Low risk	High-risk	Low risk	Low risk	Low risk
CORACTO	Unclear	Unclear	High-risk	Low risk	Low risk	Low risk
EUCATAX	Low risk	Low risk	High-risk	Low risk	Low risk	Low risk
COMFORTABLE	Low risk	Low risk	High-risk	Low risk	Low risk	Low risk
EXAMINATION	Low risk	Low risk	High-risk	Low risk	Low risk	Low risk
PRODIGY	Low risk	Low risk	High-risk	Low risk	Low risk	Low risk
INSPIRON	Unclear	Unclear	High-risk	Low risk	Low risk	Low risk
XIMA	Low risk	Low risk	High-risk	Low risk	Low risk	Low risk
BASKET PROVE II	Low risk	Low risk	High-risk	Low risk	Low risk	Low risk
LEADERS-FREE	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
ZEUS	Low risk	Low risk	High-risk	Low risk	Low risk	Low risk
ELISA-3	Low risk	Low risk	Low-risk	Low risk	Low risk	Low risk
NORSTENT	Low risk	Low risk	High-risk	Low risk	Low risk	Low risk
MASTER	Low risk	Low risk	High-risk	Low risk	Low risk	Low risk
SENIOR	Low risk	Low risk	High-risk	Low risk	Low risk	Low risk

Table S6. Landmark analysis at 30-days and 1-year follow-up.

	LAD/LM Patients (n=13,650)				Non-LAD/LM Patients (n=12,781)				P-inter between subgroups
	DES n=7346	BMS n=6304	HR (95%CI)	P-value	DES n=6622	BMS n=6159	HR (95%CI)	P-value	
Cardiac death or MI									
0-30 days	264 (3.60)	285 (4.54)	0.76 (0.60-0.96)	0.021	177 (2.72)	172 (2.94)	0.87 (0.65-1.18)	0.382	0.539
31-365 days	182 (2.61)	288 (4.86)	0.54 (0.45-0.64)	<0.001	185 (2.97)	203 (3.62)	0.84 (0.69-1.03)	0.092	0.003
>365 days	262 (9.14)	226 (9.42)	1.06 (0.89-1.27)	0.503	277 (9.04)	255 (9.44)	1.02 (0.86-1.22)	0.788	0.823
All-cause death									
0-30 days	80 (1.09)	98 (1.56)	0.77 (0.56-1.06)	0.106	58 (0.89)	43 (0.74)	1.28 (0.84-1.97)	0.255	0.055
31-365 days	175 (2.43)	198 (3.22)	0.77 (0.63-0.94)	0.012	170 (2.66)	129 (2.24)	1.23 (0.98-1.56)	0.079	0.004
>365 days	258 (7.60)	251 (7.98)	0.96 (0.80-1.14)	0.620	271 (7.70)	250 (8.69)	1.04 (0.88-1.24)	0.644	0.533
Cardiac death									
0-30 days	69 (0.96)	85 (1.37)	0.79 (0.56-1.11)	0.177	47 (0.74)	40 (0.70)	1.10 (0.69-1.76)	0.675	0.248
31-365 days	96 (1.36)	122 (2.02)	0.68 (0.52-0.88)	0.004	81 (1.30)	71 (1.26)	1.08 (0.78-1.49)	0.655	0.043
>365 days	100 (2.73)	81 (2.73)	1.10 (0.82-1.47)	0.546	93 (2.52)	91 (3.48)	0.96 (0.72-1.29)	0.781	0.512
Myocardial infarction									
0-30 days	212 (2.90)	228 (3.63)	0.72 (0.54-0.95)	0.022	145 (2.23)	145 (2.48)	0.81 (0.56-1.15)	0.236	0.700
31-365 days	110 (1.58)	203 (3.43)	0.46 (0.37-0.58)	<0.001	115 (1.85)	146 (2.61)	0.71 (0.55-0.91)	0.007	0.016
>365 days	204 (7.78)	174 (8.01)	1.09 (0.89-1.34)	0.391	223 (7.70)	202 (8.02)	1.04 (0.86-1.26)	0.684	0.760
TVR									
0-30 days	70 (0.96)	90 (1.44)	0.75 (0.53-1.05)	0.092	46 (0.71)	72 (1.24)	0.53 (0.36-0.79)	0.002	0.187
31-365 days	246 (3.47)	499 (8.28)	0.39 (0.34-0.46)	<0.001	166 (2.63)	358 (6.32)	0.38 (0.32-0.46)	<0.001	0.853
>365 days	180 (5.17)	191 (7.11)	0.81 (0.66-0.99)	0.044	191 (6.38)	182 (6.42)	0.93 (0.76-1.14)	0.472	0.349
Definite stent thrombosis									
0-30 days	39 (0.54)	54 (0.87)	0.63 (0.40-1.01)	0.053	15 (0.23)	33 (0.57)	0.33 (0.16-0.67)	0.002	0.114
31-365 days	18 (0.25)	30 (0.50)	0.48 (0.27-0.87)	0.015	9 (0.14)	17 (0.30)	0.41 (0.19-0.88)	0.022	0.928
>365 days	15 (0.37)	19 (0.68)	0.74 (0.38-1.43)	0.364	26 (0.81)	17 (0.53)	1.40 (0.76-2.59)	0.286	0.128

BMS: bare-metal stents; HR: hazard ratio; MI: myocardial infarction; ST: stent thrombosis; TVR: target-vessel revascularization.

Table S7. Heterogeneity between studies.

	I^2	P_{het}
LAD/LM (n=13,650)		
Cardiac death or MI	0	0.651
All-cause death	6.9	0.376
Cardiac death	0	0.863
Myocardial infarction	8.4	0.358
Target-vessel revascularization	0	0.685
Definite stent thrombosis	0	0.572
No-LAD/LM (n=12,781)		
Cardiac death or MI	26	0.162
All-cause death	28.2	0.141
Cardiac death	35.3	0.100
Myocardial infarction	18.6	0.246
Target-vessel revascularization	18.2	0.231
Definite stent thrombosis	0	0.888

Heterogeneity is reported at maximum follow-up and was calculated with a two-stage meta-analysis.

Table S8. Sensitivity analysis after the exclusion of patients receiving early-generation DES.

	LAD/LM Patients (N=13,550)				No-LAD/LM Patients (N=12,268)				P-value for interaction
	DES N=7,246	BMS N=6,304	HR (95% CI)	P-value	DES N=6,416	BMS N=5,852	HR (95% CI)	P-value	
At longest FU									
Cardiac death or MI	694 (14.35)	799 (17.73)	0.76 (0.68-0.85)	<0.001	626 (14.24)	630 (15.30)	0.94 (0.83-1.05)	0.275	0.020
All-cause death	500 (10.60)	547 (12.34)	0.84 (0.75-0.96)	0.007	494 (11.15)	422 (11.40)	1.13 (0.99-1.29)	0.069	0.002
Cardiac death	261 (4.96)	288 (6.00)	0.82 (0.69-0.97)	0.024	221 (4.60)	202 (5.36)	1.04 (0.85-1.27)	0.699	0.105
Myocardial infarction	513 (11.49)	605 (14.40)	0.74 (0.65-0.84)	<0.001	470 (11.47)	493 (12.65)	0.89 (0.77-1.02)	0.101	0.068
TVR	489 (9.30)	780 (16.03)	0.53 (0.47-0.59)	<0.001	397 (9.60)	612 (13.42)	0.56 (0.49-0.64)	<0.001	0.324
Definite stent thrombosis	71 (1.14)	103 (2.04)	0.60 (0.44-0.83)	0.002	49 (1.20)	67 (1.39)	0.63 (0.43-0.93)	0.019	0.740
At 5 years follow-up									
Cardiac death or MI	685 (12.54)	784 (15.03)	0.76 (0.68-0.85)	<0.001	610 (12.14)	619 (12.99)	0.92 (0.82-1.04)	0.204	0.034
All-cause death	494 (9.57)	540 (11.43)	0.84 (0.74-0.95)	0.007	483 (9.89)	407 (9.22)	1.14 (1.00-1.31)	0.05	0.002
Cardiac death	259 (4.72)	283 (5.29)	0.83 (0.70-0.98)	0.031	219 (4.38)	196 (4.25)	1.06 (0.87-1.30)	0.56	0.089
Myocardial infarction	504 (9.62)	591 (11.71)	0.74 (0.65-0.85)	<0.001	454 (9.30)	482 (10.27)	0.87 (0.76-1.01)	0.062	0.110
TVR	486 (8.83)	773 (14.30)	0.53 (0.47-0.59)	<0.001	385 (7.75)	607 (12.04)	0.55 (0.48-0.62)	<0.001	0.490
Definite stent thrombosis	71 (1.14)	102 (1.92)	0.61 (0.44-0.84)	0.002	47 (0.98)	66 (1.27)	0.61 (0.41-0.90)	0.013	0.863
At 1 year follow-up									
Cardiac death or MI	443 (6.17)	573 (9.17)	0.62 (0.54-0.72)	<0.001	357 (5.63)	375 (6.46)	0.86 (0.73-1.02)	0.08	0.007
All-cause death	254 (3.53)	296 (4.73)	0.77 (0.65-0.91)	0.003	225 (3.54)	172 (2.96)	1.24 (1.01-1.52)	0.044	0.001
Cardiac death	164 (2.32)	207 (3.36)	0.71 (0.58-0.88)	0.002	128 (2.06)	111 (1.96)	1.09 (0.84-1.43)	0.514	0.020
Myocardial infarction	319 (4.45)	431 (6.94)	0.56 (0.47-0.67)	<0.001	255 (4.03)	291 (5.03)	0.75 (0.61-0.92)	0.006	0.041
TVR	313 (4.42)	589 (9.60)	0.43 (0.38-0.50)	0.000	212 (3.38)	430 (7.48)	0.41 (0.35-0.49)	<0.001	0.848
Definite stent thrombosis	57 (0.80)	84 (1.36)	0.58 (0.40-0.83)	0.003	24 (0.38)	50 (0.87)	0.37 (0.22-0.61)	<0.001	0.201

Effect of drug-eluting stents (DES) vs. bare-metal stents (BMS) in patients undergoing percutaneous coronary intervention in the LAD/LM vs. no-LAD/LM territory. Outcomes are displayed after the exclusion of early-generation drug-eluting stents (Cypher SES and Taxus PES). Data are shown at maximum, 5-year, and 1-year follow-up. HR: hazard ratio. MI: myocardial infarction. ST: stent thrombosis. TVR: target-vessel revascularization.

Figure S1. Kaplan-Meier curves Kaplan-Meier curves for the primary and secondary outcomes in patients undergoing percutaneous coronary intervention in the LAD/LM (red line) vs. no-LAD/LM territory (blue line).

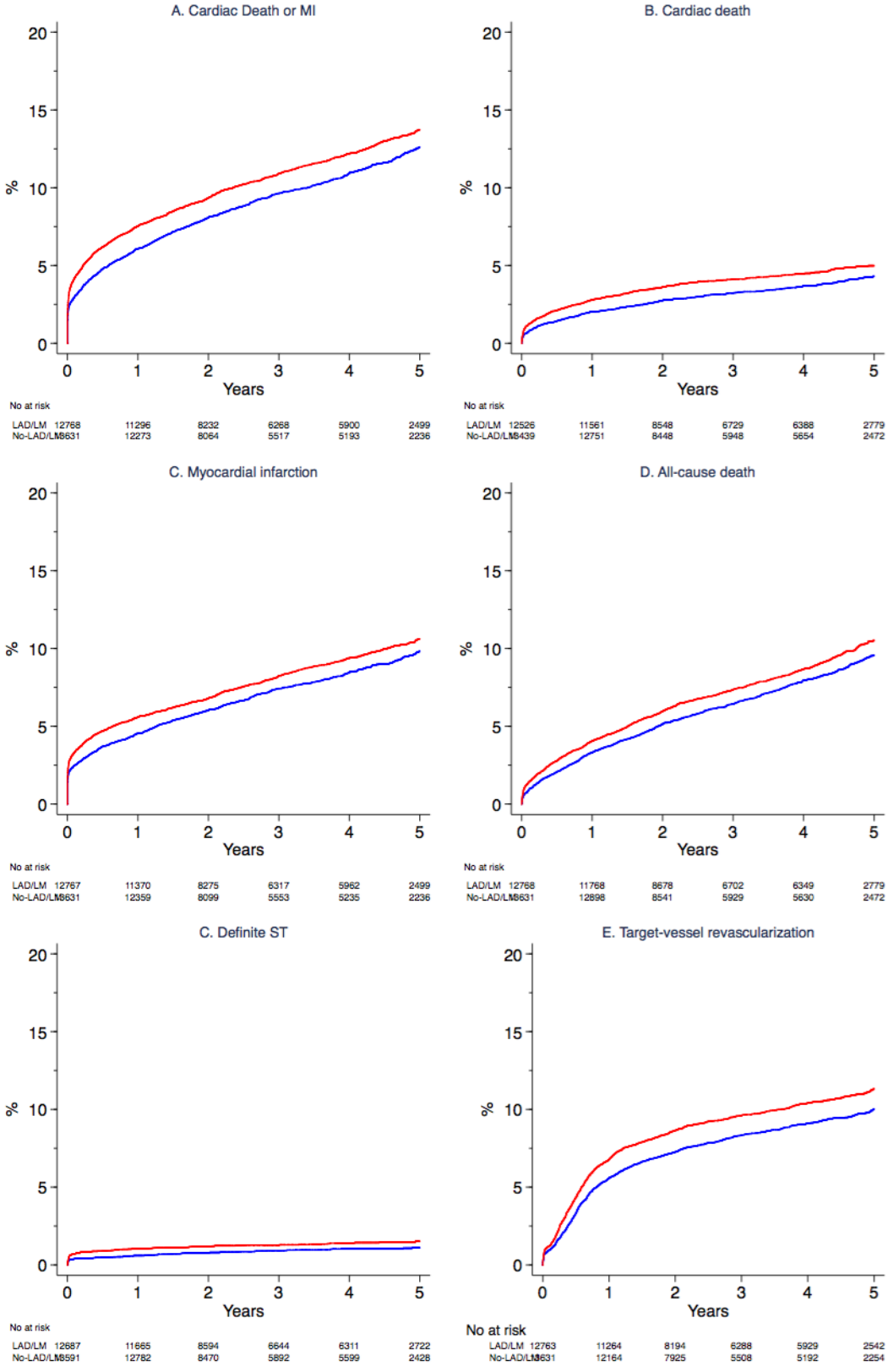

Figure S2. Two-stage random effects meta-analysis comparing DES vs. BMS in patients undergoing percutaneous coronary intervention in the LAD/LM territory.

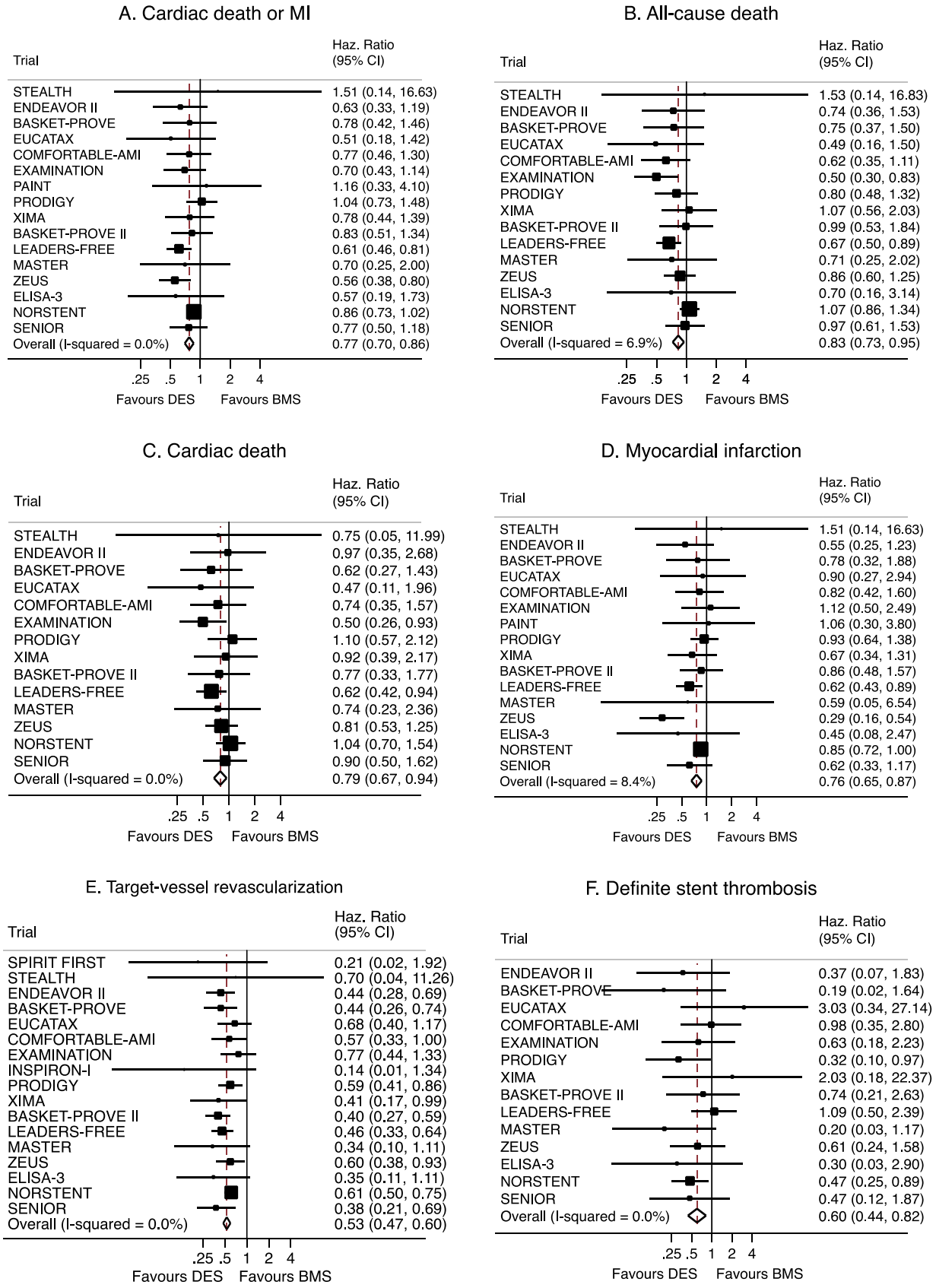

Figure S3. Two-stage random effects meta-analysis comparing DES vs. BMS in patients undergoing percutaneous coronary intervention in the no-LAD/LM territory.