Drug-eluting stents versus bare-metal stents in saphenous vein grafts: a double-blind, randomised trial

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Summary

Background—Few studies have examined the efficacy of drug-eluting stents (DES) for reducing aortocoronary saphenous vein bypass graft (SVG) failure compared with bare-metal stents (BMS) in patients undergoing stenting of de-novo SVG lesions. We assessed the risks and benefits of the use of DES versus BMS in de-novo SVG lesions.

Methods—Patients were recruited to our double-blind, randomised controlled trial from 25 US Department of Veterans Affairs centres. Eligible participants were aged at least 18 years and had at least one significant de-novo SVG lesion (50–99% stenosis of a 2·25–4·5 mm diameter SVG) requiring percutaneous coronary intervention with intent to use embolic protection devices. Enrolled patients were randomly assigned, in a 1:1 ratio, by phone randomisation system to receive a DES or BMS. Randomisation was stratified by presence or absence of diabetes and number of target SVG lesions requiring percutaneous coronary intervention (one or two or more) within each participating site by use of an adaptive scheme intended to balance the two stent type groups on marginal totals for the stratification factors. Patients, referring physicians, study coordinators, and outcome assessors were masked to group allocation. The primary endpoint was the 12-month incidence of target vessel failure, defined as the composite of cardiac death, target vessel myocardial infarction, or target vessel revascularisation. The DIVA trial is registered with ClinicalTrials.gov, number NCT01121224.

Findings—Between Jan 1, 2012, and Dec 31, 2015, 599 patients were randomly assigned to the stent groups, and the data for 597 patients were used. The patients' mean age was 68·6 (SD 7·6) years, and 595 (>99%) patients were men. The two stent groups were similar for most baseline characteristics. At 12 months, the incidence of target vessel failure was 17% (51 of 292) in the DES group versus 19% (58 of 305) in the BMS group (adjusted hazard ratio 0·92, 95% CI 0·63–1·34, p=0·70). Between-group differences in the components of the primary endpoint, serious

adverse events, or stent thrombosis were not significant. Enrolment was stopped before the revised target sample size of 762 patients was reached.

Interpretation—In patients undergoing stenting of de-novo SVG lesions, no significant differences in outcomes between those receiving DES and BMS during 12 months of follow-up were found. The study results have important economic implications in countries with high DES prices such as the USA, because they suggest that the lower-cost BMS can be used in SVG lesions without compromising either safety or efficacy.

Introduction

Coronary artery bypass graft (CABG) surgery is one of the most common surgical procedures in the USA and Europe, with an estimated 400 000 CABG surgeries done in the USA during 2010.[1] Patients who undergo CABG often develop bypass graft failure, especially in saphenous vein grafts (SVGs).[2–5] Approximately one in five patients undergoing percutaneous coronary intervention (PCI) in the USA has had previous CABG, and 6% of all PCIs in the USA are done in SVGs.[4,6] Stents are the current standard of care for PCI. Although drug-eluting stents (DES) improve outcomes compared with bare-metal stents (BMS) in native coronary artery lesions,[7] their efficacy and safety in SVG lesions has received little study.[8–13] Four randomised studies have been done with conflicting results (three studies showed benefit with DES[11–13] and one showed harm[9]). These studies were limited by small size,[9,11,13] absence of blinding,[11–13] routine angiographic follow-up,[9,11,12] low use of embolic protection devices[12] and use of first-generation DES.[9,11–13]

We, therefore, examined the risks and benefits of DES versus BMS in SVGs in a prospective, double-blind, randomised trial.

Methods

Study design and participants

The DIVA trial[14] was a multicentre, randomised, double-blind controlled trial done at 25 US Department of Veterans Affairs centres. The DIVA trial study design has been published.[14] A planning committee and an executive committee designed the study, managed the study conduct and data collection, and made the decision to submit the manuscript for publication. The trial was approved by the Department of Veterans Affairs Central Institutional Review Board, and each participating site's Research and Development Committee.

Patients with previous CABG undergoing cardiac catheterisation at participating sites were evaluated for enrolment. Eligible patients were aged at least 18 years, had at least one significant de-novo SVG lesion (50–99% stenosis of a 2·25–4·5 mm diameter SVG) requiring PCI with intent to use embolic protection devices, and agreed to participate and take medication as prescribed. Patients were excluded if they had planned non-cardiac surgery within 12 months of screening; presented with ST-segment elevation acute myocardial infarction; had a target SVG that was the last remaining vessel or was a left main equivalent; had any previous percutaneous treatment of the target vessel within the previous 12 months; had haemorrhagic diatheses, or refused to receive blood transfusions; required warfarin administration for the following 12 months and were considered to be at high risk

of bleeding with triple anticoagulation/antiplatelet therapy; had recent positive pregnancy test, breast feeding, or possibility of a future pregnancy; had coexisting conditions that limited life expectancy to less than 12 months; had a history of allergic reaction or significant sensitivity to any drug or metal included in DES; were allergic to clopidogrel and did not present with acute coronary syndrome at sites that use blinded study medication; or were already participating in another interventional randomised trial. All patients provided written informed consent.

Randomisation and masking

Enrolled patients were randomly assigned, by phone randomisation system in a 1:1 ratio, to receive DES or BMS in the target SVGs. Each patient received as many stents as clinically indicated on the basis of operator judgment. Randomisation was stratified by presence or absence of diabetes and number of target SVG lesions requiring PCI (one *vs* two or more lesions) within each participating site by use of an adaptive scheme intended to balance the two stent-type groups on marginal totals for the stratification factors.

The cardiac interventionalist was not masked to the group assignment, but patients, referring physicians, primary study coordinators, and outcome assessors (clinical events committee and angiographic and intravascular ultrasonography core laboratories), were masked to group allocation. An independent clinical events committee adjudicated possible target vessel failure events (all deaths, myocardial infarctions not reported as non-target vessel, and target vessel revascularisations), reported by the sites that occurred during the first 12 months of follow-up. In addition, the study's angiographic and electro cardio graphic core laboratories reviewed the angiograms and electrocardiographs in a blinded manner to verify that events reported by the sites as definite stent thrombosis met the definition used in DIVA. Counts for all other event types are based on cases reported by the sites.

To preserve the study blinding, at sites where standard of care was to treat patients receiving BMS with 1 month of a P2Y12 inhibitor, patients who did not present with an acute coronary syndrome and who did not require at least 12 months of P2Y12 inhibitor for clinical reasons were given clopidogrel or matching placebo after the first month for another 11 months.

Procedures

Stents used in the trial were commercially available in clinical practice during the study period. Operators were allowed to use the DES or BMS of their choice. PCI was done with standard techniques, at the discretion of each operator. In patients with multiple lesions, the same type of stent was used for all lesions whenever possible. All patients were prescribed aspirin as per standard of care.

Patients were followed up every 3 months during the first year and every 6 months thereafter. Quality-of-life questionnaires were administered by the study coordinators at baseline and 1, 6, 12, 18, and 24 months.

Outcomes

The primary endpoint was the 12-month incidence of target vessel failure, defined as the composite of cardiac death, target vessel myocardial infarction, or target vessel revascularisation. All events that were part of the primary endpoint were centrally assessed. Periprocedural myocardial infarction was not included in the primary endpoint. Secondary endpoints included procedural success and complications; all-cause death and cardiac death; follow-up myocardial infarction;[15] stent thrombosis;[16] target lesion revascularisation; non-target vessel revascularisation; the composite endpoint of any death, any myocardial infarction, or target vessel revascularisation (patient-oriented composite endpoint); the composite endpoint of cardiac death, target vessel myocardial infarction, or target lesion revascularisation (device-oriented composite endpoint for target lesion failure);[16] stroke; and incremental cost-effectiveness of DES relative to BMS (not included in this manuscript). The definitions of the study endpoints were published in the DIVA design paper.[14] Adverse events that were part of the primary endpoint were adjudicated by a clinical events committee.

Statistical analysis

We estimated a sample size of 519 participants at 25 sites would provide 123 participants with a primary outcome (12-month target vessel failure) and 90% power for detection of the difference between the two groups, assuming a 12-month target vessel failure rate of 30% in BMS and 18% in DES (corresponding hazard ratio [HR] 0·556).[9,10,17,18] Because of a lower than anticipated overall target vessel failure rate of 16% after 384 randomisations, the sample size was increased to 762 to provide 86% power to detect a group difference on the basis of 122 participants with target vessel failure, an overall target vessel failure rate of 16%, and 40% relative reduction for the DES group (corresponding HR 0·573). Two interim analyses were planned, at approximately 25% and 60% of target-adjudicated primary outcomes, to allow early stopping for efficacy (on the basis of O'Brien-Fleming boundary) or futility (on the basis of conditional power).

The analyses for all outcomes followed the intention-to-treat principle. The primary analysis was the comparison of time to first target vessel failure between the DES and BMS groups in the initial 12 months following index stent implantation. Cumulative incidence curves for time to target vessel failure were calculated by stent group. Participants lost to follow-up were censored at the time of last contact. Log-rank tests were used to compare the time to target vessel failure. This test was stratified by presence or absence of diabetes and by number of target SVG lesions requiring percutaneous coronary intervention (one *vs* more than one). Additionally, the Cox proportional hazards model[19] was used to assess the effect of stent type and various covariates on time to target vessel failure. Participant and graft characteristics thought to be potentially predictive of SVG patency, including diabetes, number of target SVG lesions (one or more than one), reference vessel diameter, stent length, the SVG recipient vessel (left anterior descending artery, circumflex, right coronary artery), lesion location (aorto-ostial, body, distal anastomotic), and baseline thrombolysis in myocardial infarction flow (three *vs* less than three), were first entered into the regression model. Stent assignment (DES *vs* BMS) was then added to the model to see if it was a statistically significant predictor of target vessel failure above and beyond the participant-

graft characteristics. Interaction terms between stent type and other significant participant graft characteristics were also assessed. Potential time-varying stent effects were assessed by plotting the scaled Schoenfeld residuals against time with the Grambsch and Therneau test. [20] We also assessed piecewise constant HRs for the time period up to 1 year of follow-up (the interval for the primary endpoint) versus after 1 year. A two-sided p value of 0·05 from the stratified log-rank test was used as the level of significance for the primary outcome. As a preplanned secondary analysis, we did similar analyses as above to compare time to target vessel failure on the basis of all follow-up data.

The procedural success rate and the incidence of postprocedural myocardial infarction and postprocedural GUSTO moderate or severe bleeding[21,22] were compared between the DES and BMS groups by the difference between two independent proportions. Cumulative incidence curves and stratified log-rank tests were used to compare the two stent groups on the incidence of the secondary clinical outcomes listed above. When appropriate, competing risks analyses with plots of cumulative incidence curves and comparisons of cumulative incidences with Gray's test[23] and Fine and Gray's[24] methods were done. Proportional hazards regression for subdistributions of competing risks were also done. SAS 9.2 (TS2M3; SAS Institute, Cary, NC, USA) and R version 3.4.4 were used for the analyses.

The DIVA trial is registered with ClinicalTrials.gov, number NCT01121224.

Role of the funding source

The funder was involved in study design, data collection, site monitoring, data analysis, data interpretation, and writing of the report, but did not influence the interpretation of the trial results nor the decision to submit the paper for publication. Members of the executive committee had full access to all the data in the study. The corresponding author had final responsibility for the decision to submit for publication.

Results

Between Jan 1, 2012, and Dec 31, 2015, 3482 patients with previous CABG undergoing cardiac catheterisation at the participating centres were screened for participation in the trial, and 597 (17%) patients were randomly assigned to either the BMS or DES group and were included in the final analysis (figure 1). The first interim analysis was done on Oct 13, 2015, when there were 35 adjudicated primary outcomes (29% information time); at that time, 576 participants had been randomly assigned. The data monitoring committee recommended the study continue. Trial enrolment was terminated on Dec 31, 2015, because of slower than expected enrolment and funding issues; the final number of randomisations was 599. No additional interim analysis was done. We only report data for 597 patients because the consent process was done improperly for two patients. Study follow-up ended on Dec 31, 2016. The minimum length of follow-up was 1 year and the maximum was 5 years. The study with 109 adjudicated primary outcomes has 86% post-hoc power to detect the originally hypothesised HR of 0·556 and 83% power to detect the revised hypothesised HR of 0·573.

The study groups were well balanced for most clinical and angiographic characteristics (table 1), except for SVG age and race categories. During the index procedure, 77 (13%) of 597 patients had one target SVG with multiple SVG lesions treated, 23 (4%) had multiple SVGs treated, and 95 (16%) had native coronary artery lesions treated. An embolic protection device was used in 409 (69%) patients across both groups. In the group receiving DES, 256 (88%) of 292 participants received second-generation DES (63% everolimus-eluting stents and 26% zotarolimus-eluting stents, with some participants receiving both). Newer generation BMS with thin struts were used in the BMS group. The names and manufacturers of all types of stents that were implanted at baseline are given in the appendix. The median follow-up was 2·7 years (IQR 1·7–3·7).

At 12 months, the incidence of target vessel failure was 17% (51 of 292) in the DES group and 19% (58 of 305) in the BMS group (stratified log-rank test; HR adjusted for stratification of randomisation 0·92, 95% CI 0·63–1·34, p=0·70; table 2; figure 2). Log-rank tests unstratified by diabetes status and one versus two or more SVG lesions also were not significant (data not shown). The between-group difference in the primary outcome after adjustment for baseline imbalance in SVG age (median <13·5 years *vs* 13·5 years) was not significant. The results for target vessel failure were consistent in subgroups defined by demo graphic, clinical, lesion, and procedural characteristics (appendix). Adding stent assignment to the proportional hazards model with participant and graft characteristics as covariates did not significantly increase the model's predictive ability (p=0·83) of target vessel failure at 12 months.

Analyses of the 12-month incidence of target vessel failure with non-cardiac death as a competing risk, target vessel or indeterminate myocardial infarction with any death as a competing risk, and target vessel revascularisation with any death as a competing risk showed no significant effects from stent assignment on any cause-specific hazard.

The between-group difference in the 12-month incidence of all-cause death, any myocardial infarction, definite or probable stent thrombosis, stroke, or other secondary outcomes was not significant (table 2; appendix).

Median follow-up was 2·7 years, with 406 (68%) of 597 participants followed up for at least 2 years and 235 (39%) followed up for at least 3 years. Over the entire length of follow-up, the incidence of target vessel failure was 37% (108 of 292) in the DES group and 34% (105 of 305) in the BMS group (adjusted HR 1·10, 95% CI 0·84 to 1·43, p=0·44; table 3; appendix). The results for target vessel failure over the entire follow-up were consistent in subgroups defined by demographic, clinical, lesion, and procedural characteristics (appendix). There was no significant evidence of non-proportional hazards (Grambsch-Therneau test p=0·08). In a post-hoc analysis, the between-group difference in the primary outcome after adjustment for baseline imbalance in SVG age (<13·5 years *vs* 13·5 years) was not significant.

Between-group differences in the incidence of all-cause death, myocardial infarction during follow-up, definite or probable stent thrombosis, stroke, or other secondary outcomes were not significant (table 3; appendix). The proportion of participants reporting one or more

serious adverse events overall, and by classification by use of the Medical Dictionary for Regulatory Activities (MedDRA), was not significant (table 4). Most repeat revascularisations were done in patients who presented with an acute coronary syndrome (70% [133 of 191]) or stable angina (24% [46 of 191]).

A post-hoc analysis for the combination of target vessel failure or SVG occlusion that was intervened on, or both, showed no difference between treatment groups at 12 months (table 2) and during the entire duration of follow-up (table 3).

Discussion

We did not find a significant difference between DES and BMS in the incidence of the combined endpoint of cardiac death, target vessel myocardial infarction, or target vessel revascularisation during the first 12 months and over the entire length of follow-up (median 2·7 years) among patients undergoing stenting of de-novo SVG lesions. There was also no difference in the risk for stent thrombosis or bleeding. DIVA did not mandate angiographic follow-up, which is known to increase the rates of repeat revascularisation in favour of DES. [25] DIVA had higher use of embolic protection devices (69% [409 of 597 patients]) than any previous SVG stenting trial.

Our findings are in contrast with those of three[11–13] of the four randomised controlled trials done to date that showed benefit with DES over BMS in SVGs. The ISAR-CABG trial[12] randomly assigned 610 participants to a first-generation DES or a BMS, and reported lower 12-month incidence of target vessel revascularisation in the DES group (7% *vs* 13%, p=0·01), and no significant differences in all-cause mortality, myocardial infarction, and definite or probable stent thrombosis as compared with BMS. ISAR-CABG had planned angiographic follow-up as did two smaller studies.[9–11] The first study[9] showed harm (higher mortality with DES compared with BMS at 3 years [29% *vs* 0%, p=0·001], although most deaths were due to non-cardiac events) and similar target vessel revascularisation in both groups. The second study[10,11] showed lower risk for myocardial infarction and target lesion revascularisation with DES than BMS. The BASKET-SAVAGE trial[13] randomly assigned 173 patients to receive either DES or BMS, had no planned angiographic follow-up, and had lower incidence of target vessel revascularisation in the DES group (4·5% *vs* 19·1% at 3 years, p<0·001). The absence of improved outcomes with DES in DIVA was observed despite the use of second-generation DES in 256 (88%) of 292 patients in the DES group, whereas first-generation DES were used in all previous studies.[9,11–13]

The absence of benefit with DES in DIVA could be related to the different pathophysiology of SVG atherosclerosis (more concentric and diffuse with less well defined fibrous cap) compared with native coronary artery atherosclerosis.[26,27] The absence of benefit with DES could also be because of the large burden of comorbidities among patients with a previous CABG,[14] or the use of thin-strut bare-metal stents that might have lower risk for restenosis as compared with thicker strut stents that were used in previous SVG PCI studies; 9,11–13 it is unlikely to be because of differences in stenting technique and concomitant medications, since those characteristics were similar in both groups. Unknown confounders could have played a role, but are unlikely given randomisation. The study results have important

economic implications in countries with high DES prices such as the USA, because they suggest that the lower cost BMS can be used in SVG lesions without compromising either safety or efficacy. The financial implications of the study might differ between countries, depending on local stent pricing. An alternative treatment approach would be to recanalise the native coronary artery instead of the diseased SVG,[4,28] although such interventions can be technically challenging.[29,30]

Our study has limitations. As is typical in Veterans Affairs studies, nearly all study participants were men, which limits the extrapolation of the results to women, although most patients undergoing PCI after CABG are men.[31] The interventionalists doing the index SVG PCI were not masked to the type of stent used, although the patients, clinicians, and event adjudicators were masked. The study was stopped before completion of the revised enrolment target, yet the number of patients recruited was greater than originally planned and the post-hoc power (86%) was similar to the pre-hoc power (90%) to detect the originally hypothesised HR of 0·556.

In summary, in our evaluation of the clinical outcomes of 597 patients undergoing PCI of de-novo SVG lesions, we found no significant difference in the 12-month and long-term (median 2·7 years) incidence of cardiac death, target vessel myocardial infarction, or target vessel revascularisation.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Research in context

Evidence before this study

Saphenous vein graft failure can be challenging to treat because of high rates of periprocedural complications and in-stent restenosis. We searched PubMed for all published randomised controlled trials of drug-eluting versus bare-metal stents in saphenous vein graft lesions. Drug-eluting stents appeared to provide improved outcomes in three of the four randomised controlled trials done to date, driven by lower rates of target lesion revascularisation compared with bare-metal stents. However, these studies were limited by small size, absence of blinding, routine angiographic follow-up, low use of embolic protection devices, and use of first-generation drug-eluting stents.

Added value of this study

The DIVA trial investigated the efficacy and safety of drug-eluting stents versus bare-metal stents in patients presenting with de-novo saphenous vein graft lesions and did not mandate routine angiographic follow-up. At 12 months, the incidence of target vessel failure (composite of cardiac death, target vessel myocardial infarction, or target vessel revascularisation) was not significantly different between groups. Similarly, during a median follow-up of 2·7 years, target vessel failure occurred in approximately one in three patients, with no difference between bare-metal and drug-eluting stents.

Implications of all the available evidence

The common clinical perception is that patients who need stenting of saphenous vein graft lesions derive benefit from drug-eluting stent implantation. The results of the DIVA trial show that drug-eluting stents and bare-metal stents are associated with similar clinical outcomes. Given their lower cost compared with drug-eluting stents, bare-metal stents might be preferred in saphenous vein graft lesions.
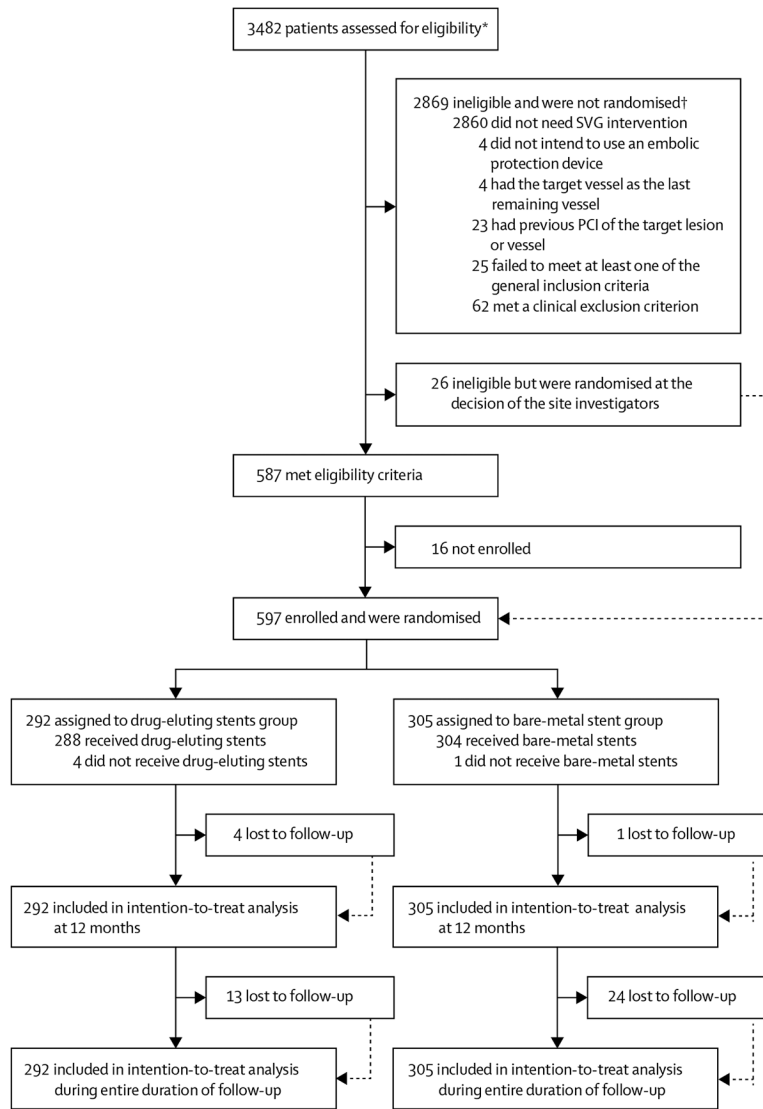
Figure 1: Enrolment, randomisation, and follow-up
The number of patients who were eligible is lower than the number randomly assigned, because some ineligible patients were randomly assigned. SVG=saphenous vein aortocoronary bypass graft. PCI=percutaneous coronary intervention. *Two patients who were screened and randomly assigned without proper consent are not included. †Criteria are not mutually exclusive.
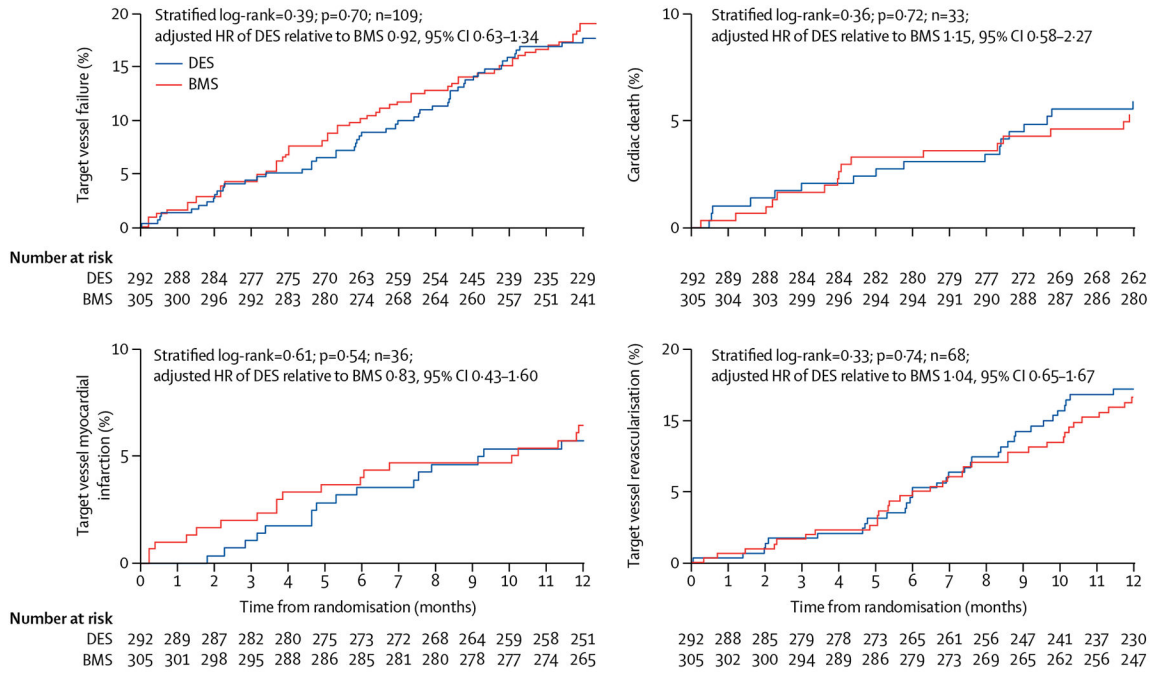
Figure 2: Clinical outcomes at 12 months

Kaplan-Meier plot of cumulative incidence curves for patients who received drug-eluting stents (DES) or bare-metal stents (BMS) for the primary outcome of target vessel failure (composite outcome of cardiac death, target vessel myocardial infarction, or target vessel revascularisation), cardiac death, target vessel myocardial infarction, and target vessel revascularisation. HR=hazard ratio.

Table 1:

Baseline clinical and angiographic characteristics of the study patients and lesions, procedural techniques, and outcomes

	Drug-eluting stents (n=292)	Bare-metal stents (n=305)
Patient characteristics		
Age, years	69.0 (7.4)	68.2 (7.7)
Men	290/292 (99%)	305/305 (100%)
Race		
White	263/287 (92%)	254/299 (85%)
Black	17/287 (6%)	32/299 (11%)
Hispanic	16/286 (6%)	14/300 (5%)
Body-mass index, kg/m^2	30.6 (5.6), n=288	30.4 (5.3), n=301
Waist circumference, inches	41.8 (6.0), n=240	41.7 (5.4), n=254
Time since coronary artery bypass graft surgery, years	13.9 (6.7), n=291	12.8 (6.8), n=303
Number of diseased coronary vessels		
One	3/291 (1%)	8/304 (3%)
Two	30/291 (10%)	25/304 (8%)
Three	258/291 (89%)	271/304 (89%)
Indication for PCI		
Stable angina	117/289 (40%)	105/304 (35%)
Unstable angina	89/289 (31%)	95/304 (31%)
Non-ST-segment elevation acute MI	66/289 (23%)	74/304 (24%)
Other	17/289 (6%)	30/304 (10%)
Hypertension	278/292 (95%)	296/305 (97%)
Hyperlipidaemia	287/292 (98%)	294/305 (96%)
Diabetes	173/292 (59%)	187/305 (61%)
Current smoker	61/292 (21%)	72/305 (24%)
Previous MI	163/292 (56%)	153/305 (50%)
History of atrial fibrillation	51/292 (17%)	57/305 (19%)
Congestive heart failure	92/292 (32%)	118/305 (39%)
Ejection fraction	52.5 (47.0), n=175	49.4 (13.3), n=182
Peripheral arterial disease	51/292 (17%)	56/305 (18%)
Lesion characteristics		
Target graft recipient vessel	301	315
Left anterior descending	9 (3%)	13 (4%)
Diagonal artery	53 (18%)	62 (20%)
Circumflex or obtuse marginal	122 (41%)	129 (41%)
Right coronary artery or posterior descending artery	117 (39%)	111 (35%)
SVG target lesion location	330	359
Ostial	68 (21%)	88 (25%)
Body	234 (71%)	240 (67%)

	Drug-eluting stents (n=292)	Bare-metal stents (n=305)
Distal anastomosis	28 (8%)	31 (9%)
Prestenting target SVG lesion flow		
0	2 (1%)	3 (1%)
1	10 (3%)	14 (4%)
2	54 (16%)	42 (12%)
3	264 (80%)	300 (84%)
Post-stenting target SVG lesion flow		
0	1 (0%)	1 (0%)
1	1 (0%)	0 (0%)
2	7 (2%)	4 (1%)
3	321 (97%)	354 (99%)
Index procedure characteristics		
Arterial access		
Femoral	267 (91%)	279 (91%)
Radial	20 (7%)	23 (8%)
Anticoagulant		
Unfractionated heparin	166 (57%)	177 (58%)
Bivalirudin	123 (42%)	137 (45%)
Glycoprotein IIb/IIIa inhibitor	44 (15%)	43 (14%)
Staged PCI	30 (10%)	35 (11%)
Haemodynamic support during PCI	1 (0%)	3 (1%)
Embolic protection device used	199 (68%)	210 (69%)
Number of target SVGs intervened per patient	1.0 (0.2)	1.0 (0.2)
Patients who underwent PCI of more than one target SVG lesion	42 (14%)	54 (18%)
Number of target SVG lesions intervened per patient	1.2 (0.5)	1.2 (0.5)
Number of stents in target SVG lesions per patient	1.3 (0.6)	1.4 (0.8)
Number of non-target lesions intervened per patient	1.4 (0.6)	1.4 (0.7)
Type of drug-eluting stent used in target lesions		
First generation	21 (7%)	0 (0%)
Second generation	256 (88%)	8 (3%)
Total length of stents in target lesion per patient, mm	27.0 (19.0)	26.6 (18.3)
Target lesion stent diameter, mm	3.38 (0.50)	3.42 (0.56)
Intravascular ultrasound guidance	64 (22%)	57 (19%)
Angiographic success	274 (94%)	291 (95%)
Any procedural complication	15 (5%)	22 (7%)
Periprocedural MI[*]	9 (3%)	23 (8%)

Data are mean (SD), n/N (%), n, or n (%). Summary statistics in all tables are based on the number of participants who provided a response for each given characteristic. PCI=percutaneous coronary intervention. MI=myocardial infarction. SVG=saphenous vein aortocoronary bypass graft.

*Defined as an increase at least three times the upper limit of normal in patients with normal baseline creatine kinase-muscle/brain (CK-MB) and at least a 50% increase in patients with elevated baseline CK-MB; p=0·0156.

Table 2:

Clinical events during 12-month follow-up and medications administered during follow-up

	Drug-eluting stents (n=292)	Bare-metal stents (n=305)	Adjusted hazard ratio (95% CI)	p value[*]
TVF	51 (17%)	58 (19%)	0.92 (0.63–1.34)	0.70
Death from any cause	23 (8%)	21 (7%)	1.17 (0.65–2.12)	0.63
Cardiac or unknown cause of death (component of TVF)	17 (6%)	16 (5%)	1.15 (0.58–2.27)	072
Cardiac	15 (5%)	11 (4%)	1.47 (0.68–3.20)	0.35
Non-cardiac	6 (2%)	5 (2%)	1.23 (0.37–4.05)	073
Unknown cause	2 (1%)	5 (2%)	0.43 (0.08–2.24)	0.30
Any MI during follow-up	28 (10%)	31 (10%)	0.94 (0.56–1.57)	075
Target vessel or indeterminate MI during follow-up (component of TVF)	16 (5%)	20 (7%)	0.83 (0.43–1.60)	054
Non-target vessel MI during follow-up	13 (4%)	13 (4%)	1.05 (0.49–2.27)	0.96
Any revascularisation	56 (19%)	53 (17%)	1.11 (0.76–1.61)	0.44
Any PCI	55 (19%)	53 (17%)	1.09 (0.74–1.58)	0.51
Any CABG	2 (1%)	0 (0%)	..	0.50
Target vessel revascularisation (component of TVF)	34 (12%)	34 (11%)	1.04 (0.65–1.67)	0.74
With PCI	33 (11%)	34 (11%)	1.01 (0.62–1.63)	0.85
With CABG	2 (1%)	0 (0%)	..	0.50
Non-target vessel revascularisation	33 (11%)	26 (9%)	1.34 (0.80–2.24)	0.20
With PCI	32 (11%)	26 (9%)	1.30 (0.77–2.18)	0.25
With CABG	2 (1%)	0 (0%)	..	0.50
Target lesion revascularisation	26 (9%)	25 (8%)	1.09 (0.63–1.88)	0.62
With PCI	25 (9%)	25 (8%)	1.04 (0.60–1.82)	0.73
With CABG	2 (1%)	0 (0%)	..	0.50
Patient-oriented composite endpoint (composite of all-cause death, any MI, and target lesion revascularisation)	62 (21%)	68 (22%)	0.94 (0.67–1.33)	0.81
Target lesion failure (composite of cardiac or unknown death, target vessel MI, and target lesion revascularisation)	45 (15%)	51 (17%)	0.93 (0.62–1.38)	076
Definite stent thrombosis	6 (2%)	7 (2%)	0.85 (0.28–2.53)	0.81
Definite or probable stent thrombosis	14 (5%)	17 (6%)	0.87 (0.43–1.76)	0.70
Stroke	2 (1%)	3 (1%)	0.72 (0.12–4.32)	0.71
Post-procedural bleed	0 (0%)	2 (1%)	..	0.50

	Drug-eluting stents (n=292)	Bare-metal stents (n=305)	Adjusted hazard ratio (95% CI)	p value*
TVF or SVG occlusion that did not undergo intervention	51 (17%)	59 (19%)	0.90 (0.62–1.31)	0.64
Medications during follow-up				
Patients who had a 12-month visit	258	270	NA	0.95
Aspirin at 12 months	241 (93%)	249 (92%)	NA	0.58
P2Y12 inhibitor at 12 months	230 (89%)	240 (89%)	NA	0.92
Clopidogrel at 12 months	220 (85%)	217 (80%)	NA	0.13
Ticlopidine at 12 months	0 (0%)	1 (0%)	NA	1.00
Prasugrel at 12 months	6 (2%)	16 (6%)	NA	0.0385
Ticagrelor at 12 months	4 (2%)	7 (3%)	NA	0.40
Statin at 12 months	240 (93%)	251 (93%)	NA	0.97
Patients who had a 24-month visit	198	211	NA	0.72
Aspirin at 24 months	179 (90%)	192 (91%)	NA	0.84
P2Y12 inhibitor at 24 months	110 (56%)	131 (62%)	NA	0.18
Clopidogrel at 24 months	103 (52%)	118 (56%)	NA	0.43
Ticlopidine at 24 months	0	0	NA	NA
Prasugrel at 24 months	4 (2%)	6 (3%)	NA	0.75
Ticagrelor at 24 months	3 (2%)	7 (3%)	NA	0.34
Statin at 24 months	184 (93%)	192 (91%)	NA	0.47
Patients who had a 36-month visit	130	133	NA	0.82
Aspirin at 36 months	110 (85%)	111 (83%)	NA	0.73
P2Y12 inhibitor at 36 months	62 (48%)	58 (44%)	NA	0.66
Clopidogrel at 36 months	51 (39%)	55 (41%)	NA	0.57
Ticlopidine at 36 months	0	0	NA	NA
Prasugrel at 36 months	7 (5%)	1 (1%)	NA	0.07
Ticagrelor at 36 months	4 (3%)	2 (2%)	NA	0.68
Statin at 36 months	115 (88%)	118 (89%)	NA	0.38

Data are n (%) or n. TVF=target vessel failure. MI=myocardial infarction. PCI=percutaneous coronary intervention. CABG=coronary artery bypass graft surgery. SVG=saphenous vein aortocoronary bypass graft. NA=not applicable.

*
The p value has been calculated from the stratified log-rank test.

Table 3:

Clinical events during entire duration of follow-up (median 2·7 years)

	Drug-eluting stents (n=292)	Bare-metal stents (n=305)	Adjusted hazard ratio (95% CI)	p value[*]
TVF	108 (37%)	105 (34%)	1.10 (0.84–1.43)	0.44
Death from any cause	55 (19%)	51 (17%)	1.14 (0.78–1.67)	0.51
Cardiac or unknown cause of death (component of TVF)	41 (14%)	41 (13%)	1.08 (0.70–1·66)	0.75
Cardiac	25 (9%)	21 (7%)	1.28 (0.72–2.29)	0.41
Non-cardiac	14 (5%)	10 (3%)	1.39 (0.61–3.14)	0.42
Unknown cause	16 (5%)	20 (7%)	0.86 (0.44–1.66)	0.65
Any MI during follow-up	53 (18%)	62 (20%)	0.89 (0.61–1.28)	0.52
Target vessel or indeterminate MI during follow-up (component of TVF)	35 (12%)	40 (13%)	0.90 (0.57–1.42)	0.66
Non-target vessel MI during follow-up	25 (9%)	31 (10%)	0.85 (0.50–1.43)	0.53
Any revascularisation	107 (37%)	96 (31%)	1.20 (0.91–1.59)	0.11
Any PCI	102 (35%)	94 (31%)	1.16 (0.87–1.53)	0.20
Any CABG	6 (2%)	4 (1%)	1.57 (0.44–5.59)	0.37
Target vessel revascularisation (component of TVF)	68 (23%)	58 (19%)	1.23 (0.87–1.75)	0.15
With PCI	64 (22%)	56 (18%)	1.19 (0.83–1.71)	0.24
With CABG	5 (2%)	4 (1%)	1.27 (0.34–4.78)	0.56
Non-target vessel revascularisation	69 (24%)	60 (20%)	1.25 (0.89–1.77)	0.14
With PCI	64 (22%)	59 (19%)	1.17 (0.82–1.67)	0.30
With CABG	6 (2%)	1 (0%)	6.33 (0.76–52.71)	0.0355
Target lesion revascularisation	47 (16%)	40 (13%)	1.23 (0.80–1.87)	0.22
With PCI	44 (15%)	39 (13%)	1.17 (0.76–1.81)	0.33
With CABG	4 (1%)	1 (0%)	4.20 (0.47–37.78)	0.13
Patient-oriented composite endpoint (composite of all-cause death, any MI, and target lesion revascularisation)	127 (43%)	127 (42%)	1.06 (0.83–1.36)	0.55
Target lesion failure (composite of cardiac or unknown death, target vessel MI, and target lesion revascularisation)	94 (32%)	95 (31%)	1.05 (0.79–1.39)	0.65
Definite stent thrombosis	9 (3%)	10 (3%)	0.90 (0.36–2.22)	0.88
Definite or probable stent thrombosis	26 (9%)	30 (10%)	0.90 (0.53–1.52)	0.74
Stroke	10 (3%)	12 (4%)	0.88 (0.38–2.03)	0.84
TVF or SVG occlusion that did not undergo intervention	112 (38%)	110 (36%)	1.09 (0.84–1.42)	0.44

Data are n (%). TVF=target vessel failure. MI=myocardial infarction. PCI=percutaneous coronary intervention. CABG=coronary artery bypass graft surgery. SVG=saphenous vein aortocoronary bypass graft.

*
The p value has been calculated from the stratified log-rank test.

Table 4:

Serious adverse events

	DES(n=292)	BMS (n=305)	p value
Number of participants with serious adverse events	231 (79%)	244 (80%)	079
Number of serious adverse events	1066	1110	NA
Serious adverse events attributed to stent	NA	NA	045
Not attributed	906	959	NA
Possibly attributed	102	90	NA
Yes, attributed	56	54	NA
Serious adverse events attributed to thienopyridine	NA	NA	0.33
Not attributed	1014	1049	NA
Possibly attributed	49	53	NA
Yes, attributed	1	5	NA
MedDRA higher level term group			
Cardiac arrhythmias	36 (12%)	38 (12%)	0.96
Coronary artery disorders	134 (46%)	140 (46%)	1.00
Heart failure	52 (18%)	58 (19%)	0.70
Complications associated with device	25 (9%)	28 (9%)	0.79
General system disorders NEC	35 (12%)	34 (11%)	0.75
Bacterial infectious disorders	19 (7%)	13 (4%)	0.22
Infections—pathogen unspecified	51 (17%)	51 (17%)	0.81
Procedural related injuries and complications NEC	15 (5%)	14 (5%)	0.76
Electrolyte and fluid balance conditions	14 (5%)	18 (6%)	0.55
CNS vascular disorders	20 (7%)	23 (8%)	0.74
Renal disorders (excluding nephropathies)	28 (10%)	30 (10%)	0.92
Bronchial disorders (excluding neoplasms)	15 (5%)	8 (3%)	0.11
Decreased and non-specific blood pressure disorders and shock	11 (4%)	16 (5%)	0.38

Data are n or n (%). Tallies of participants and events, including participants with at least one serious adverse event by MedDRA classification experienced by at least 5% of participants in one or both treatment arms. DES=drug-eluting stent. BMS=bare metal stent. NA=not applicable. NEC=not elsewhere classified.