Individual Patient Data Meta-Analysis of Drug-Eluting vs. Bare-Metal Stents for Percutaneous Coronary Intervention in Chronic vs. Acute Coronary Syndromes

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Brief title: DES vs. BMS in Chronic vs. Acute Coronary Syndrome.

Abstract

New-generation drug-eluting stents (DES) provide strong reduction of restenosis and repeat revascularization compared with bare-metal stents (BMS) for percutaneous coronary intervention. There is residual uncertainty as to whether other prognostically relevant outcomes are affected by DES vs. BMS in relation to initial presentation (chronic coronary syndrome [CCS] vs. acute coronary syndrome [ACS]).

We performed an individual patient data meta-analysis of randomized trials comparing new-generation DES vs. BMS (CRD42017060520). The primary outcome was the composite of cardiac death or myocardial infarction (MI). Outcomes were examined at maximum follow-up and with 1-year landmark. Risk estimates are expressed as hazard ratio (HR) with 95% confidence intervals (CI).

A total of 22,319 patients were included across 14 trials; 7,691 (34.5%) with CCS and 14,628 (65.5%) with ACS. We found evidence that new-generation DES vs. BMS consistently reduced the risk of cardiac death or MI in both CCS (HR 0.83, 95%CI 0.70-0.98, P<0.001) and ACS (HR 0.83, 95%CI 0.75-0.92, P<0.001) patients (P-interaction=0.931). This benefit was mainly driven by a reduction in the risk of MI that was similar (P-interaction=0.898) for both subsets (HR_{CCS} 0.80, 95%CI 0.65-0.97; HR_{ACS} 0.79, 95%CI 0.70-0.89). In both CCS and ACS, we found a time-dependent treatment effect, with the benefit from DES accumulating during 1-year follow-up, without offsetting effects thereafter.

In conclusion, patients with CCS were slightly underrepresented in comparative clinical trials but benefit similar to ACS patients from new-generation DES instead of BMS with a sustained reduction of cardiac death or MI owing to lower event rates within 1-year.

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Keywords: Drug-eluting stents; Bare metal stents; Percutaneous coronary intervention; Chronic coronary syndrome; Acute coronary syndrome

Introduction

Myocardial revascularization with percutaneous coronary intervention (PCI) has an established role in the management of patients with coronary artery disease.[1] Although chronic (CCS) and acute coronary syndromes (ACS) encompass a broad spectrum of diseases, patients undergoing PCI remain at risk of recurrent ischemic events despite adherence to guideline-recommended secondary prevention therapies.[2,3] Prevention of stent-related failures, especially if leading to a new or recurrent myocardial infarction (MI) is central to improve the prognosis of patients undergoing PCI. This may be particularly relevant for patients with CCS in whom stent thrombosis or sudden coronary occlusion may make the prognosis of this more benign condition worse than that associated to the natural course of the disease if treated without revascularization.[4,5] In patients with CCS, contemporary, new-generation drug-eluting stents (DES) are recommended over bare-metal stents (BMS) mainly based on a lower risk of repeat revascularization procedures and, possibly, stent thrombosis.[6] Yet, it remains uncertain whether new-generation DES compared with BMS improve more prognostically relevant outcomes in patients with CCS. In fact, while there have been dedicated randomized trials comparing DES with BMS in patients with ACS,[7,8] evidence in CCS setting is more limited due to mixed patient populations enrolled in the remaining studies. The assessment of efficacy and safety of new-generation DES in CCS is also relevant in view of the findings of the International Study Of Comparative Health Effectiveness With Medical And Invasive Approaches (ISCHEMIA) trial, in which PCI with DES was the most common revascularization modality (about 60%) among patients assigned to invasive group.[9] The Coronary Stent Trialists' (CST) Collaboration gathered all randomized studies evaluating the safety and efficacy of new-generation DES vs. BMS and pre-specified to assess the consistency of treatment effects with respect to clinical presentation, which represents the focus of current analysis.

Methods

This study is an individual patient data (IPD) meta-analysis of randomized clinical trials comparing new-generation DES vs. BMS for PCI.[10] The search algorithm of the study and the assembled anonymized dataset are shown in the **web-appendix**. We included randomized trials comparing new-generation DES vs. BMS in patients undergoing PCI. New-generation DES were considered as any DES subsequent to the Cypher sirolimus-eluting stent (Cordis, Miami Lakes, Florida, USA) and the Taxus paclitaxel-eluting stent (Boston Scientific, Natick, Massachusetts, USA). We excluded trials that enrolled only patients with ACS in order to compare the risk estimates within each trial and minimize the risk of heterogeneity across studies influencing the results (ecological bias); patients with missing information on CAD status were also excluded.

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.

The prespecified primary outcome in this analysis was the composite of cardiac death or MI. Secondary outcomes included 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. Endpoint definitions are reported in the **web-appendix**.

Continuous variables were summarized by their means and standard deviation across all included patients. The two treatment groups were compared with ANOVA statistic stratified by trial. Categorical variables were summarized by the corresponding counts and percentages, and were compared with the Cochran-Mantel-Haenszel statistic stratified by trial.[11]

All outcomes were analyzed using time-to-event analysis and according to the intention-to-treat principle. 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. All analyses were performed according to the intention-to-treat principle and utilized IPD. For all analyses, the pooled risk estimates were expressed as hazard ratios (HRs) with 95% confidence intervals (CIs). For the primary analysis, we used a one-stage fixed-effect model by using Cox-regression analyses stratified by trial with robust estimator of variance. As secondary analysis, we used a two-stage random effects model and analyzed the data from each study independently, using a Cox-regression model and then combined the study-specific logarithms of the HR and the corresponding standard errors at the second stage, using the DerSimonian-Laird random effects model with Hartung-Knapp variance estimator.[10] Heterogeneity was calculated with the I^2 statistics. An interaction test was provided to evaluate the effect of treatment in patients with CCS vs. ACS as well as the treatment effect over time in the landmark analyses. All P values we calculated were based on 2-sided tests. A P-value less than 0.05 was considered significant for all analyses. We used Stata Statistical Software, release 14 (StataCorp LP, College Station, Texas)

Results

From the initial 26,616 participants, 4 trials (n=3,629) were excluded because enrolled only patients with ACS and 246 patients were excluded as information on presenting coronary syndrome was missing. Therefore, the final population consisted of 22,319 patients enrolled across 14 trials; 7,691 (34.5%) with CCS

and 14,628 (65.5%) with ACS. The **web-appendix** describes trial characteristics, patient populations, and the definitions used for outcomes (**Tables S1-S3**). Among patients with CCS, 4,047 (52.6%) were randomized to DES and 3,644 (47.4%) were randomized to BMS; whereas among those with ACS, 7,739 (52.9%) were randomized to DES and 6,889 (47.1%) were randomized to BMS. Baseline clinical characteristics were largely balanced between the two study groups (**Table 1**). In both clinical subsets, patients randomized to BMS tended to receive stents with larger diameters and shorter lengths. The majority of patients received thin-struts stents; yet DES-treated patients received more frequently thick-strut stents as compared with those allocated to BMS in both clinical subsets. Duration of dual antiplatelet therapy was longer (on average 50-60 days) in patients randomized to DES in both CCS and ACS groups. The mean (±standard deviation) follow-up time was 2.9±1.8 years (median, 2.1; interquartile range, 1.9 to 4.9). Supplementary **Table S4** 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 two trials (**Table S4**).

There was no evidence of interaction (P=0.931) between randomized treatment (DES vs. BMS) and type of clinical presentation (CCS vs. ACS) during long-term follow-up with respect to the primary outcome of cardiac death or MI (**Figure 1**). Kaplan-Meier curves for the primary outcome and its components are shown in **Figure 2**. DES were associated with a significantly lower risk of cardiac death or MI in both CCS (HR 0.83, 95%CI 0.70-0.98, P<0.001) and ACS patients (HR 0.83, 95%CI 0.75-0.92, P<0.001). For the individual components of the primary outcome, there was no difference in terms of cardiac death in CCS (HR 0.95, 95%CI 0.73-1.23) or ACS groups (HR 0.93, 95%CI 0.78-1.10; P-interaction=0.859), whereas the risk of MI was similarly reduced by DES in both CCS (HR 0.80, 95%CI 0.65-0.97) and ACS patients (HR 0.79, 95%CI 0.70-0.89; P-interaction=0.898). Kaplan-Meier curves for secondary outcomes are shown in **Figure 3.** Compared with BMS, DES were associated with reduced risk of TVR in patients with CCS (HR 0.52, 95%CI 0.45-0.61) and in those with ACS (HR 0.55, 95%CI 0.49-0.62). The risk of definite stent thrombosis was consistently reduced (P-interaction=0.772) with DES in CCS (HR 0.65, 95%CI 0.37-1.12) and ACS (HR 0.63, 95%CI 0.45-0.88) patients. Risk estimates for primary and secondary outcomes at 5- and 1-year of follow-up were consistent with those observed at time of maximum follow-up (**Table 2**). In the 1-year landmark analysis (**Table 3**), we found significant heterogeneity for the primary outcome with respect to DES vs. BMS in both CCS (P-interaction=0.007) and ACS (P-interaction<0.001) groups. Compared with BMS, DES were associated with reduced risk of cardiac death or MI at 1-year follow-up in both clinical subsets, but not thereafter. A similar signal of heterogeneity was present for MI and TVR endpoints. In the sensitivity analysis with two landmark

timepoints, DES in CCS patients were associated with reduced risks of primary outcome (HR 0.65, 95%CI 0.50-0.85), MI (HR 0.54, 95%CI 0.39-0.76) and TVR (HR 0.35, 95%CI 0.28-0.43) from 1- to 12-months. (**Table S5**). Risk estimates by using two-stage random effects model were consistent to the main analysis using a one-stage approach (**Table S6**). We did not find clinically relevant heterogeneity between trials in both CCS and ACS groups (**Table S6**).

Discussion

Using the totality of available evidence from randomized trials comparing new-generation DES with BMS, our collaborative IPD analysis provides strong evidence that DES reduce the risk of cardiac death or MI compared with BMS in patients with CCS. The observed treatment effect in the CCS population was similar to that observed in patients with ACS, who represented the majority of included patients. There is also robust evidence that DES compared with BMS decrease the risk of MI and TVR in patients with CCS. The time-dependency of treatment effect of DES vs. BMS was not influenced by type of coronary syndrome (CCS vs. ACS), suggesting strong benefits with DES within the first year and substantial equipoise thereafter in both chronic and acute populations.

While coronary artery bypass grafting has been shown to improve survival compared with medical therapy in patients with CCS, a survival benefit has not been yet demonstrated for patients undergoing PCI in any individual trial. However, a network meta-analysis of 100 trials in 93,553 patients with 262,090 patient years of follow-up, demonstrated that newer generation DES, but not early-generation DES, BMS or balloon angioplasty were associated to a potential survival benefit in CCS as compared to medical therapy.[12]

In the COURAGE (Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation) trial, PCI did not reduce the primary endpoint of all-cause death or MI compared with medical therapy in patients with CCS at a mean follow-up of 4.6 years.[13] Also, no difference between PCI and medical therapy was noted for spontaneous MI or hospitalization for ACS. It is noteworthy that DES in the COURAGE were implanted in less than 3% of patients in the PCI arm and that 50% of PCI-patients requiring a second angiogram throughout follow-up had in-stent restenosis.[14] By contrast, roughly 70% of patients randomized to medical therapy having a new angiogram presented, as index lesion, an untreated stenosis ≥50%. The only angiographic predictor of MI in the COURAGE was the number of lesions originally ≥50% that had not been revascularized.[14] These data suggest that addressing flow-limiting stenoses in CCS with PCI may prevent MI events as long as stent failures are minimized. When stent-related events, such as TVR and stent thrombosis, occur at higher rates, the benefit derived from revascularization is overridden by the clinical sequelae

associated with stent failures. In fact, stent thrombosis is clinically manifest as MI (or death) and a remarkable proportion of patients with in-stent restenosis, up to one third, has an ACS at hospital admission. This concept is supported by the results of the FAME (Fractional Flow Reserve versus Angiography for Multivessel Evaluation) II trial that combined a PCI strategy based on new-generation DES with a fractional flow reserve (FFR) guided management. At 5 years, the initial FFR-guided PCI strategy was associated with a significantly lower rate of the primary composite endpoint of death, MI, or urgent revascularization than medical therapy alone.[15] Further, when the initial penalty period, represented by peri-procedural events occurring during first 7 days, was censored, PCI was associated with a consistent benefit in terms of MI from 8 days to 3 years (66% relative risk reduction) and from 3 to 5 years (40% relative risk reduction).[15] The ISCHEMIA trial did not show a benefit from an invasive strategy for the primary endpoint of cardiovascular death, MI, hospitalization for unstable angina, heart failure or resuscitated cardiac arrest compared with a conservative treatment strategy.[9] Yet, the rates of spontaneous MI were lower and quality of life improved among patients randomized to the experimental arm, in whom the use of new-generation DES for PCI patients was recommended.[16]

Although the present study does not support *per se* the role of PCI in patients with CCS, its findings highlight the impact of progress in stent technology on clinical outcomes in CCS setting. New-generation DES were developed featuring thinner struts, novel durable or biodegradable polymer coatings, and different antiproliferative agents at lower dosages.[17] Newer devices successfully addressed the problem of restenosis inherent to BMS, due to potent suppression of neointimal hyperplasia, and the delayed healing response of the stented coronary vessel following to early-generation DES implantation. In our analysis, the relative hazard for TVR was almost halved by DES compared with BMS and this robust effect is relevant given a higher absolute event rate in CCS compared with ACS. Even more importantly, there was a 20% relative risk reduction for MI with DES that was consistent in both CCS and ACS groups. There is evidence showing that restenosis after coronary stenting is associated with a higher risk of mortality in patients undergoing angiographic surveillance;[18] and even elective and uncomplicated revascularization in the target-vessel is associated with an increased risk of mortality, partly explained by a higher risk of MI following repeat revascularization.[19] The large reduction in restenosis attainable with new-generation DES in CCS might also underpin the more durable results in terms of quality of life and angina observed in newer (FAME II and ISCHEMIA) vs. older trials (COURAGE) in CCS setting.[9,15,16,20]

Our previous study, including more than 26,000 patients undergoing PCI, showed a reduced risk of definite stent thrombosis among patients randomized to DES.[10] Although the point estimate for the hazard of stent thrombosis was similar between the main PCI population and CCS patients (0.63 vs. 0.65), the relatively

small numbers of stent thrombosis in patients with CCS (22 vs. 29 cases in DES and BMS, respectively) may have contributed to the imprecision of risk estimates with wide 95% confidence intervals. Conversely, in the inflammatory milieu of ACS lesions where the event rate is more frequent, DES significantly reduced stent thrombosis by maintaining a similar hazard (0.63).

Limitations of our study should be noted. First, the study has limitations inherent in patient-level, pooled analyses reflecting the shortcomings of the original studies. Second, a mixture of new-generation DES was used in the experimental arm, even though the majority of patients received a limited number of DES, as previously shown.[10] Third, we investigated the effect of DES vs. BMS at the maximum follow-up of 6 years; nevertheless, the mean follow-up of the study was about 3 years. Whether differences between DES and BMS exist in the very late follow-up remains unaddressed by this study. Fourth, although we presented risk estimates for ACS patients, the study was planned to evaluate the role of DES compared with BMS in CCS. ACS population mainly served as subgroup to test the within-trial interaction between DES and BMS vs. type of clinical presentation. Consequently, in order to minimize ecological bias and avoid across trial interaction, we excluded trials that included solely patients with ACS.[21] Finally, BMS no longer represent standard practice for patients undergoing PCI. Nonetheless, the study is significant because it highlights the performance of new-generation DES, which are currently recommended by societal guidelines for PCI.

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 with CCS is associated with a sustained reduction in the risk of cardiac death or myocardial infarction, with time-dependent treatment effect consisting of a lower risk of the composite endpoint matured over the first year, without tradeoff between efficacy and safety during the subsequent years.

Figure Legend

Figure 1. Effect of drug-eluting stents (DES) vs. bare-metal stents (BMS) at maximum follow-up by clinical presentation at the time of percutaneous coronary intervention. HR: hazard ratio. TVR: target-vessel revascularization.

Figure 2. Primary outcome of cardiac death or myocardial infarction and its components in patients with chronic vs. acute coronary syndrome randomized to new-generation drug-eluting stents or bare-metal stents. ACS: acute coronary syndrome. CCS: chronic coronary syndrome. MI: myocardial infarction.

Figure 3. Secondary outcomes in patients with chronic vs. acute coronary syndrome randomized to new-generation drug-eluting stents or bare-metal stents. ACS: acute coronary syndrome. CCS: chronic coronary syndrome. ST: stent thrombosis.

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Table 1. Baseline characteristics stratified by type of coronary syndrome and randomization.

	Chronic Coronary Syndrome (n=7,691)			Acute Coronary Syndrome (n=14,628)		
	DES (N=4,047)	**BMS (N=3,644)**	**P-value**	**DES (N=7,739)**	**BMS (N=6,889)**	**P-value**
Age (years)	67.8±11.3	68.3±11.3	0.320	65.9±12.6	66.5±2.7	0.636
Men	2916 (72.1%)	2661 (73.0%)	0.344	5777 (74.6%)	5013 (72.8%)	0.017
Smoker	746 (18.8%)	686 (19.3%)	0.056	2520 (34.0%)	2197 (33.3%)	0.879
Hypertension	2803 (69.4%)	2492 (68.6%)	0.571	4276 (55.5%)	3790 (55.3%)	0.298
Hyperlipidemia	2849 (70.7%)	2547 (70.2%)	0.737	4003 (52.3%)	3574 (52.4%)	0.822
Diabetes mellitus	920 (22.8%)	787 (21.6%)	0.367	1414 (18.3%)	1228 (17.9%)	0.241
Insulin-treated	132 (16.7%)	120 (17.4%)	0.417	269 (24.6%)	208 (23.0%)	0.455
Previous MI	894 (22.2%)	824 (22.7%)	0.700	1043 (13.5%)	996 (14.5%)	0.283
Previous PCI	822 (28.3%)	776 (30.8%)	0.128	867 (18.2%)	859 (21.6%)	0.788
Previous CABG	423 (10.5%)	483 (13.3%)	0.376	437 (5.6%)	476 (6.9%)	0.940
Indication to PCI						
Chronic coronary syndrome	4047 (100%)	3644 (100%)		-	-	
Unstable angina pectoris	-	-		1833 (23.7%)	1730 (25.1%)	0.573
Non-ST-elevation MI	-	-		3245 (42.0%)	2924 (42.5%)	0.439
ST-elevation MI	-	-		2404 (31.1%)	1973 (28.7%)	0.679
Gp IIb/IIIa receptor inhibitors	157(4.9%)	128 (4.4%)	0.907	1762 (24.4%)	1477 (23.0%)	0.884
Multivessel coronary disease	1805 (44.6%)	1556 (42.7%)	0.591	3444 (44.5%)	2946 (42.8%)	0.450
Implanted stents (numbers)	1.6±1.0	1.6±1.0	0.244	1.7±1.0	1.7±1.1	0.266
Total stent length (mm)	27.2±19.2	25.6±17.3	<0.001	28.8±20.4	27.6±19.7	<0.001
Mean stent diameter (mm)	3.2±0.5	3.2±0.6	0.008	3.3±0.5	3.3±0.6	0.001
Overlapping stent	552 (14.9%)	467 (14.1%)	0.104	1403 (18.8%)	1316 (19.9%)	0.873
Number of stented segments			0.572			0.202
0	1 (0.0%)	0 (0.0%)		4 (0.1%)	5 (0.1%)	
1	2926 (72.4%)	2664 (73.2%)		5434 (70.3%)	4840 (70.4%)	

2	812 (20.1%)	729 (20.0%)		1663 (21.5%)	1508 (21.9%)	
3	227 (5.6%)	189 (5.2%)		477 (6.2%)	384 (5.6%)	
4	58 (1.4%)	40 (1.1%)		121 (1.6%)	97 (1.4%)	
5	13 (0.3%)	14 (0.4%)		26 (0.3%)	38 (0.6%)	
6	3 (0.1%)	1		6 (0.1%)	4 (0.1%)	
7	2 (0.0%)	1		1	0	
Target coronary artery						
Left main	361(9.0%)	228(6.3%)	0.950	640 (8.3%)	349 (5.1%)	0.468
Left anterior descending	1850 (45.9%)	1662 (45.8%)	0.949	3580 (46.6%)	3286 (47.9%)	0.469
Left circumflex	1229 (30.5%)	1028 (28.4%)	0.517	2393 (31.1%)	2020 (29.5%)	0.482
Right coronary	1417 (35.2%)	1195 (33.0%)	0.025	2910 (37.9%)	2662 (38.8%)	0.869
Thin-strut stent (<100 μm)	3198 (79.2%)	3175 (87.3%)	<0.001	6371 (82.5%)	6115 (88.9%)	<0.001
Type of $P2Y_{12}$ receptor inhibitor			0.851			0.683
None	0	0		0	0	
Clopidogrel	2941 (84.2%)	2897 (90.2%)		6333 (85.6%)	6045 (91.7%)	
Ticagrelor	9 (0.3%)	9 (0.3%)		54 (0.7%)	45 (0.7%)	
Prasugrel	544 (15.6%)	304(9.5%)		1009 (13.6%)	504 (7.6%)	
Duration of DAPT (days)	253.7±194.6	192.1±166.4	<0.001	n=7333, 297.3±171.7	n=6506, 254.7±173.4	<0.001

BMS: bare-metal stents. CABG: coronary artery bypass grafting; DAPT: dual antiplatelet therapy; DES: drug-eluting stents Gp: glycoprotein; MI: myocardial infarction.

Table 2. Clinical outcomes at 1- and 5-year follow-up stratified by type of coronary syndrome and randomization.

Variable	Chronic Coronary Syndrome (n=7,691)				Acute Coronary Syndrome (n=14,628)				P-value for interaction
	DES (N=4,047)	BMS (N=3,644)	HR (95% CI)	P-value	DES (N=7,739)	BMS (N=6,889)	HR (95% CI)	P-value	
1-year follow-up									
Cardiac death or MI	198 (4.95%)	246 (6.82%)	0.67 (0.54-0.85)	0.001	535 (6.97%)	636 (9.31%)	0.70 (0.61-0.80)	<0.001	0.881
All-cause death	110 (2.76%)	102 (2.83%)	1.05 (0.80-1.38)	0.715	311 (4.04%)	315 (4.59%)	0.92 (0.78-1.09)	0.331	0.472
Cardiac death	61 (1.54%)	69 (1.92%)	0.84 (0.59-1.20)	0.348	184 (2.40%)	208 (3.05%)	0.83 (0.68-1.03)	0.084	0.942
Myocardial infarction	152 (3.80%)	196 (5.44%)	0.58 (0.44-0.77)	<0.001	403 (5.26%)	499 (7.35%)	0.63 (0.54-0.74)	<0.001	0.729
TVR	171 (4.32%)	377 (10.55%)	0.40 (0.33-0.48)	<0.001	283 (3.74%)	529 (7.89%)	0.44 (0.38-0.51)	<0.001	0.582
Definite stent thrombosis	16 (0.40%)	23 (0.64%)	0.62 (0.32-1.18)	0.143	46 (0.60%)	74 (1.09%)	0.51 (0.34-0.76)	0.001	0.526
5-year follow-up									
Cardiac death or MI	325 (11.03%)	351 (11.73%)	0.83 (0.70-0.99)	0.038	831 (13.77%)	892 (15.99%)	0.82 (0.74-0.91)	<0.001	0.827
All-cause death	255 (8.97%)	235 (9.43%)	1.04 (0.87-1.25)	0.654	594 (10.51%)	559 (10.80%)	0.99 (0.88-1.12)	0.923	0.746
Cardiac death	116 (3.87%)	112 (3.88%)	0.96 (0.74-1.25)	0.775	281 (4.57%)	278 (4.77%)	0.94 (0.79-1.12)	0.497	0.854
Myocardial infarction	250 (8.83%)	274 (9.24%)	0.80 (0.65-0.98)	0.031	651 (11.26%)	723 (13.53%)	0.78 (0.69-0.88)	<0.001	0.777
TVR	279 (9.16%)	479 (15.26%)	0.51 (0.44-0.60)	<0.001	464 (7.93%)	718 (12.43%)	0.54 (0.48-0.61)	<0.001	0.692
Definite stent thrombosis	21 (0.59%)	28 (0.89%)	0.63 (0.36-1.11)	0.11	66 (1.06%)	91 (1.49%)	0.62 (0.44-0.88)	0.006	0.787

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

Table 3. Landmark analysis at 1-year follow-up.

Variable	Chronic Coronary Syndrome (n=7,691)					Acute Coronary Syndrome (n=14,628)					P-inter between subgroups
	DES (N=4,047)	BMS (N=3,644)	HR (95%CI)	P-value	P-interaction	DES (N=7,739)	BMS (N=6,889)	HR (95%CI)	P-value	P-interaction	
Cardiac death or MI											
from 0 to 365 days	198 (4.95%)	246 (6.82%)	0.67 (0.54-0.85)	0.001	0.007	535 (6.97%)	636 (9.31%)	0.70 (0.61-0.80)	<0.001	<0.001	0.881
>365 days	137 (8.86%)	118 (9.94%)	1.06 (0.83-1.36)	0.642		312 (9.32%)	269 (9.34%)	1.07 (0.91-1.26)	0.431		0.927
All-cause death											
from 0 to 365 days	110 (2.76%)	102 (2.83%)	1.05 (0.80-1.38)	0.715	1.00	311 (4.04%)	315 (4.59%)	0.92 (0.78-1.09)	0.331	0.244	0.472
>365 days	154 (8.19%)	140 (8.39%)	1.05 (0.83-1.32)	0.700		292 (7.67%)	259 (8.12%)	1.06 (0.89-1.25)	0.530		0.903
Cardiac death											
from 0 to 365 days	61 (1.54%)	69 (1.92%)	0.84 (0.59-1.20)	0.348	0.33	184 (2.40%)	208 (3.05%)	0.83 (0.68-1.03)	0.084	0.079	0.942
>365 days	58 (2.93%)	48 (3.24%)	1.09 (0.74-1.60)	0.669		98 (2.30%)	76 (2.60%)	1.16 (0.85-1.58)	0.343		0.798
Myocardial infarction											
from 0 to 365 days	152 (3.80%)	196 (5.44%)	0.58 (0.44-0.77)	<0.001	0.001	403 (5.26%)	499 (7.35%)	0.63 (0.54-0.74)	<0.001	<0.001	0.729
>365 days	108 (7.73%)	91 (8.74%)	1.10 (0.83-1.45)	0.511		264 (8.36%)	236 (8.57%)	1.04 (0.87-1.24)	0.650		0.808
TVR											
from 0 to 365 days	171 (4.32%)	377 (10.55%)	0.40 (0.33-0.48)	<0.001	<0.001	283 (3.74%)	529 (7.89%)	0.44 (0.38-0.51)	<0.001	<0.001	0.582
>365 days	115 (6.63%)	106 (7.82%)	0.94 (0.72-1.22)	0.653		190 (5.45%)	197 (6.32%)	0.84 (0.69-1.03)	0.093		0.520
Definite stent thrombosis											
from 0 to 365 days	16 (0.40%)	23 (0.64%)	0.62 (0.32-1.18)	0.143	0.759	46 (0.60%)	74 (1.09%)	0.51 (0.34-0.76)	0.001	0.050	0.526
>365 days	6 (0.37%)	6 (0.46%)	0.75 (0.27-2.10)	0.581		21 (0.54%)	18 (0.49%)	1.08 (0.57-2.02)	0.820		0.689

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

Figure 1. Effect of drug-eluting stents (DES) vs. bare-metal stents (BMS) at maximum follow-up by clinical presentation at the time of percutaneous coronary intervention.

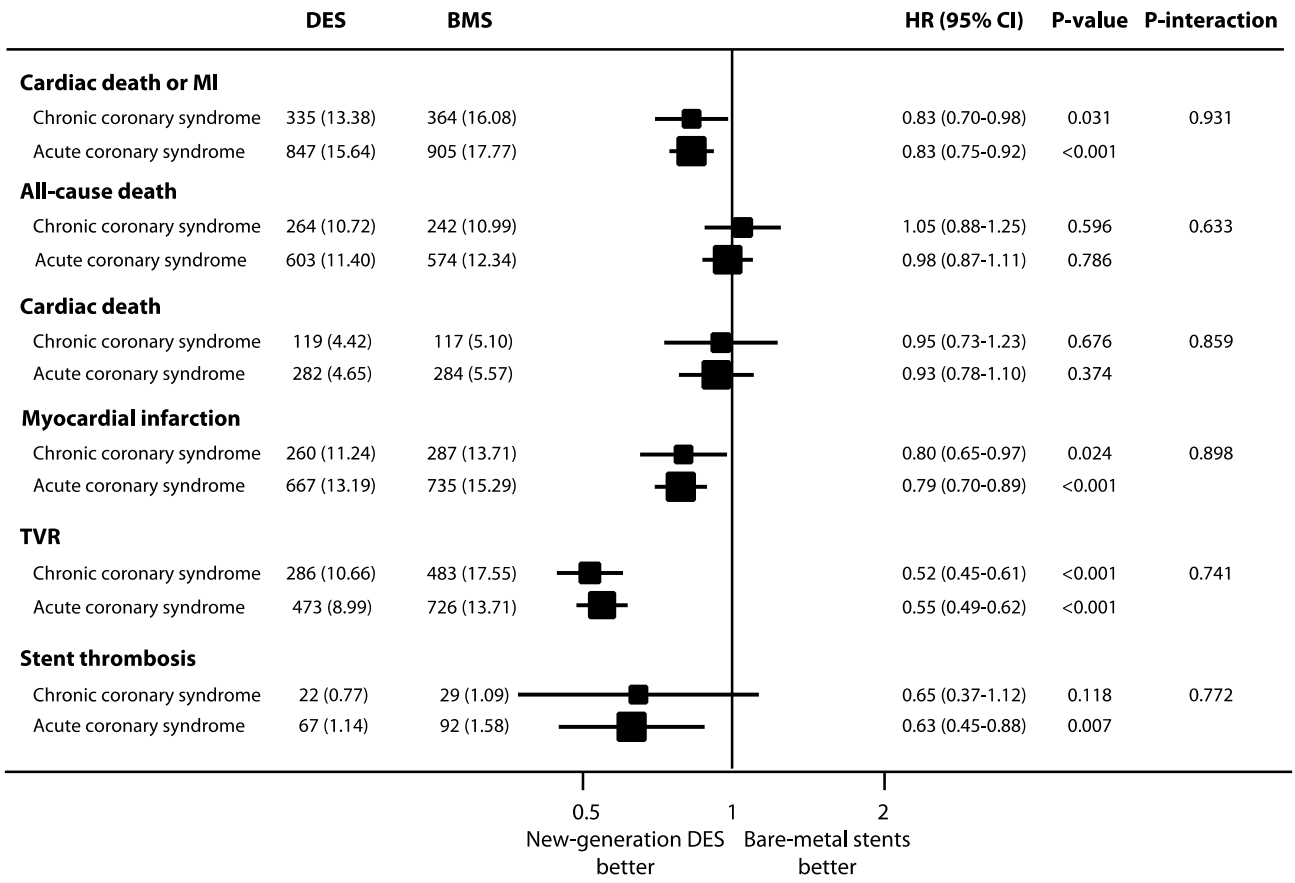


Figure 2

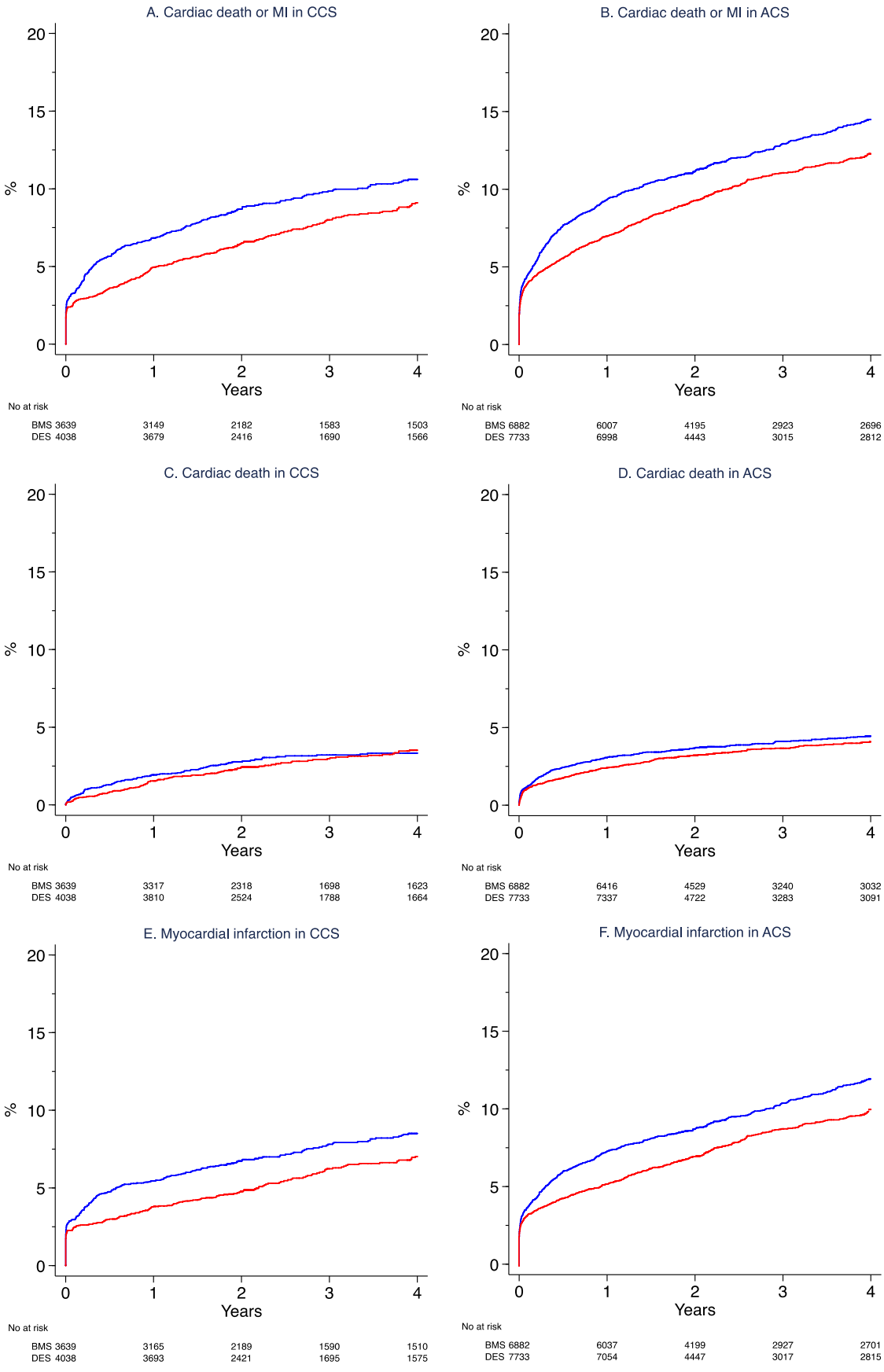
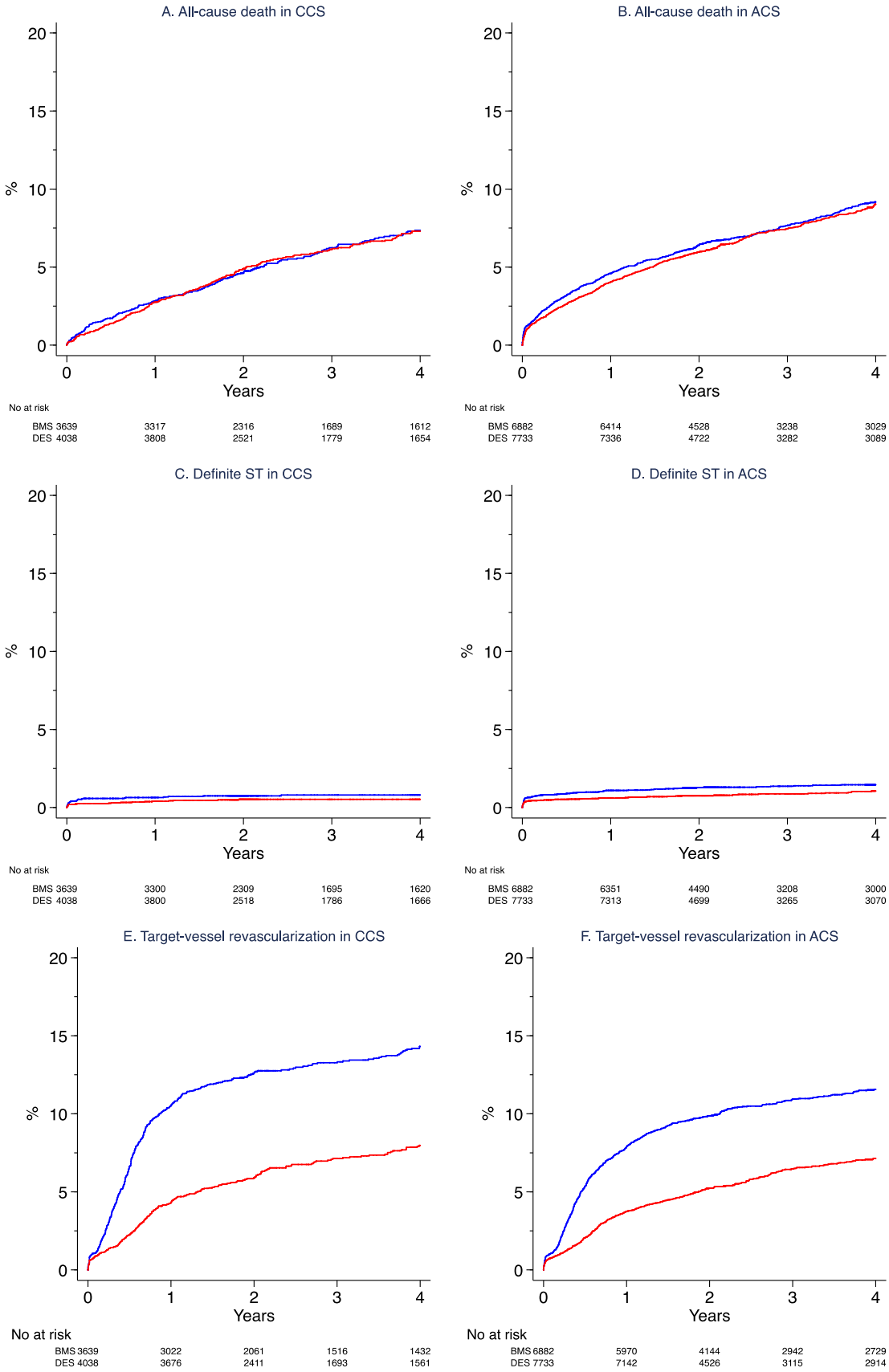

A. Cardiac death or MI in CCS
B. Cardiac death or MI in ACS
C. Cardiac death in CCS
D. Cardiac death in ACS
E. Myocardial infarction in CCS
F. Myocardial infarction in ACS
%
Years
No at risk
BMS 3639 3149 2182 1583 1503
DES 4038 3679 2416 1690 1566
BMS 6882 6007 4195 2923 2696
DES 7733 6998 4443 3015 2812
BMS 3639 3317 2318 1698 1623
DES 4038 3810 2524 1788 1664
BMS 6882 6416 4529 3240 3032
DES 7733 7337 4722 3283 3091
BMS 3639 3165 2189 1590 1510
DES 4038 3693 2421 1695 1575
BMS 6882 6037 4199 2927 2701
DES 7733 7054 4447 3017 2815

Figure 3


A. All-cause death in CCS
B. All-cause death in ACS
C. Definite ST in CCS
D. Definite ST in ACS
E. Target-vessel revascularization in CCS
F. Target-vessel revascularization in ACS
%
Years
No at risk
BMS 3639 3317 2316 1689 1612
DES 4038 3808 2521 1779 1654
BMS 6882 6414 4528 3238 3029
DES 7733 7336 4722 3282 3089
BMS 3639 3300 2309 1695 1620
DES 4038 3800 2518 1786 1666
BMS 6882 6351 4490 3208 3000
DES 7733 7313 4699 3265 3070
BMS 3639 3022 2061 1516 1432
DES 4038 3676 2411 1693 1561
BMS 6882 5970 4144 2942 2729
DES 7733 7142 4526 3115 2914