Choice of stent for percutaneous coronary intervention of saphenous vein grafts

Short title: Stent for SVG PCI

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What is Known:

- There are limited studies comparing bare metal stents (BMS) to drug eluting stents (DES) for percutaneous coronary intervention (PCI) for saphenous vein grafts (SVG).
- In general, these studies suggest that DES are associated with reduced repeat revascularization but no survival benefit.
- These studies are mainly of 1st generation DES and there are now 2nd generation stents and more recent studies suggest that newer generation stents have lower mortality than BMS but no differences in mortality between newer and 1st generation DES.

What the Study Adds:

- We observe that patients receiving DES for the treatment of SVG disease have lower rates of in-hospital MACE, 30-day mortality and 1-year mortality, compared with those receiving BMS.
- The reduction in adverse outcomes is greatest with newer generation DES.
- Patients undergoing PCI for SVG disease should be considered for treatment with DES, unless there are any contraindications such as higher risk of bleeding with DAPT or requirement for a short DAPT course.

Abstract

Background: There are limited data on comparison of contemporary drug eluting stent platforms (DES), previous generation DES and bare metal stents (BMS) for percutaneous coronary intervention (PCI) in saphenous vein grafts (SVG). We aimed to assess clinical outcomes following PCI to SVG in patients receiving bare metal stents (BMS), 1st generation DES and newer generation DES in a large unselected national dataset from the British Cardiovascular Intervention Society (BCIS).

Methods and Results: Patients undergoing PCI to SVG in the UK from January 2006 to December 2013 were divided into three groups according to stent use: BMS, 1st generation DES and newer generation DES group. Study outcomes included in-hospital major adverse cardiovascular events (MACE), 30-day and 1-year mortality. 15,003 patients underwent PCI to SVG in England and Wales during the study period. Of these 38% received BMS, 15% received 1st generation DES and 47% received 2nd generation DES. The rates of in-hospital MACE were significantly lower in patients treated with 2nd generation DES (OR 0.51, 95% CI 0.38-0.68, P<0.001), but not with 1st generation DES, compared with BMS treated patients. Similarly, 30-day mortality (OR 0.43, 95% CI 0.32-0.59, p<0.001) and 1-year mortality (OR 0.60, 95% CI 0.51-0.71, p<0.001) were lower in patients treated with 2nd generation DES, but not with 1st generation DES, compared to the patients treated with BMS.

Conclusion: Patients receiving 2nd generation DES for the treatment SVG disease have lower rates of in-hospital MACE, 30-day mortality and 1-year mortality, compared with those receiving BMS.

Keywords: Coronary artery bypass graft, saphenous vein graft, percutaneous coronary intervention, mortality, cardiovascular events

Introduction

Coronary artery bypass graft surgery (CABG) with one or more saphenous vein grafts (SVGs) is a commonly selected mode of revascularization for patients with multi-vessel coronary artery disease. The long-term patency rates of SVGs, when compared to arterial conduits, remain poor despite optimal secondary prevention therapy.[1] A sizeable proportion (10-40%) of SVGs occlude within the first year and with inexorable attrition at a rate of 2-5% annually, which accelerates with graft age.[2-10] Although patients can undergo redo CABG, there is high morbidity and mortality associated with this. Therefore, percutaneous coronary intervention (PCI) of SVGs is often a preferred revascularization modality in patients with significant SVG disease[11,12] with 5-10% of all PCI procedures being undertaken in SVGs.[11,13]

For treating native coronary arteries, drug eluting stents (DES) are preferred over the bare metal stents (BMS) as DES have been shown to reduce repeat revascularization and major adverse cardiac events (MACE).[14] However, there are situations where a BMS can be more appropriate, for example when a short duration of dual antiplatelet therapy is desirable or for treating focal lesions in large diameter vessels.[14,15] As old degenerative SVGs are usually of a large calibre and these patients are frequently old and frail with multiple comorbidities, BMS may be considered an appropriate choice. Indeed, different registries have shown that from one-third to half of patients undergoing PCI of SVGs receive BMS. However, more recent data suggest a growing use of newer generation DES in treating SVG disease.[16]

Only a few studies have compared BMS and DES for PCI of SVGs and generally shown that use of DES in SVGs can reduce the need for repeat revascularization but with no survival benefit.[17-22] However, these studies have largely compared either only 1st generation DES or a combination of 1st and newer generation DES against BMS with limited data on contemporary DES platforms. Conversely, data from the DELAYED RRISC trial reported

worse outcomes for patients with 1st generation sirolimus-eluting stents compared to BMS (29% vs 0%, p<0.001 for mortality, 58% vs 41%, p=0.13 for MACE during 3 year follow up).[20] In contrast, more contemporary registry data from the Veterans Affairs CART Program suggests use of newer generation DES is associated with lower mortality than BMS (HR 0.72, 95% CI 0.57-0.89) and similar rates of MI (HR 0.94, 95% CI 0.71-1.24) at long term follow up (>2 years), but there was no difference in mortality or MI between 1st and newer generation DES in this study.[16] In view of limited and divergent results in the literature, we aimed to assess stent choice and clinical outcomes following PCI to SVGs in patients receiving BMS, 1st generation DES and newer generation DES in a large unselected all-comer national dataset from the British Cardiovascular Intervention Society (BCIS).

Methods

Study design and data collection

The BCIS database records information on PCI procedures in UK with data collection managed by the National Institute of Cardiovascular Outcomes Research (NICOR).[23-27] This is a retrospective analysis of prospectively collected national data for all patients undergoing PCI of SVGs in the UK from January 2006 to December 2013. Using the Medical Research Information Services, we tracked participants in this database via the patient's NHS number, a unique identifier for any person registered within the NHS in England and Wales, for mortality and adverse outcomes. Institutional review board approval and patient consent was not obtained because this study was an analysis routinely collected anonymized data.

Variables and outcomes collected

We collected data on participants' demographics (age, gender, smoking status, family history of heart disease) and comorbidities (diabetes, hypertension, hyperlipidemia, previous myocardial infarction (MI), stroke, peripheral vascular disease, and renal disease). In

addition, data were also collected on left ventricular ejection fraction (LVEF), access site, use of glycoprotein IIb/IIIa inhibitor, use of thrombectomy device, cardiogenic shock, use of intra-aortic balloon pump, use of ventilatory support and use of distal protection devices.

Patients undergoing PCI to an SVG were grouped into three cohorts based on stent type i.e. BMS group (including Titan-2®), 1st generation DES (Cypher®, Taxus Liberte®, Eucatax®, Achieve®, Sorin®, Costar® stents) and newer generation DES (Promus®, Xience®, Resolute®, Biomatrix®, Endeavor®, Biofreedom®, Nobori® and Yukon® stents).

We evaluated all-cause mortality at 30-days and 1-year follow up and major adverse cardiovascular events (MACE, defined as a composite of in-hospital mortality, in-hospital myocardial re-infarction and target vessel revascularization).

Statistical methods

We excluded patients with missing data for 30-day mortality, stent type or age. A flow diagram graphically describes how the final cohort was derived (Figure 1). Summary statistics are presented as mean ± standard deviation for continuous data and percentage or proportions for categorical variables, according to stent group (BMS, 1st generation DES and 2nd generation DES). The clinical characteristics of the three groups were compared using ANOVA or Chi-square tests for continuous and categorical variables respectively. The risk of adverse outcomes was estimated with multiple logistic regressions with imputation for missing variables. Multiple imputations by chained equations was performed using *mi impute chained* function in Stata to generate 10 complete datasets. We also calculated the propensity score for each stent group and used it to match and estimate adjusted risk estimates in pairwise stent group comparisons (BMS vs 1st generation DES, BMS vs 2nd generation DES and 1st generation vs 2nd generation DES). To achieve this we used the *teffects psmatch* function in Stata to estimate the average treatment effects while accounting for baseline differences across the groups. For each group member, we calculated propensity scores using

all the covariates across the 10 imputed datasets. Using the standard setting for matching, a minimum of one neighbour was matched for all observations. Tolerance for the overlap assumption was set to 10^{-5}. For consistency with the main analyses and an easier comparison, we transformed the differences in probability to odds ratios, after making assumptions about the baseline probability risk with BMS. Statistical analyses were performed using Stata v13 (Stata Corp., Texas, USA).

Results

Study cohort

A total of 18,985 patients underwent PCI to at least one SVG in England and Wales from January 2006 to December 2013. The study cohort with complete data for stent type and 30-day mortality was 15,003 (79.0%) as 3,982 patients had missing values for type of stent used (3671 patients) or 30-day mortality (311 patients) (Figure 1). The characteristics of those included in the study and those excluded are shown in Supplementary Table 1. A total of 5,685 (38%) patients received BMS and 9,318 (62%) received DES. Among patients receiving DES, 2,265 (24.3%) received 1st generation DES and 7,053 (75.7%) received 2nd generation DES. There was a temporal change in the use of stents (Figure 2). In 2007, 42% of patients received BMS with the remainder receiving 1st generation DES. By 2013 use 1st generation DES had ceased with the ratio of newer generation DES to BMS being 78% to 22% respectively.

Characteristics of participants

The characteristics of patients in the three groups are shown in Table 1. There were significant differences in the demographic and clinical characteristics within groups, in particular, patients treated with 1st generation DES being younger. Comorbidities such as diabetes, hypertension, hyperlipidemia, previous MI, and peripheral vascular disease were more prevalent in patients receiving 2nd generation DES. Multi-vessel disease was

significantly different among stent types (21% vs 27% vs 14%) for 2nd generation DES, 1st generation DES and BMS, respectively.

Clinical outcomes

The highest un-adjusted rates of in-hospital MACE and 30-day and 1-year mortality were observed in the BMS group. We found that the in-hospital MACE rate according to stent type was 3% (n=167), 1% (n=31) and 2% (103) for BMS, 1st generation DES and 2nd generation DES, respectively. Mortality rates were also significantly lower for DES compared to BMS at both 30 days (3% (n=171), 0.9% (n=21) and 1% (n=94)) and 365 days (9% (n=491) vs 5% (n=106) vs 6% (n=371)). The specific components of MACE according to stent type is shown in Supplementary Table 2. Adjusted MACE and mortality were also significantly lower with the use of DES (Table 2). For in-hospital MACE, 2nd generation stent use was associated with a significant reduction in odds of MACE (OR 0.51, 95% CI 0.38-0.68, p<0.001) compared to BMS. The risk for adjusted 30-day mortality was significantly lower in patients with 2nd generation DES (OR 0.43, 95% CI 0.32-0.59, p<0.001) with a trend towards lower risk that was not significant for 1st generation DES (OR 0.63, 95% CI 0.37-1.10; p=0.104) compared to BMS. At longer follow up of 1 year, only 2nd generation stents were associated with decreased mortality (OR 0.60 95% CI 0.51-0.71, p<0.001) compared to BMS.

Propensity score matching for adverse outcomes

The results of propensity score matching are shown in Table 3 and the matching success diagnostics is shown in Supplementary Table 3. For in-hospital MACE, use of both 1st and 2nd generation DES significantly reduced events compared with BMS (Table 3). Similarly, use of 1st or 2nd generation DES was associated with significant reductions in 30-day mortality (p<0.001 and p<0.001) when compared with BMS. For 1-year mortality, there was a reduction with use of 2nd generation DES (p<0.001) but not with 1st generation DES

(p=0.373), compared with BMS. The effects were generally small, but statistically significant because the outcomes are rare (see Table 1). For example, 1st generation DES was estimated 1.29% less likely to be associated with in-hospital MACE than BMS, but the baseline probability risk for BMS is 3%. The results after transforming probabilities to odds ratios are reported in Supplementary Table 4. In the propensity score matching analyses, we continued observing the positive associations for both 1st and 2nd generation DES with outcomes, compared to BMS.

Discussion

Our data, derived from a large all-comer national registry of patients undergoing PCI of SVG, suggest that use of DES is associated with better outcomes compared with BMS. There is reduction is MACE and mortality in DES treated patients, in particular those receiving newer generation DES.

Our study overcomes the limitations of small sample size seen in the three randomized trial (RRISC, SOS, and ISAR-CABG) comparing DES and BMS in SVG lesions. RRISC (Reduction of Restenosis In Saphenous vein grafts with Cypher stent) was a prospective, double blind, randomized trial of patients (n=75 patients, 96 SVG lesions) treated with 1st generation sirolimus-eluting Cypher (Cordis Ltd., New Jersey, USA) DES (n=38 patients, 60 stents) or BMS (n=37 patients, 54 stents). The two groups were well balanced for baseline clinical and angiographic characteristics. At six months follow-up, the DES group had less in-stent restenosis (DES 11.3% vs BMS 30.6%; RR 0.37; 95% CI 0.15-0.97, p=0.024), target lesion revascularization (DES 5.3% vs BMS21.6%; RR 0.24, 95% CI 0.05-1.0, p=0.047) and target vessel revascularization (DES 5.3% vs BMS 27%; RR 0.19; 95% CI 0.05-0.83, p=0.012). Median neo-intimal volume on intravascular ultrasound (IVUS) was also substantially reduced in DES group (DES 1 mm^3 vs BMS 24 mm^3, p<0.001). Death

and MI rates were not different at 6-months.[19] A post-hoc, long-term follow-up, DELAYED RRISC (Death and Events at Long-term follow-up AnalYsis: extended duration of Reduction of Restenosis In Saphenous vein grafts with Cypher stent) was subsequently conducted to report clinical events up to three years (median 32 months) after the index procedure. An increase in death rate in DES patients (DES 29% vs BMS 0% p<0.001) was observed, though the trial was not powered for clinical outcomes. There were eleven all-cause and seven cardiac deaths in the DES group. Stent thrombosis according to ARC criteria occurred in five DES patients.[20] However, patients receiving DES were mandated to receive dual anti-platelet therapy for only 2 months, which could potentially explain higher rates of stent thrombosis and mortality in the DES group. The SOS (Stenting of Saphenous Vein Grafts) trial randomized 80 patients with 112 lesions in 88 SVGs to a BMS (39 patients, 43 grafts, 55 lesions) or 1st generation paclitaxel-eluting Taxus® (Boston Scientific Corp., Minnesota, USA) DES (41 patients, 45 grafts, 57 lesions). Binary angiographic restenosis was substantially lower in DES group (DES 9% vs BMS 51%; RR 0.18, 95% CI 0.07-0.48, P<0.001). During a median follow-up of 1.5 years the DES group had less target lesion revascularization (28% vs. 5%; HR 0.38; 95% CI 0.15-0.74, p=0.003) and target vessel failure (46% vs. 22%; HR 0.65, 95% CI 0.42-0.96, p=0.03), a trend toward less target vessel revascularization (31% vs. 15%; HR 0.66, 95% CI 0.39-1.05, p=0.08) and MI (31% vs. 15%; HR 0.67, 95% CI 0.40-1.08, p=0.10).[21] However, there was no difference in mortality (5% vs. 12%; HR 1.56, 95% CI 0.72-4.11, p=0.27) at 1.5 years.[21] Extended clinical follow-up (median of 35 months) was subsequently obtained showing no difference in all-cause (HR 2.04, p=0.19) or cardiac mortality (HR 0.62, p=0.51).[22] However, the DES group had a lower incidence of MI (HR 0.32, p=0.01), target lesion revascularization (HR 0.20, p=0.004), target vessel revascularization (HR 0.41, p=0.03), and target vessel failure (HR 0.34, p=0.001) as well as a trend toward less definite or probable stent thrombosis (HR: 0.15, p=0.08).[22] The

larger ISAR-CABG trial (n=610) randomized patients with diseased SVGs to DES (one of three types: permanent-polymer paclitaxel-eluting stents, permanent-polymer sirolimus-eluting stents, or biodegradable-polymer sirolimus-eluting stents) and BMS and reported a reduction in the primary endpoint of MACE at 1-year in the DES group (DES 15.4% vs. BMS 22.1%, p=0.03) which was mainly driven by a near 50% relative reduction in the risk of target lesion revascularization (DES 7.2% vs. BMS 13.1%, p=0.02), with no significant differences in mortality.[18] A meta-analysis comparing DES with BMS in SVG intervention (which also included nonrandomized studies) has reported lower mortality, MACE, target lesion revascularization, and target vessel revascularization without increased risk of MI or stent thrombosis.[28] Multiple other meta-analyses comparing DES with BMS in SVG intervention have demonstrated consistent results of improved efficacy with DES and no significant safety hazards.[29-35]

Our data provide supportive evidence that use of newer generation DES is associated with improved outcomes and survival in patients undergoing PCI in SVGs. These findings are consistent with another contemporary registry of PCI in SVGs.[16] It is possible that the difference in outcomes are due to the fact that BMS are being used in older or high-risk patients or in patients with other morbidities that are not collected in registry datasets. Nevertheless, propensity-matching analysis from the Veterans Affairs CART Program,[16] data from older patients in the Medicare-linked NCDR CathPCI Registry[36] and our propensity-matched analysis suggest that the advantage seen with DES use may not be all due to differences in conventionally-measured patient characteristics. It is therefore possible that this survival advantage with 2nd generation DES is a real entity. DES use reduces restenosis, need for repeat revascularization and associated adverse events. However, it is also plausible that this is not the only mechanism for improved outcomes. The newer generation DES with biocompatible and bioresorbable polymers have very low rate for stent thrombosis, which is

definitely lower than 1st generation DES and possibly also lower than BMS. Moreover, DES use is generally associated with longer duration of dual anti-platelet therapy, which may in turn be associated with a reduction in adverse ischemic and thrombotic events.[37] The association with a survival advantage seen with newer generation DES in the treatment of SVGs is also consistent with recently reported meta-analysis of 51 clinical trials (n=52,158 patients) showing that newer generation DES are associated with lower rates of mortality, stent thrombosis, and MI than BMS and 1st generation DES for the treatment of native coronary arteries.[38] An adequately powered randomized controlled trial is warranted to confirm these findings.

There are no randomized data comparing newer vs. 1st generation DES for the treatment of SVG disease. In a multicenter analysis of 172 real-world patients comparing first-generation DES, SVG intervention with sirolimus- and paclitaxel-eluting stents resulted in non-significant differences in survival (HR: 1.28, 95% CI: 0.39 to 4.25, p = 0.69) and target vessel revascularization (HR: 2.54, 95% CI: 0.84 to 7.72, p = 0.09).[39] Previously, there have been very limited data on use of newer generation DES for PCI to SVGs. In the SOS-Xience V (Stenting of Saphenous Grafts with Xience V) study, 40 patients with SVG lesions were treated with a newer generation everolimus-eluting stent (Xience-V, Abbott Vascular Ltd., Santa Clara, USA). Out of these 40 patients, 27 underwent 12-month coronary angiography and 12 (only 1 of whom had in-stent restenosis) also had follow-up OCT evaluation. OCT strut-level analysis (n=2584 struts) showed that 96% struts were covered at 12-months; however, 9% struts were mal-apposed.[40] These findings can potentially create uncertainty about the role of newer generation DES in treating SVG lesions. Our data from a large all-comer national registry and propensity-matched cohort provide further reassurance that the newer generation DES appear effective and safe for the treatment of SVG disease.

Finally, whilst BMS have conventionally been used in older, multi-morbid patients at

higher risk of bleeding complications where shorter DAPT duration would be preferable, the recent LEADERS FREE trial using a polymer and carrier-free biolimus coated BioFreedom stent (Biosensors Europe) was superior to a bare-metal stent with respect to the primary safety and efficacy end points when used with a 1-month course of dual antiplatelet therapy[41] in patients at high risk of bleeding complications. It is therefore likely that the use of BMS in SVG will decline further.

Study strengths and limitations

The strengths of these data are that it represents amongst the largest analysis of PCI to SVG in contemporary practice, including an almost complete collection of all PCI procedures performed in England and Wales. It therefore reflects an all-comers, real-world experience that includes many high-risk patients who are often excluded from randomized controlled trials.

This study has several potential limitations. First, whilst mortality tracking within the UK is very robust, the cause of death is not currently available, and the MACE outcomes are self-reported and are not formally adjudicated. Therefore, the analysis is subject to reporting biases, and complications may be under-reported. Secondly, we do not have data for duration of DAPT. Thirdly, our analysis report outcomes derived from grafts as the BCIS dataset does not differentiate between venous and arterial grafts. Previous data derived from the National Cardiovascular Data Registry (NCDR) CathPCI registry suggests that arterial grafts represented 2.5% of all PCI procedures undertaken to bypass grafts in the United States hence it is likely that the majority of graft interventions reported here are those undertaken in saphenous vein grafts.[42] Finally, our analysis is observational, with inherent limitations of any such data analysis. Nonetheless, we used robust statistical analyses including multiple logistic regression and propensity-matching to adjust for known confounders.

Conclusion

In one of the largest analyses to date, we have observed that patients receiving DES (particularly newer generation DES) for the treatment of SVG disease have lower rates of in-hospital MACE, 30-day mortality and 1-year mortality, compared with those receiving BMS. Patients undergoing PCI for SVG disease should therefore receive a DES, unless any contraindication or higher risk of bleeding with DAPT or requirement for a short DAPT course.

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Disclosures

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Table 1: Descriptive statistics

Variable	Bare metal stent (BMS)	1st gen. DES	2nd gen. DES	p-value		
	n=5,685	n=2,265	n=7,053	1st gen. DES vs BMS	2nd gen. DES vs BMS	2nd vs 1st gen. DES
Age	70 (±10)	68 (±9)	69 (±10)	<0.001	<0.001	<0.001
Male gender	4,757 (84%)	1,868 (83%)	5,891 (84%)	0.22	0.98	0.21
Smoking status				0.053	<0.001	0.038
Never	1,629 (33%)	632 (34%)	2,332 (37%)			
Ex-smoker	2,643 (54%)	1,013 (55%)	3,230 (52%)			
Smoker	651 (13%)	204 (11%)	705 (11%)			
Diabetes	1,565 (29%)	645 (31%)	2,236 (33%)	0.096	<0.001	0.050
Hypertension	3,539 (64%)	1,351 (63%)	4,674 (68%)	0.54	<0.001	<0.001
Hyperlipidemia	3,564 (65%)	1,440 (67%)	4,740 (69%)	0.014	<0.001	0.22
Previous MI	3,250 (61%)	1,231 (60%)	4,071 (61%)	0.23	0.66	0.36
Previous stroke	373 (7%)	111 (5%)	467 (7%)	0.012	0.94	0.009
Peripheral vascular disease	592 (11%)	198 (9%)	680 (10%)	0.064	0.13	0.41
Renal disease	267 (5%)	90 (4%)	317 (5%)	0.24	0.57	0.43
Previous PCI	1,836 (34%)	903 (43%)	2,862 (42%)	<0.001	<0.001	0.21
Left ventricular ejection fraction				0.033	<0.001	0.017
Good	1,497 (53%)	640 (57%)	2,097 (57%)			
Moderate	1,004 (35%)	355 (32%)	1,288 (35%)			
Poor	342 (12%)	123 (11%)	316 (9%)			
Family history of CAD	2,404 (52%)	994 (55%)	2,967 (49%)	0.019	0.004	<0.001
Radial access	1,402 (25%)	373 (17%)	2,435 (35%)	<0.001	<0.001	<0.001
Glycoprotein IIb/IIIa inhibitor	1,374 (25%)	675 (32%)	1,351 (20%)	<0.001	<0.001	<0.001
Bivalirudin	95 (2%)	30 (2%)	167 (2%)	0.37	0.013	0.010
Multivessel disease	820 (14%)	604 (27%)	1,511 (21%)	<0.001	<0.001	<0.001

Cardiogenic shock	125 (2%)	9 (0.5%)	73 (1%)	<0.001	<0.001	0.010
Intra-aortic balloon pump	134 (2%)	30 (1%)	77 (1%)	0.008	<0.001	0.26
Thrombus aspiration	481 (9%)	68 (3%)	603 (9%)	<0.001	0.83	<0.001
Ventilatory support	83 (2%)	10 (0.6%)	61 (1%)	0.001	0.001	0.098
Embolic protection device	875 (16%)	311 (14%)	1,021 (15%)	0.13	0.19	0.56
Diagnosis Stable angina NSTEMI STEMI	 2,082 (38%) 2,682 (49%) 693 (13%)	 1,122 (51%) 980 (45%) 88 (4%)	 2,689 (39%) 3,521 (51%) 686 (10%	<0.001	<0.001	<0.001
In-hospital MACE	167 (3%)	31 (1%)	103 (2%)	<0.001	<0.001	0.87
Death at 30 days	171 (3%)	21 (0.9%)	94 (1%)	<0.001	<0.001	0.13
Death at 365 days	491 (9%)	106 (5%)	371 (6%)	<0.001	<0.001	0.058

BMS=bare metal stent, DES=drug eluting stent, gen.=generation, MI=myocardial infarction, PCI=percutaneous coronary intervention, CAD=coronary artery disease, NSTEMI=non-ST-elevated myocardial infarction, STEMI=ST-elevation myocardial infarction, MACE=major adverse cardiovascular events.

Table 2: Multivariable logistic regression for adverse outcomes according to stent type with multiple imputations

Outcomes*	Odds ratio (95% CI)	p-value
In-hospital MACE (n=15,003)		
Bare metal stent	1.00 (reference)	
1st generation DES	0.77 (0.50-1.21)	0.262
2nd generation DES	0.51 (0.38-0.68)	<0.001
Mortality at 30 days (n=15,003)		
Bare metal stent	1.00 (reference)	
1st generation DES	0.63 (0.37-1.10)	0.104
2nd generation DES	0.43 (0.32-0.59)	<0.001
Mortality at 365 days (n=15,003)		
Bare metal stent	1.00 (reference)	
1st generation DES	0.78 (0.61-1.01)	0.059
2nd generation DES	0.60 (0.51-0.71)	<0.001

MACE=major adverse cardiovascular events, DES=drug eluting stent

Multivariable estimates with 10 imputations and adjusted for age, sex, smoking status, diabetes, hypertension, hyperlipidemia, previous myocardial infarction, previous stroke, peripheral vascular disease, renal disease, previous percutaneous coronary intervention, left ventricular ejection fraction, family history of coronary artery, radial access, glycoprotein IIb/IIIa inhibitor, bivalirudin, multivessel disease, cardiogenic shock, intra-aortic balloon pump, thrombus aspiration, ventilatory support, embolic protection device and diagnosis.

Table 3: Propensity score matching analysis on 10 imputed datasets, reporting average treatment effects (ATE).*

Analysis	Method	Group	Coefficient†	95% CI		p-value
In-hospital MACE	Propensity score matching, ATE	1st gen. DES vs BMS (n=7,950)	-0.0129	-0.0212	-0.0047	0.002
		2nd gen. DES vs BMS (n=12,738)	-0.0096	-0.0165	-0.0028	0.006
30 day mortality	Propensity score matching, ATE	1st gen. DES vs BMS (n=7,950)	-0.0166	-0.0233	-0.0099	<0.001
		2nd gen. DES vs BMS (n=12,738)	-0.0146	-0.0218	-0.0074	<0.001
1 year mortality	Propensity score matching, ATE	1st gen. DES vs BMS (n=7,950)	-0.0198	-0.0639	0.0244	0.373
		2nd gen. DES vs BMS (n=12,738)	-0.0332	-0.0457	-0.0207	<0.001

MACE=major adverse cardiovascular event, DES=drug eluting stent, BMS=bare metal stent, gen.=generation, ATE=average treatment effect.
*To better control for the baseline differences across the groups, multiple imputation propensity score matching (*mi estimate:teffects psmatch* on Stata) was used to estimate the average treatment effect (ATE). The method used all the predictors in Table 1 in three separate multiple imputation logistic regression models (1st generation DES vs BMS, 2nd generation DES vs BMS and 2nd generation DES vs 1st generation DES), calculating propensity scores for group membership. Standard settings for the matching algorithm were used. A minimum of one neighbour was requested and all observations were considered as potential matches regardless of how dissimilar their propensity scores were. Tolerance for the overlap assumptions was set to 10^{-5}. Simple logistic regression models were run (the only predictor being group membership) to obtain the ATE and the ATE is a measure of the difference in mean outcomes between participants assigned to the treatment and participants assigned to the control. The output of the *teffects psmatch* on Stata are coefficients and 95% confidence intervals rather than odds ratios.
† The coefficient is the difference in probability. Using the first row as an example, a coefficient of -0.0129 means that 1st generation DES are 1.29% less likely to be associated with in-hospital MACE than BMS.

Figure 1. Flow diagram of participant inclusion. PCI indicates percutaneous coronary intervention.

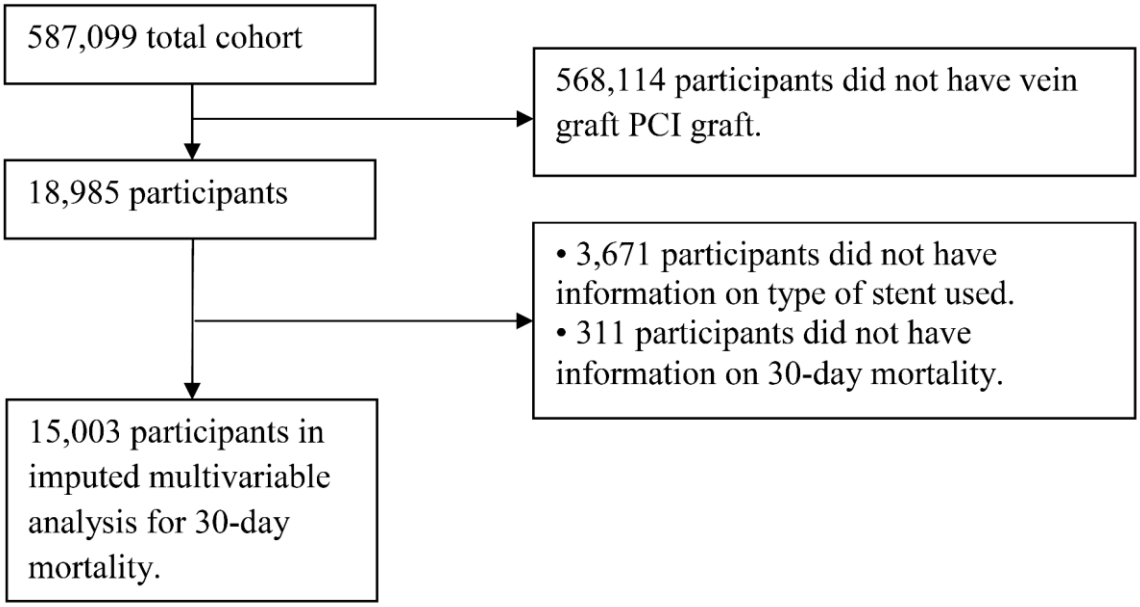
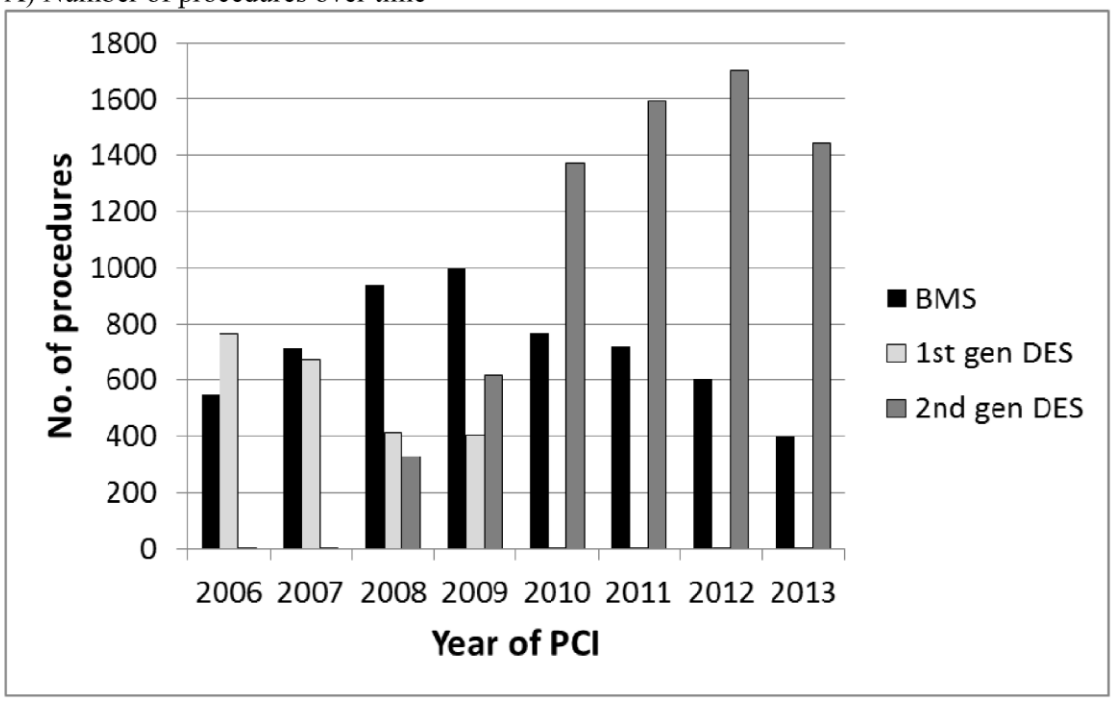
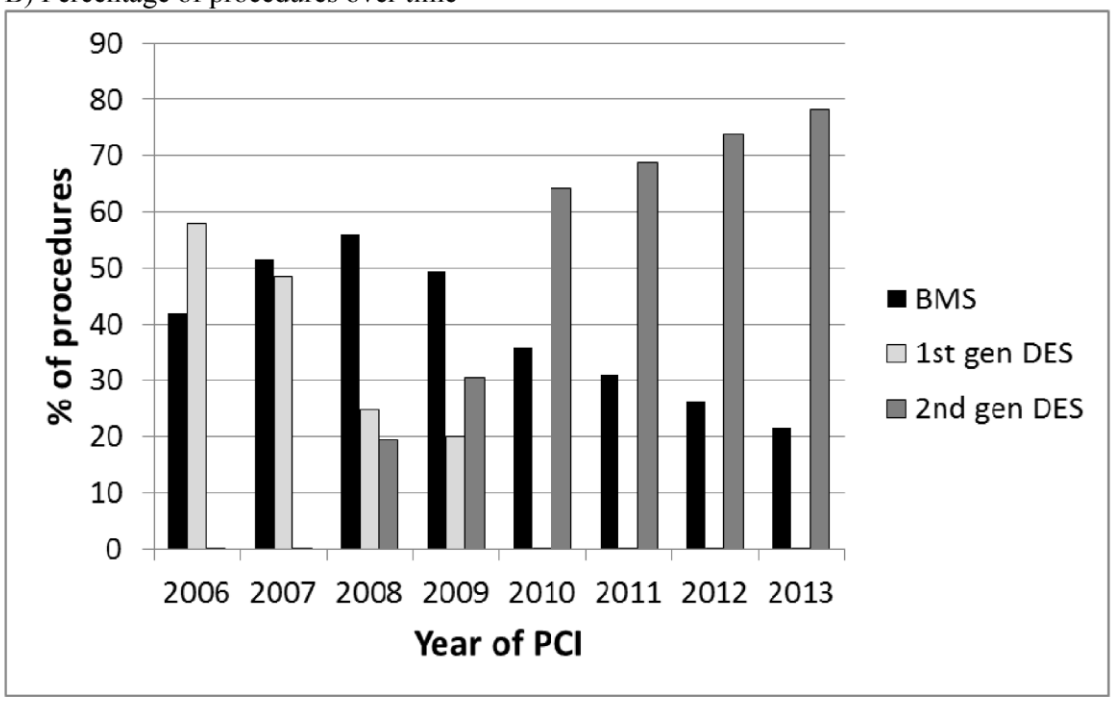


Figure 2. Changes in use of stents over time. BMS indicates bare metal stents; DES, drug-eluting stent; and PCI, percutaneous coronary intervention.

A) Number of procedures over time



B) Percentage of procedures over time



SUPPLEMENTARY MATERIAL

Supplemental Table 1: Missing data

Variable	Number of available values (%)	Number of missing values (%)
Age	14,998 (99.97%)	5 (0.03%)
Male gender	14,969 (99.8%)	34 (0.2%)
Smoker (current or ex)	13,039 (87%)	1,964 (13%)
Diabetes	14,383 (96%)	620 (4%)
Hypertension	14,539 (97%)	464 (3%)
Hyperlipidemia	14,539 (97%)	464 (3%)
Previous MI	14,041 (94%)	962 (6%)
Previous stroke	14,539 (97%)	464 (3%)
Peripheral vascular disease	14,539 (97%)	464 (3%)
Renal disease	14,785 (99%)	218 (1%)
Previous PCI	14,433 (96%)	570 (4%)
Left ventricular ejection fraction	7,662 (51%)	7,341 (49%)
Family history of CAD	12,515 (83%)	2,488 (17%)
Radial access	14,644 (98%)	359 (2%)
Glycoprotein IIb/IIIa inhibitor	14,107 (94%)	896 (6%)
Bivalirudin use	13,999 (93%)	1,004 (7%)
Multivessel disease	12,068 (80%)	2,935 (20%)
Cardiogenic shock	13,589 (91%)	1,414 (9%)
Use of intra-aortic balloon pump	14,309 (95%)	694 (5%)
Thrombus aspiration	14,414 (96%)	589 (4%)
Ventilatory support	13,288 (89%)	1,715 (11%)
Embolic protection device	14,502 (97%)	501 (3%)
Diagnosis	14,543 (97%)	460 (3%)
Year	15,003 (100%)	0 (0%)
MACE	14,470 (96%)	533 (4%)
Death at 30 days	15,003 (100%)	0 (0%)
Death at 365 days	14,268 (95%)	735 (5%)

MI=myocardial infarction, PCI=percutaneous coronary intervention, MACE=major adverse cardiovascular event.

Supplemental Table 2: Outcomes which collectively combine to produce in-hospital MACE

Variable	Bare metal stent (BMS)	1st gen. DES	2nd gen. DES	p-value		
	6,680	2,101	5,987	1st gen. DES vs BMS	2nd gen. DES vs BMS	2nd vs 1st gen. DES
Non-q wave myocardial infarction	31 (0.46%)	11 (0.52%)	23 (0.38%)	0.73	0.49	0.40
Death in-hospital	100 (1.5%)	13 (0.62%)	52 (0.87%)	0.002	0.001	0.27
Reinfarction	7 (0.10%)	2 (0.10%)	6 (0.10%)	0.91	0.94	0.95
Reintervention PCI	32 (0.48%)	5 (0.24%)	14 (0.23%)	0.14	0.022	0.97

BMS=bare metal stent, DES=drug eluting stent, gen.=generation, PCI=percutaneous coronary intervention.

Supplemental Table 3: Matching success diagnostics for propensity model

Comparison	Group	Mean (SD)	Median (IQR)
1st generation DES vs BMS	Case (1st gen DES)	0.7151 (0.2231)	0.7000 (0.5236-0.9939)
	Control (BMS)	0.7151 (0.2230)	0.7000 (0.5235-0.9940)
	Abs(Case-Control)	0.00029 (0.00110)	0.00011 (0.00004-0.00027)
2nd generation DES vs BMS	Case (2nd gen DES)	0.4563 (0.2558)	0.3400 (0.2541-0.6320)
	Control (BMS)	0.4463 (0.2557)	0.3400 (0.2542-0.6319)
	Abs(Case-Control)	0.00019 (0.00139)	0.00005 (0.00002-0.00014)

BMS=bare metal stent, DES=drug eluting stent, gen.=generation, PCI=percutaneous coronary intervention, IQR=interquartile range.

Distribution of propensity scores and residual propensity score differences between pairing for each comparison are shown and quality of matching for propensity matched imputed cohort.

Supplemental Table 4: Propensity score matching analysis on 10 imputed datasets, reporting odds ratios (transformed from the average treatment effect reported in Table 3 of the main paper)

Analysis	Method	Group	Odds ratio	95% CI		p-value
In-hospital MACE	Propensity score matching, ATE	1st gen. DES vs BMS (n=7,950)	0.56	0.29	0.84	0.002
		2nd gen. DES vs BMS (n=12,738)	0.67	0.44	0.90	0.006
30 day mortality	Propensity score matching, ATE	1st gen. DES vs BMS (n=7,950)	0.44	0.22	0.66	<0.001
		2nd gen. DES vs BMS (n=12,738)	0.51	0.27	0.75	<0.001
1 year mortality	Propensity score matching, ATE	1st gen. DES vs BMS (n=7,950)	0.76	0.27	1.31	0.373
		2nd gen. DES vs BMS (n=12,738)	0.61	0.47	0.75	<0.001

MACE=major adverse cardiovascular events, BMS=bare metal stent, DES=drug eluting stent, gen.=generation, ATE=average treatment effects.