**Drug Eluting Stents vs. Bare Metal Stents in Saphenous Vein Grafts: a Randomized,
Double-Blind, Trial**

Emmanouil S. Brilakis, MD, PhD¹⁻³—~~(Full Professor)~~

Robert Edson, MA⁴

Deepak L. Bhatt, MD, MPH⁵⁻⁷—~~(Full Professor)~~

Steven Goldman, MD⁸—~~(Full Professor)~~

David R. Holmes, Jr., MD⁹—~~(Full Professor)~~

Sunil V. Rao, MD^{10, 11}

Kendrick Shunk, MD, PhD^{12,13}—~~(Full Professor)~~

Bavana V. Rangan, BDS, MPH^{1,3}

Kreton Mavromatis, MD^{14,15}

Kodangudi Ramanathan, MD^{16,17}

Anthony A. Bavry, MD, MPH^{18,19}

~~Edward O. McFalls, MD, PhD^{20,21}~~

Santiago Garcia, MD^{20,21}

~~Hoang Thai, MD^{22,23}~~

~~Barry F. Uretsky, MD^{24,25}~~

Faisal Latif, MD^{22,23}

Ehrin Armstrong, MD^{24,25}

~~Jose Ortiz, MD^{30,31}~~

Hani Jneid, MD^{26,27}

~~Jayson Liu, MD³⁴~~

~~Kul Aggarwal, MD~~^{35,36}

Todd A. Conner, PharmD^{28,37}

Todd Wagner, PhD^{29,30,38,39}

Judit Karacsonyi, MD^{1,3}

Lauren Uyeda, MA, MBA⁴

Beverly Ventura⁴

Aaron Alsleben, BA, MSN⁴

Ying Lu, PhD^{30,39}-(Full Professor)

Mei-Chiung Shih, PhD^{4, 30,39}-(Full Professor)

Subhash Banerjee, MD^{1, 3}-(Full Professor)

On behalf of the DIVA Trial Investigators*

*DIVA trial investigators would be listed at the end of the paper

¹ VA North Texas Health Care System, 4500 S. Lancaster Road (111A), Dallas, Texas 75216

² Minneapolis Heart Institute, 920 E 28th Street #300, Minneapolis, Minnesota 55407

³ University of Texas Southwestern Medical School, Dallas, Texas

⁴ VA Cooperative Studies Program Coordinating Center, Palo Alto CSPCC (151K), 701-B N. Shoreline Blvd, Mountain View, California 94043-3208

⁵ VA Boston Healthcare System, Boston, Massachusetts

⁶ Brigham and Women's Hospital Heart and Vascular Center, Boston, Massachusetts

⁷ Harvard Medical School, 75 Francis Street, Boston, Massachusetts 02115

⁸ University of Arizona, Sarver Heart Center, 1501 North Campbell Avenue, PO Box 245046, Tucson, Arizona 85724

⁹ Mayo Clinic School of Graduate Medical Education, 200 First St. SW, Rochester, Minnesota 55905

¹⁰ Durham VA Medical Center, 508 Fulton Street, B3001, Durham, North Carolina 27705

¹¹ Duke University, Durham, North Carolina

¹² San Francisco VA Medical Center, 4150 Clement Street, Cardiology 111C, San Francisco, California 94121

¹³ University of California San Francisco, San Francisco, California

¹⁴ Atlanta VA Medical Center, 1670 Clairmont Road, Mailcode 111B, Atlanta, Georgia 30033

¹⁵ Emory University, Atlanta, Georgia

¹⁶ Memphis VA Medical Center, 1030 Jefferson Ave (111-E1), Memphis, Tennessee 38014

¹⁷ University of Tennessee, Memphis, Tennessee

¹⁸ North Florida/South Georgia Veterans Health System, 1601 SW Archer Road, 111-D, Room A129-1, Gainesville, Florida 32608

¹⁹ University of Florida, Gainesville, Florida

²⁰ Minneapolis VA Medical Center, Cardiology 111-C, One Veterans Drive, Minneapolis, Minnesota 55417

²¹ University of Minnesota, Minneapolis, Minnesota

~~²² Tucson VA Medical Center, Tucson, Arizona~~

~~²³ Desert Cardiology of Tucson, 6080 N La Cholla Blvd, Ste 200, Tucson, Arizona 85741~~

~~²⁴ John L McClellan Memorial VA Medical Center, 4300 W. 7th Street, Little Rock, Arkansas 72205~~

²⁵~~University of Arkansas of Medical Sciences, Little Rock, Arkansas~~

²² Oklahoma VA Medical Center, 901 NE 13th Street, Mailstop 111B, Oklahoma City, Oklahoma 73104

²³ University of Oklahoma, Oklahoma City, Oklahoma

²⁴ Denver VA Medical Center, 1055 Clermont Street, 111B, Denver, Colorado 80220

²⁵ University of Colorado, Denver, Colorado

³⁰~~Louis Stokes Cleveland VA Medical Center, 10701 East Boulevard, Mail Symbol 111B (W), Cleveland, Ohio 44016~~

³¹~~Case Western Reserve University, Cleveland, Ohio~~

²⁶ Michael E. DeBakey VA Medical Center, MEDVAMC-2002 Holcombe Blvd, Cardiology 3C-320C, Houston, Texas 77030

²⁷ Baylor College of Medicine, Houston, Texas

³⁴~~Edward Hines Jr. VA Medical Center, Section of Cardiology, 5th Avenue and Roosevelt Rd., Hines, Illinois 60140~~

³⁵~~Harry S. Truman Memorial VA Medical Center, Room B165, Mail Code SC/ Cardiology, 800 Hospital Drive, Columbia, Missouri 65201~~

³⁶~~University of Missouri, Columbia, Missouri~~

²⁸³⁷ VA Cooperative Studies Program Clinical Research Pharmacy Coordinating Center, 2401 Centre Ave SE, Albuquerque, New Mexico 87106

²⁹³⁸ VA Health Economics Resource Center, VA Palo Alto HCS, 795 Willow Road (152MPD), Menlo Park, California 94025

³⁰³⁹ Stanford University, Dept of Health Research and Policy, HRP Redwood Building, T101B, 259 Campus Drive, Mail Code 5464, Stanford, California 94305

Corresponding author: Emmanouil S. Brilakis, MD, PhD
Minneapolis Heart Institute
920 E 28th Street #300
Minneapolis, Minnesota 55407
Tel: (612) 863-3900
Fax: (612) 863 -6441
E-mail: esbrilakis@gmail.com

Abbreviations

ACS = Acute Coronary Syndrome

BASKET-SAVAGE = Basel Kosten Effektivitäts Trial – Saphenous Venous Graft Angioplasty
Using Glycoprotein 2b/3a Receptor Inhibitors and Drug-Eluting Stents

BMS = Bare Metal Stent(s)

CABG = Coronary Artery Bypass Graft surgery

CEC = Clinical Events Committee

DES = Drug Eluting Stent(s)

DIVA = Drug-Eluting Stents vs. Bare Metal Stents In Saphenous Vein Graft Angioplasty

EPD = Embolic Protection Device

ISAR-CABG = Is Drug-Eluting-Stenting Associated with Improved Results in Coronary Artery
Bypass Grafts?

MI = Myocardial Infarction

PCI = Percutaneous Coronary Intervention

RRISC = Reduction of Restenosis In Saphenous vein grafts with Cypher™ sirolimus-eluting
stent

SOS = Stenting Of Saphenous vein grafts

SVG = Saphenous Vein aortocoronary bypass Graft

TIMI = Thrombolysis in Myocardial Infarction

TLR = Target Lesion Revascularization

TVF = Target Vessel Failure

TVR = Target Vessel Revascularization

VA = US Department of Veterans Affairs

Summary

Background: Few studies have examined the efficacy of drug-eluting stents (DES) for reducing aortocoronary saphenous vein bypass graft (SVG) failure when compared with bare metal stents (BMS) in patients undergoing stenting of *de novo* SVG lesions.

Methods: We performed a prospective, double-blind, randomised controlled trial of DES vs BMS in *de novo* SVG lesions. The primary endpoint was the 12-month incidence of target vessel failure (TVF, defined as the composite of cardiac death, target vessel myocardial infarction, or target vessel revascularization). Secondary endpoints included all-cause death, myocardial infarction during follow-up, and target lesion revascularization. Enrollment was stopped before reaching the revised target sample size of 762 patients.

Findings: A total of 599 patients were randomised over the phone and the data for 597 were used. Mean age was 68.6 ± 7.6 years and over 99% (595 of 597) of the patients were men. The two study groups were similar for most baseline characteristics. At 12 months the incidence of TVF was 17% (51 of 292) in the DES group vs. 19% (58 of 305) in the BMS group (adjusted hazard ratio 0.92, 95% confidence interval [CI] 0.63 to 1.34, $p=0.7067$). There were no significant between group differences in the components of the primary endpoint or stent thrombosis. Over the entire length of follow-up (median: 2.7 years), the incidence of TVF was 37% in the DES group vs. 34% in the BMS group (hazard ratio, 1.11, 95% CI 0.85 to 1.45, $p=0.46$).

Interpretation: In patients undergoing stenting of *de novo* SVG lesions there were no significant differences in outcomes between those receiving DES and BMS during 12-month and long-term follow-up.

Funding: This research was supported by the Department of Veterans Affairs, Cooperative Studies Program (125), 810 Vermont Ave NW, Washington, DC 20420. The views expressed in this article are those of the authors and do not necessarily represent the views of the Department of Veterans Affairs or any US government agency.

Keywords: Percutaneous Coronary Intervention, Saphenous Vein Grafts, Outcomes

Research in context

Evidence before this study

Saphenous vein graft failure can be challenging to treat due to high rates of periprocedural complications and in-stent restenosis. Drug-eluting stents appeared to provide improved outcomes as compared with bare metal stents in three of the four randomised-controlled trials performed to date, driven by lower rates of target lesion revascularization. However, these studies were limited by small size, lack of blinding, routine angiographic follow-up, low use of embolic protection devices (EPDs), and use of first generation DES.

Added value of this study

DIVA investigated the efficacy and safety of DES versus BMS in patients presenting with de novo saphenous vein graft lesions. At 12 months there was no significant difference in the incidence of target vessel failure (composite of cardiac death, target vessel myocardial infarction, or target vessel revascularization). Similarly, during a median follow-up of 2.7 years, target vessel failure occurred in approximately 1 in 3 patients, without 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, ~~the only~~ blinded, randomised placebo-controlled trial of drug-eluting stents vs. bare metal stents in saphenous vein grafts that did not mandate routine angiographic follow-up, show that drug-eluting stents and bare metal stents were associated with similar clinical outcomes. Given their lower cost, bare metal stents may be preferred in saphenous vein graft lesions

Introduction

Coronary bypass graft surgery (CABG) is one of the most commonly performed surgical procedures with an estimated 400,000 cases performed in the US 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 US has had prior CABG and 6% of all PCIs in the United States are performed in SVGs.^{4,6} Stents improve outcomes as compared with balloon angioplasty in SVG PCI and are the current standard of care. 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 limited study.⁸⁻¹³ Four randomised studies have been performed with conflicting results (three studies showed benefit with DES¹¹⁻¹³ and one showed harm⁹). These studies were limited by small size,^{9,11,13} lack of blinding,¹¹⁻¹³ routine angiographic follow-up,^{9,11,12} low use of embolic protection devices (EPDs)¹² and use of first generation DES.^{9,11-13}

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

Methods

Study design

The Drug-Eluting Stents vs. Bare Metal Stents In Saphenous Vein Graft Angioplasty (DIVA) Trial was a multicenter, randomised trial conducted at 25 VA centers. The DIVA trial study design has been published.¹⁴ The trial was funded by the Department of Veterans Affairs' Cooperative Studies Program. A planning committee and a steering 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. All patients provided written informed consent.

Participants

Between January 2012 and December 2015, 3,482 patients with prior CABG undergoing cardiac catheterization at participating sites were evaluated for enrollment (Figure 1). Eligible patients were those who were at least 18 years of age and who 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 EPD, agreed to participate and take medication as prescribed, and provided informed consent. 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 prior 12 months; had hemorrhagic 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

(ACS) at sites that use blinded study medication; or participated in another interventional randomised trial.

Randomisation, masking, and procedures

Enrolled patients were randomly assigned using a phone system in a 1:1 ratio to receive DES or BMS in the target SVG(s). Each patient received as many stents as clinically indicated based on operator judgment. Randomisation was stratified by presence/absence of diabetes, and number of target SVG lesions requiring PCI (1 or ≥ 2) within each participating site [using an adaptive scheme intended to balance the two stent type groups on marginal totals for the stratification factors.](#)

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. To preserve the study blinding, at sites where standard of care was to treat patients receiving only BMS with one month of a P2Y₁₂ inhibitor, study patients who did not present with an ACS and who did not require ≥ 12 months of P2Y₁₂ inhibitor for clinical reasons were given clopidogrel or matching placebo for 12 months. All patients were prescribed aspirin as per standard of care.

PCI was performed using standard techniques at the discretion of each operator. Intent to use an EPD was required for inclusion in the study. In patients with multiple lesions the same type of stent was used for all lesions whenever possible.

Outcomes

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

The primary endpoint of the study was the 12-month incidence of target vessel failure (TVF), defined as the composite of cardiac death, target vessel myocardial infarction (MI), or target vessel revascularization (TVR). 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 MI¹⁵; stent thrombosis¹⁶; target lesion revascularization (TLR); non-target vessel revascularization; the composite endpoint of any death, any MI, or TVR (patient-oriented composite endpoint); the composite endpoint of cardiac death, target vessel MI, or TLR (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

The cardiac interventionalist was not blinded to the stent assignment, but the participants, the referring physicians, the (primary) study coordinators and the outcome assessors (clinical events committee and angiographic and intravascular ultrasonography core laboratories) were blinded. An independent clinical events committee (CEC) adjudicated possible TVF events (all deaths, MIs not reported as non-target vessel, and TVRs) reported by the sites that occurred during the first 12 months of follow-up. In addition, the study's angiographic and electrocardiographic core laboratories reviewed the angiograms and electrocardiograms 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.

Statistical analysis

We estimated that a total sample size of 519 participants at 25 sites would provide [123 participants with primary outcome \(12-month TVF\) and 90% power for detecting the difference between the two groupsprimary outcome during the first year of follow-up](#), assuming 12-month TVF rate 30% in BMS and 18% in DES [\(corresponding hazard ratio 0.556\)](#).^{9,10,17,18} [Because of a lower than anticipated overall TVF rate of 16% after 384 randomisations, the sample size was increased to 762 which would provide 86% power to detect a group difference based on 122 participants with TVF, an overall TVF rate of 16%, and 40% relative reduction for the DES group \(corresponding hazard ratio 0.573\).](#) Two interim analyses were planned, at approximately 25% and 60% of target adjudicated primary outcomes, to allow early stopping for efficacy (based on O'Brien-Flemming boundary) or futility (based on conditional power). The first interim analysis was performed on October 13, 2015, when there were 35 adjudicated primary outcomes (29% information time); at that time 576 participants were randomized. The Data Monitoring Committee (DMC) recommended the study to continue. ~~the TVF rate was lower than anticipated, hence the sample size was increased to 762.~~ Trial enrollment was terminated on December 31, 2015 due to slower than expected enrollment and funding issues; the final number of randomisations was 599. We only report data for 597 because for two participants the consent process was performed improperly. The study follow-up ended on December 31, 2016. The minimum length of follow-up was one year and the maximum was five years. The ~~post-hoc power of the study~~ [with 109 adjudicated primary outcomes has 86% post-hoc power](#) to detect the originally hypothesized ~~difference between DES and BMS~~ [hazard ratio 0.556 and 83% power to detect the revised hypothesized hazard ratio 0.573.](#)

The analyses for all outcomes followed the intention-to-treat principle. The primary analysis was the comparison of time to first TVF between the DES and BMS groups in the initial 12 months following index stent implantation. Cumulative incidence curves for time to TVF were calculated by stent group. Participants who were lost to follow-up were censored at the time of last contact. Log rank tests were used to compare the time to TVF. This test was stratified by presence or absence of diabetes and by number of target SVG lesions that were treated (one vs. >1). Additionally, the Cox proportional hazards model¹⁹ was used to assess the effect of stent type as well as various covariates on time to TVF. Participant and graft characteristics thought to be potentially predictive of SVG patency, including diabetes mellitus, number of target SVG lesions (1 or >1), 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 TIMI flow (3 vs. <3), 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 TVF 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 using the scaled Schoenfeld residuals against time and using the Grambsch and Therneau (1994) test.²⁰ We also assessed piecewise constant hazard ratios for the time period up to one year of follow-up (the interval for the primary endpoint) versus after one year to test for non-constant hazards. ~~Interaction terms between stent type and other significant participant-graft characteristics were also assessed.~~ 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 pre-planned secondary analysis, we performed similar analyses as above to compare time to TVF based on all follow-up data.

The procedural success rate and the incidence of post-procedural MI and post-procedural [GUSTO moderate or severe](#) bleeding^{21,22} were compared between the DES and BMS groups using the difference between two independent proportions. Cumulative incidence curves and 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 using Gray's (1988) test²³ and Fine & Gray's (1999)²⁴ methods were performed. Proportional hazards regression for sub-distributions of competing risks were also performed.

The DIVA trial is registered with ClinicalTrials.gov, number NCT 01121224.

Role of the funding source

The funder (Veterans Affairs Cooperative Studies Program) 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

Patients and follow-up

Between January 1, 2012 and December 31, 2015, a total of 3,482 patients with prior CABG undergoing cardiac catheterization at the participating centers were screened for participation in the trial and 597 (17%) were randomised and included in the final analysis (Figure 1). The two study groups were well balanced for most clinical and angiographic characteristics (Table 1), except for SVG age and race categories. During the index procedure, 13%% (77 of 597) of the patients had one target SVG with multiple SVG lesions treated, 4%%

(23 of 597) had multiple SVGs treated, and 16% (95 of 597) had native coronary artery lesions treated. An embolic protection device was used in 69% (409 of 597) of patients in both groups. In the group receiving DES, 88% (256 of 292) of 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 shown in Table S1 in the Supplementary Appendix. The median follow-up time was 32 months (range: 0.23 to 59).

Study outcomes

At 12 months, the incidence of TVF was 17% (51 of 292) in the DES group and 19% (58 of 305) in the BMS group (using the stratified log rank test; hazard ratio ~~was~~ adjusted for stratification of randomisation was 0.92, 95% confidence intervals [CI] 0.63 to 1.34, $p=0.7067$) (Table 2 and Figure 2). Log rank tests ~~un~~stratified by diabetes status and 1 versus ≥ 2 SVG lesions also were not significant (data not shown). There was also no significant between-group difference in the primary outcome after adjustment for baseline imbalance in SVG age (less than versus at least the median age of 13.5 years). The results for TVF were consistent in subgroups defined by demographic, clinical, lesion, and procedural characteristics (Table S2 in the Supplementary Appendix). Also, adding stent assignment to the proportional hazards model with participant and graft characteristics as covariates did not significantly increase the model's predictive ability ($p=0.837$) of TVF at 12 months.

Analyses of the 12-month incidence of TVF with noncardiac death as a competing risk, target vessel or indeterminate MI with any death as a competing risk, and TVR with any death as

a competing risk showed no significant effects from stent assignment on any cause-specific hazard.

There were no significant between-group differences in the 12-month incidence of all-cause death, any myocardial infarction, definite or probable stent thrombosis, stroke, or other secondary outcomes (Table 2 and Figure S1 in the Supplementary Appendix).

Median length of follow-up was 2.7 years with 68% (406 of 597) of the participants followed for at least two years and 39% (235 of 597) followed for at least three years. Over the entire length of follow-up (~~median: 2.7 years~~), the incidence of TVF was 37% (108 of 292) in the DES group and 34% (105 of 305) in the BMS group (~~adjusted~~ hazard ratio 1.104, 95% confidence intervals [CI] 0.845 to 1.435, P=0.446) (Table 3 and Figure S2 in the Supplementary Appendix). ~~There was no significant between-group difference in the primary outcome after adjustment for baseline imbalance in SVG age (<13.5 years versus ≥13.5), and t~~ The results for TVF over the entire follow-up were consistent in subgroups defined by demographic, clinical, lesion, and procedural characteristics (Table S2 in the Supplementary Appendix). ~~A test using piecewise constant hazard ratios for the time periods up to before and after one year of follow-up versus after one year showed~~ There was no significant evidence of non-proportional ~~constant~~ hazards (Grambsch-Therneau test p=0.08). In a post-hoc analysis, there was no significant between-group difference in the primary outcome after adjustment for baseline imbalance in SVG age (<13.5 years versus ≥13.5).

There were no 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 (Table 3 and Figure S3 in the Supplementary Appendix). There were also no differences in the percent of participants reporting one or more serious adverse events overall

and by classification using the Medical Dictionary for Regulatory Activities (MedDRA; Tables S3 and S4 in the Supplemental Appendix). Most ~~patients requiring repeat revascularizations were performed 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 TVF and/or SVG occlusion that was intervened upon showed no difference between treatment groups at 12 months (Table 2) and during the entire duration of follow-up (Table 3).

DISCUSSION

In DIVA, 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 revascularization 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 ~~was the first trial of SVG stenting to use stent type blinding and the second that~~ did not mandate angiographic follow-up, which is known to increase the rates of repeat revascularization in favor of DES.²⁵ DIVA had higher use of embolic protection devices (69% [409 of 597]) than any prior SVG stenting trial.

Our findings are in contrast with the findings of three¹¹⁻¹³ of the four randomised-controlled trials performed to date that showed benefit with DES over BMS in SVGs. The “Is Drug-Eluting-Stenting Associated with Improved Results in Coronary Artery Bypass Grafts?” (ISAR-CABG) trial randomised 610 participants to a first generation DES or a BMS and reported lower 12-month incidence of TVR in the DES group (7% vs. 13%, $p=0.01$), and no significant differences in all-cause mortality, MI, and definite or probable stent thrombosis as compared with BMS.¹² ISAR-CABG had planned angiographic follow-up as did two smaller

studies: the first study showed harm (higher mortality with DES at 3 years [29% vs. 0%, $p=0.001$],⁹ although most deaths were due to non-cardiac causes) and similar TVR in both groups. The second study showed lower risk for myocardial infarction and target lesion revascularization with DES.^{10,11} The most recent trial (Basel Kosten Effektivitäts Trial – Saphenous Venous Graft Angioplasty Using Glycoprotein 2b/3a Receptor Inhibitors and Drug-Eluting Stents [BASKET-SAVAGE]), randomised 173 patients, had no planned angiographic follow-up, and revealed lower incidence of TVR in the DES group (4.5% vs. 19.1% at 3 years, $p<0.001$).¹³ The lack of improved outcomes with DES in DIVA was observed despite using second generation DES in 88.8% (256 of 292) of the DES group patients, whereas first generation DES were used in all prior studies.^{9,11-13}

The lack 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} It could also be due to the large burden of comorbidities among prior CABG patients,¹⁴ or the use of thin-strut bare metal stents that may have lower risk for restenosis as compared with thicker strut stents that were used in prior SVG PCI studies.^{9,11-13} It is unlikely to be due to 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 randomization. The study results have important economic implications in countries with high DES prices such as the US, as 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 may differ between countries, depending on local stent pricing. An alternative treatment approach would be to recanalize 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 VA studies, nearly all study participants were men, limiting extrapolation of the results to women, although most patients undergoing PCI after CABG are men.³¹ The interventionalists performing the index SVG PCI were not blinded to the type of stent used, although the patients, clinicians, and event adjudicators were blinded. The study was stopped before completion of the revised enrollment 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 hypothesized hazard ratio 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 revascularization.

Contributors

ESB, RE, DLB, StG, DRH, SVR, KS, BVR, TAC, TW, YL, MCS and SB designed the study, analysed and interpreted data, and wrote and revised the manuscript. KM, KR, and AAB, EOM, SaG, HT, BFU, FL, EA, JO, HJ, JL, and KA implemented the study, enrolled patients, interpreted data, and wrote the manuscript. JK, BV, and AA analysed and interpreted data and wrote the manuscript. RE, LU, MCS analysed data, did the statistical analyses, and wrote the manuscript. ESB wrote the first draft and submitted the final version of the manuscript. All authors approved the final version of the manuscript

Declaration of interests

Emmanouil Brilakis: consulting/speaker honoraria from Abbott Vascular, Amgen, Asahi, Boston Scientific, Cardinal Health, CSI, Elsevier, GE Healthcare, Medtronic, and Nitiloop; research support from Boston Scientific, InfraRedx and Osprey; spouse was employee of Medtronic.

Robert Edson: none

Deepak L. Bhatt: Advisory Board: Cardax, Elsevier Practice Update Cardiology, Medscape Cardiology, Regado Biosciences; Board of Directors: Boston VA Research Institute, Society of Cardiovascular Patient Care; Chair: American Heart Association Quality Oversight Committee; Data Monitoring Committees: Cleveland Clinic, Duke Clinical Research Institute, Harvard Clinical Research Institute, Mayo Clinic, Mount Sinai School of Medicine, Population Health Research Institute; Honoraria: American College of Cardiology (Senior Associate Editor, Clinical Trials and News, ACC.org), Belvoir Publications (Editor in Chief, Harvard Heart Letter), Duke Clinical Research Institute (clinical trial steering committees), Harvard Clinical Research Institute (clinical trial steering committee), HMP Communications (Editor in Chief, Journal of Invasive Cardiology), Journal of the American College of Cardiology (Guest Editor; Associate Editor), Population Health Research Institute (clinical trial steering committee), Slack Publications (Chief Medical Editor, Cardiology Today's Intervention), Society of Cardiovascular Patient Care (Secretary/Treasurer), WebMD (CME steering committees); Other: Clinical Cardiology (Deputy Editor), NCDR-ACTION Registry Steering Committee (Chair), VA CART Research and Publications Committee (Chair); Research Funding: Amarin, Amgen, AstraZeneca, Bristol-Myers Squibb, Chiesi, Eisai, Ethicon, Forest Laboratories, Ironwood, Ischemix, Lilly, Medtronic, Pfizer, Roche, Sanofi

Aventis, The Medicines Company; Royalties: Elsevier (Editor, Cardiovascular Intervention: A Companion to Braunwald's Heart Disease); Site Co-Investigator: Biotronik, Boston Scientific, St. Jude Medical (now Abbott); Trustee: American College of Cardiology; Unfunded Research: FlowCo, Merck, PLx Pharma, Takeda.

Steven Goldman: research support from the National Institutes of Health, the VA Cooperative Studies Program, the Arizona Biomedical Research Commission, Merck Pharmaceuticals. Co-founder of Avery Therapeutic.

David R. Holmes, Jr.: none

Sunil V. Rao: consultant Medtronic

Kendrick Shunk: consulting: Medeon Bio Inc, TransAortic Medical, Terumo; research support: Siemens Medical Systems, Medinol.

Kreton Mavromatis: none

Kodangudi Ramanathan: none

Anthony A. Bavry: consultant for American College of Cardiology

Edward O. McFalls: none

Santiago Garcia: consultant for Surmodics, Osprey medical, Medtronic and Boston Scientific. Research grants from Edwards Life Sciences and VA Office of Research and Development.

Hoang Thai: none

Barry F. Uretsky: none

Faisal Latif: speaker for Abbott Vascular, consulting for Medicare.

Ehrin Armstrong: consultant to Abbott Vascular, Boston Scientific, Cardiovascular Systems, Medtronic, Spectranetics

~~Jose Ortiz: none~~

~~Hani Incid: none~~

~~Jayson Liu: none~~

~~Kul Aggarwal: none~~

Todd A. Conner: none

Todd Wagner: none

Judit Karacsonyi: none

Bavana V. Rangan: research grant from InfraRedx and from the Spectranetics Corporation.

Salary support from the VA Cooperative Studies Program.

Lauren Uyeda: none

Beverly Ventura: none

Aaron Alsleben: none

Ying Lu: consultant to PTC Therapeutics (Mock FDA Advisory Committee meeting) and

PaxVax (Safety Monitoring Committee).

Mei-Chiung Shih: none

Subhash Banerjee: speaker honoraria: AstraZeneca, CSI, Gore, Medtronic and institutional research grants: Boston Scientific Corporation, Merck.

Acknowledgements

Formatted: Highlight

The following persons contributed to DIVA:

Planning Committee: Emmanouil Brilakis, MD, PhD (Study Co-Chair), *Dallas, TX and Minneapolis, MN*; Subhash Banerjee, MD, FACC, FSCAI (Study Co-Chair), *Dallas, TX*; David R. Holmes, Jr., MD, *Rochester, MN*; Kendrick Shunk, MD, PhD, *San Francisco, CA*; John Rumsfeld, MD, PhD, *Denver, CO*; Biswajit Kar, MD, *Houston, TX*; Steven Goldman, MD, *Tucson, AZ*; Philip Lavori, PhD, *Stanford, CA*; Mark Holodniy, MD, *Palo Alto, CA*; Mike Sather, PhD, *Albuquerque, NM*; Mei Chiung Shih, PhD, *Palo Alto, CA*; Robert Edson, MA, *Palo Alto, CA*; Cindy Colling, RPh, MS, *Albuquerque, NM*; Mark Smith, PhD, *Palo Alto, CA*; Lori Nielsen, BA, *Palo Alto CA*;

Executive Committee: Emmanouil Brilakis, MD, PhD (Study Co-Chair), *Dallas, TX and Minneapolis, MN*; Subhash Banerjee, MD, (Study Co-Chair), *Dallas, TX*; Deepak Bhatt, MD, MPH, *Boston, MA*; Todd Conner, PharmD, *Albuquerque, NM*; Robert Edson, MA, *Palo Alto, CA*; Steven Goldman, MD, *Tucson, AZ*; David Holmes, Jr., MD, *Rochester, MN*; Bavana Rangan, BDS, MPH, *Dallas, TX*; Sunil Rao, MD, *Durham, NC*; Kendrick Shunk, MD, PhD, *San Francisco, CA*; Beverly Ventura, BS, *Palo Alto, CA*; Todd Wagner, PhD, *Palo Alto, CA*; Holly Wise, RN, (past), *Dallas, TX*; Rob Ringer, PharmD, *Albuquerque, NM* (past); Mark Smith, PhD, *Palo Alto, CA* (past); Lisa Zehm, MS, *Palo Alto, CA* (past); Regan Dodson, *Palo Alto, CA* (past).

Data Monitoring Committee (DMC): George Dangas, MD, PhD (Chair), *New York, NY*; Paul Heidenreich, MD, *Palo Alto, CA*; Motomi Mori, PhD, *Portland, OR*; Srihari Naidu, MD, *New York, NY*; Paul Sorajja, MD, *Rochester, MN*; George Williams, PhD, *Thousand Oaks, CA*;

Chairs' Office, Dallas VA Medical Center: *National Clinical Coordinator:* Bavana Rangan, BDS, MPH, Holly Wise, RN (past).

Participating VA Medical Centers: (Site Investigators, Study Coordinators, and Cath Lab Technicians): *Albuquerque*—Devona Ratliff, MD (past); Patricia Richardson (past); Robyn Elliott, MD (past); Ronald Angst (past); Stephen Zalewski (past). *Ann Arbor*—Claire Duvernoy, MD; Amer Ardati, MD (past); Brahmajee Nallamothu, MD; Daniel Menees, MD; Hitinder Gurm, MD; Michael Thomas, MD; Paul Grossman, MD; Patricia Rose; Wendy Warshal; Genevieve Bautista (past). *Asheville*—Kristine Owen, MD; On Topaz, MD; Valerie Allen; Mariette Coyle; Michael Bouchard; Richard Ziobro. *Atlanta*—Kreton Mavromatis, MD; Gautam Kumar, MD; Jeanne Dow; Nikki Leslie; Pankaj Manocha; Charlene Brown (past); Sumati Raghavan; Zohreh Forghani. *Cleveland*—Jose Ortiz, MD; Joseph Jozic, MD; David Zidar, MD; Hiram Bezerra, MD; Jonathan Goldberg, MD; Mohammed Osman, MD; Noah Rosenthal, MD; Sahil Parikh, MD; Deborah Nogle; Denise Poesik (past); Angela Krupka (past); Donna Rosin; Gale Schmidt (past); James Jones (past); Jessica Smith (past); Taissa Zappernick; Vinay Kumaran. *Columbia*—Kul Aggarwal, MD; Albert Chan, MD; Arun Kumar, MD; Jamie Easley; Alisa Lau-Sieckman; Effie Barba; John Schafer; Karen Johnston; Lisa Dodds; Robert Dykes (past); Samantha Hawkins; Vicki Pareel. *Dallas*—Jerrold Grodin, MD; Subhash Banerjee, MD; Emmanouil Brilakis, MD (past); Preeti Kamath; Atif Mohammad; Cyenthia Willis; Evaster Bennett; Judi Bennett; Lisa Justus-Donawho; Michelle Lytal; Swagata Das (past); Wanda Frey (past). *Denver*—Ehrin Armstrong, MD; Brack Hattler, MD; Stephen Waldo, MD; Thomas Tsai, MD; Caitlin Hutchinson; Celeste Canel; Darcy Donaldson (past); Jeanne Kalhoff; Jill Adams (past); Katherine Surman; Cathy Clark; Damianos Kokkinidis; Trish Ellkins; Marsha Hallahan (past). *Durham*—Sunil Rao, MD; Thomas Powsie, MD; William Jones, MD; Kenneth Morris;

MD; Mitchell Krucoff, MD; Kristen Mathis; Christopher Paterno (past); Marilyn Powell; Kathy Aristy. **Gainesville**—Anthony Bavry, MD; Calvin Choi, MD; Ki Park, MD; Tempa Curry; Alice Boyette (past); Cila Wright (past); Debra Robertson; Kris Finley. **Hines**—Jayson Liu, MD; Lonnie Edwards, MD; Conor McBurney; Sherri LaVela; AnJelique Leslie (past); Anne Garabedian (past); Jacalyn Harvey-Jaconetty (past); David Przychocki; Katherine Miskovic; Linda McClendon. **Houston**—Hani Jneid, MD; David Paniagua, MD; Biswajit Kar, MD (past); Emily Broussard; Jo Ann Malarchick; Leah Palmer; Celso De Los Santos; Cynthia Boudreaux (past); Minhaj Siddiqui (past); Nancy Logan (past); Pamela Harvie (past). **Indianapolis**—Islam Bolad, MD; Roopa Subbarao, MD; Jeffrey Breall, MD (past); Rita Mukerji, MD (past); Sharon Henson; Vicki Williams; Brandon Clark (past); Connie Krier (past); Lauren Hubbard; Yefim Dubrovensky. **Lexington**—Khaled Ziada, MD; Ahmed Abdel Latif, MD; David Booth, MD; Caroline Rodgers; Jennifer Isaacs; Rebekah Evans; Yvonne Taul (past); Elizabeth Moles (past); Kelli Fruch (past); Ruth Oremus (past); Wendy Wijesiri, (past); Lisa Anstine; Paige Ladenburger. **Little Rock**—Barry Uretsky, MD; Abdul Hakeem, MD; Rajesh Sachdeva, MD (past); Kristin Miller; Katherine Dishongh (past); Lauren Landers (past); Aaron Bayles (past); Brad Massey; Jacqueline Saxton; Jennifer Socia; Jesse Byrd; Michael Davis; Sandra Satterlee (past); Sandra Scharbor. **Memphis**—Kodangudi Ramanathan, MD; Rahman Shah, MD; Jesse McGee, MD; Ashley Armstrong; Lillie Johnson. **Minneapolis**—Edward McFalls, MD; Santiago Garcia, MD; Alok Sharma, MD; Rizwan Siddiqui, MD; Stephan Bertog, MD; Debra Johnson; Debra Condon (past); Tacy Meyeraan (past); Stacy McNabb (past); Elizabeth Latts (past); Hattie Williams (past); Rebekah Herrmann (past); Amy Magras (past); Cyril Malle Barlow (past); Robert Colbert (past); Joseph Brown; Lisa Bass; Michelle Rambaum. **New Orleans**—Anand Irimpen, MD; Nidal Abi Rafeh, MD; Suzanne Bowers; Kartik Munshi (past); Nana Asafu

Adaye. *New York Harbor*—Steven Sedlis, MD; Jeffrey Lorin, MD; Lau Yung, MD; Leandro Maranan; Doreas Casaula (past); John Donehey (past); Mary Keary. *Oklahoma City*—Faisal Latif, MD; Mazen Abu-Fadel, MD; Talla Rousan, MD; Udho Thadani, MD; Arleen Ramirez Jimenez; Rhonda Heim (past); Amanda Fuller; Nicole Sorick (past); *San Francisco*—Kendrick Shunk, MD; Fady Malik, MD; Jeffrey Zimmet, MD; Tony Chou, MD; Kathleen Stanley; Cynthia Huynh; Evelyn Badua (past); Karen Rehder (past); Jacqueline Williams. *St. Paul*; Shirley Sayavong. *Seattle*—Kenneth Lehmann, MD; Sohilkumar Naria; Georgia Galvin (past); Cornelia Schneider (past); Craig Ewert. *St. Louis*—Michael Forsberg, MD; Megumi Taniuchi, MD; Andrew Klein, MD (past); Caroline Rowe (past); Paul Vercher; Kristi Waidmann (past); Kristin Vargo (past). *Tucson*—Huu Tam Truong, MD; Ryan Tsuda, MD; Sergio Thal, MD; Elizabeth Juneman, MD; Kapildeo Luton, MD; Hoang Thai, MD (past); Steven Goldman, MD (past); Amani Morgan Mikail; Andrea Escalante (past); Marivic Hansen (past); Juliana Kipps (past); Alice McArthur (past); Barbara Lambeth; Brooke Finley; Katherine Center; Michael Sandoval; Sandra Velasquez; Cynthia Laughren (past); Elaine Charteris; Irma Sereno (past); Jovanka Hall (past); Linda Ferguson (past); Phyllis Houston (past); Sherry Daugherty (past); Suzette Chavez (past). *Washington, D.C.*—Vasilios Papademetriou, MD; David Lu, MD; Mary Bloom; Christiana Chrysostomou; Barbara Gregory (past); Susan Amodeo (past); Louis Hooper; Paola Chrysostomou (past). *West Roxbury*—Scott Kinlay, MBBS, PhD; David Faxon, MD; Sammy Elmariah, MD, MPH; Deepak Bhatt, MD (past); Kevin Croce, MD, PhD (past); Mariah Bundy; Simon Ostrowski (past); Samantha Ly (past); Sandra Mayo (past); Sara Jones (past); Jacquelyn My Do; Margot Quinn; Martha Nykiel; Adrianna Nava (past).

Biostatistics and Research Data Processing: *Palo Alto VA Cooperative Studies Program Coordinating Center* (Director; Chief Medical Officer; Biostatistician; Project Management

Staff; Data Management Staff; Statistical Programmer; Regulatory and Clinical Compliance Staff; Project Coordinator; Research Assistant; Informatics Staff; Administrative and Budget Staff); Mei-Chiung Shih, PhD (Acting Director), Ying Lu, PhD (past); Jennifer Lee, MD; Bob Edson, MA; Lori Nielsen, BA, Beverly Ventura, BS, Lisa Zehm, MS (past), Regan Dodson (past); Alison Quien, Nicholas Zemstov, Scott Zellner (*West Haven CSPCC*), Meredith Miller, Amy Morrow, Andres Busetto, Elizabeth Smith, Michelle Mullens, Pei-Pei Woo, Vaishali Krishnan, Vicken Sagherian, Jennifer Smith (past), Lauren Ciabattari (past), Bor-Ming Ou, MS (past); Lauren Uyeda, MA, MBA; Jennifer Cockroft, Aaron Alsleben, Martha Forrester (past); Jerry Rogers, Kahlil Mariani (past); Bobbie Hastings (past), Deanne Hirshfield (past); Kevin Chow, Tracey Tibbetts; Jeron Talbott, Sandra Stevenson, Joseph Nozzolillo (past), Cheylynne Somogyi (past).

Health Economics Resource Center (HERC): (Health Economist; Research Assistant): Todd Wagner, PhD; Nicole Flores.

Clinical Research Pharmacy: VA Cooperative Studies Program Clinical Research Pharmacy Coordinating Center (Director; Assistant Director; Clinical Research Pharmacist; Adverse Event Specialist Group; Project Manager; IT Group): Stuart Warren, J.D., PharmD, Mike Sather, PhD, (past); Thelma Salazar; Todd Conner, PharmD, Amy Suen (past), Robert Ringer, PharmD (past); Cynthia Colling, RPh, MS (past); Alexandra Scrymgeour, Amanda Snodgrass, Denise Brochetti, Jeannie Kreuch, Robin Burns, Tracy Okoro, Carol Badgett; Jeffrey Huminik, Jolene Day (past); Brandi Dillard (past); James Pontzer, Zachary Taylor.

Core Lab, Dallas VA Medical Center: Haskell Ellis, Judit Karaesonyi, Lorenza Makke, Mohammed Parupia, Peter Tajti, Rahel Iwnetu, Sheryl Poyer, Anna Kotsia (past).

Clinical Evaluation Committee (CEC): Bagai Jayant, MD, Nadella Neelima, MD, Jovin Ion, MD, Lui Charles, MD, Davies Crispin, MD, Penny William, MD, Reddy Koushik, MD, Sehob

Alan, MD, Vidovich Mladen, MD, Gigliotti Osvaldo, MD, Feldman Dmitriy, MD, Kumbhani Dharam, MD, Kakouros Nikolaos, MD, Maniu Calin, MD, Sinha Anjan, MD, Mani Kartik, MD, Arif Imran, MD.

Human Rights Committee (HRC): Charlotte Giese, Ph.D (Chair); Chaplain Fred Tittle, MDIV.

Cooperative Studies Program Central Office: (Director): Grant D. Huang, PhD, MPH (Acting); Timothy O'Leary, MD (past).

Department of Veterans Affairs, Office of Research and Development: Research and Clinical Compliance—Karen Jeans, PhD, CCRN

References

1. Hall MJ, Levant S, DeFrances CJ. Trends in inpatient hospital deaths: National Hospital Discharge Survey, 2000-2010. NCHS Data Brief 2013: 1-8.
2. Widimsky P, Straka Z, Stros P, et al. One-year coronary bypass graft patency: a randomized comparison between off-pump and on-pump surgery angiographic results of the PRAGUE-4 trial. Circulation 2004; 110: 3418-23.
3. Alexander JH, Hafley G, Harrington RA, et al. Efficacy and safety of edifoligide, an E2F transcription factor decoy, for prevention of vein graft failure following coronary artery bypass graft surgery: PREVENT IV: a randomized controlled trial. Jama 2005; 294: 2446-54.
4. Brilakis ES, Rao SV, Banerjee S, et al. Percutaneous coronary intervention in native arteries versus bypass grafts in prior coronary artery bypass grafting patients a report from the national cardiovascular data registry. JACC Cardiovascular interventions 2011; 4: 844-50.

5. Goldman S, Zadina K, Moritz T, et al. Long-term patency of saphenous vein and left internal mammary artery grafts after coronary artery bypass surgery Results from a Department of Veterans Affairs Cooperative Study. *J Am Coll Cardiol* 2004; 44: 2149-56.
6. Dehmer GJ, Weaver D, Roe MT, et al. A contemporary view of diagnostic cardiac catheterization and percutaneous coronary intervention in the United States: a report from the CathPCI Registry of the National Cardiovascular Data Registry, 2010 through June 2011. *J Am Coll Cardiol* 2012; 60: 2017-31.
7. Bona KH, Mannsverk J, Wiseth R, et al. Drug-Eluting or Bare-Metal Stents for Coronary Artery Disease. *N Engl J Med* 2016; 375: 1242-52.
8. Vermeersch P, Agostoni P, Verheye S, et al. Randomized double-blind comparison of sirolimus-eluting stent versus bare-metal stent implantation in diseased saphenous vein grafts: six-month angiographic, intravascular ultrasound, and clinical follow-up of the RRISC Trial. *J Am Coll Cardiol* 2006; 48: 2423-31.
9. Vermeersch P, Agostoni P, Verheye S, et al. Increased late mortality after sirolimus-eluting stents versus bare-metal stents in diseased saphenous vein grafts: results from the randomized DELAYED RRISC Trial. *J Am Coll Cardiol* 2007; 50: 261-7.
10. Brilakis ES, Lichtenwalter C, de Lemos JA, et al. A randomized controlled trial of a paclitaxel-eluting stent versus a similar bare-metal stent in saphenous vein graft lesions the SOS (Stenting of Saphenous Vein Grafts) trial. *J Am Coll Cardiol* 2009; 53: 919-28.
11. Brilakis ES, Lichtenwalter C, Abdel-karim AR, et al. Continued benefit from paclitaxel-eluting compared with bare-metal stent implantation in saphenous vein graft lesions during long-term follow-up of the SOS (Stenting of Saphenous Vein Grafts) trial. *JACC Cardiovascular interventions* 2011; 4: 176-82.

12. Mehilli J, Pache J, Abdel-Wahab M, et al. Drug-eluting versus bare-metal stents in saphenous vein graft lesions (ISAR-CABG): a randomised controlled superiority trial. *Lancet* 2011; 378: 1071-8.
13. Jeger R. Study to Test the Efficacy and Safety of Drug Eluting vs. Bare-Metal Stents for Saphenous Vein Graft Interventions (BASKET-SAVAGE). 2016. p. presented at the 2016 European Society of Cardiology meeting.
14. Brilakis ES, Banerjee S, Edson R, et al. Rationale and design of the Drug-Eluting Stents vs Bare-Metal Stents in Saphenous Vein Graft Angioplasty (DIVA) Trial. *Clin Cardiol* 2017; 40: 946-54.
15. Thygesen K, Alpert JS, White HD, et al. Universal definition of myocardial infarction. *Circulation* 2007; 116: 2634-53.
16. Cutlip DE, Windecker S, Mehran R, et al. Clinical end points in coronary stent trials: a case for standardized definitions. *Circulation* 2007; 115: 2344-51.
17. Keeley EC, Velez CA, O'Neill WW, Safian RD. Long-term clinical outcome and predictors of major adverse cardiac events after percutaneous interventions on saphenous vein grafts. *J Am Coll Cardiol* 2001; 38: 659-65.
18. Bansal D, Muppidi R, Singla S, et al. Percutaneous intervention on the saphenous vein bypass grafts-Long-term outcomes. *Catheter Cardiovasc Interv* 2008; 71: 58-61.
19. Cox DR. Regression Models and Life-Tables. *Journal of the Royal Statistical Society, Series B*; 34: 187-220.
20. Grambsch PM, Therneau TM. Proportional Hazards Tests and Diagnostics Based on Weighted Residuals. *Biometrika* 1994; 81: 515-26.

21. An international randomized trial comparing four thrombolytic strategies for acute myocardial infarction. The GUSTO investigators. *N Engl J Med* 1993; 329: 673-82.
22. Rao SV, O'Grady K, Pieper KS, et al. A comparison of the clinical impact of bleeding measured by two different classifications among patients with acute coronary syndromes. *J Am Coll Cardiol* 2006; 47: 809-16.
23. Gray R. A class of K-sample tests for comparing the cumulative incidence of a competing risk. *Ann Stat* 1988; 16: 1141-54.
24. Fine J, Gray R. A proportional hazards model for the subdistribution of a competing risk. *JASA* 1999; 94: 496-509.
25. Uchida T, Popma J, Stone GW, et al. The clinical impact of routine angiographic follow-up in randomized trials of drug-eluting stents: a critical assessment of "oculostenotic" reintervention in patients with intermediate lesions. *JACC Cardiovascular interventions* 2010; 3: 403-11.
26. Yahagi K, Kolodgie FD, Otsuka F, et al. Pathophysiology of native coronary, vein graft, and in-stent atherosclerosis. *Nat Rev Cardiol* 2016; 13: 79-98.
27. Yazdani SK, Farb A, Nakano M, et al. Pathology of drug-eluting versus bare-metal stents in saphenous vein bypass graft lesions. *JACC Cardiovascular interventions* 2012; 5: 666-74.
28. Brilakis ES, O'Donnell CI, Penny W, et al. Percutaneous Coronary Intervention in Native Coronary Arteries Versus Bypass Grafts in Patients With Prior Coronary Artery Bypass Graft Surgery: Insights From the Veterans Affairs Clinical Assessment, Reporting, and Tracking Program. *JACC Cardiovascular interventions* 2016; 9: 884-93.

29. Dautov R, Manh Nguyen C, Altisent O, Gibrat C, Rinfret S. Recanalization of Chronic Total Occlusions in Patients With Previous Coronary Bypass Surgery and Consideration of Retrograde Access via Saphenous Vein Grafts. *Circ Cardiovasc Interv* 2016; 9.
30. Brilakis ES, Banerjee S, Lombardi WL. Retrograde recanalization of native coronary artery chronic occlusions via acutely occluded vein grafts. *Catheter Cardiovasc Interv* 2010; 75: 109-13.
31. Brilakis ES, Wang TY, Rao SV, et al. Frequency and predictors of drug-eluting stent use in saphenous vein bypass graft percutaneous coronary interventions: a report from the American College of Cardiology National Cardiovascular Data CathPCI registry. *JACC Cardiovascular interventions* 2010; 3: 1068-73.

Figure legends

Figure 1. Enrollment, Randomisation, and Follow-up.

The number of eligible patients is lower than the number of randomized patients because some ineligible patients were randomized.

Figure 2. Clinical outcomes at 12 months.

Cumulative incidence curves for patients who received drug-eluting stents and those who received bare-metal stents for the primary outcome of target vessel failure (composite outcome of cardiac death, target vessel myocardial infarction, or target vessel revascularization, panel A), cardiac death (panel B), target vessel myocardial infarction (panel C), and target vessel revascularization (panel D).

Table 1. Baseline clinical and angiographic characteristics of the study patients and lesions, procedural techniques, and outcomes.

	DES (n = 292)	BMS (n = 305)
Characteristic		
Age (years)	69.0 ± 7.4 (n=292)	68.2 ± 7.7 (n=305)
Men, n (%)	290/ 292 (99%)	305/ 305 (100%)
Race, n (%)		
White	263/ 287 (92%)	254/ 299 (86%)
Black	17/ 287 (7%)	32/ 299 (12%)
Hispanic ethnicity, n (%)	16/ 286 (5%)	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)
Years since coronary artery bypass graft surgery	13.9 ± 6.7 (n=291)	12.8 ± 6.8 (n=303)
Number of diseased coronary vessels, n (%)		
One vessel	3/ 291 (1%)	8/ 304 (3%)
Two vessels	30/ 291 (10%)	25/ 304 (8%)
Three vessels	252/ 291 (86%)	263/ 304 (86%)
Other	6/ 291 (2%)	7/ 304 (2%)
Normal coronary arteries	0/ 291 (0%)	1/ 304 (<1%)
Indication for PCI, n (%)		
Stable angina	117/ 289 (40%)	105/ 304 (34%)
Unstable angina	89/ 289 (30%)	95/ 304 (31%)
Non-ST-segment elevation acute myocardial infarction	66/ 289 (23%)	74/ 304 (24%)
Other	17/ 289 (6%)	30/ 304 (10%)
Hypertension, n (%)	278/ 292 (95%)	296/ 305 (97%)
Hyperlipidemia, n (%)	287/ 292 (98%)	294/ 305 (96%)
Diabetes mellitus, n (%)	173/ 292 (59%)	187/ 305 (61%)
Current smoking, n (%)	61/ 292 (21%)	72/ 305 (24%)
Prior myocardial infarction, n (%)	163/ 292 (56%)	153/ 305 (50%)
History of atrial fibrillation, n (%)	51/ 292 (18%)	57/ 305 (19%)
Congestive heart failure, n (%)	92/ 292 (32%)	118/ 305 (39%)
Ejection fraction (%)	52.5 ± 47.0 (n=175)	49.4 ± 13.3 (n=182)
Peripheral arterial disease, n (%)	51/ 292 (17%)	56/ 305 (18%)

Lesion characteristics

Table 1. Baseline clinical and angiographic characteristics of the study patients and lesions, procedural techniques, and outcomes.

	DES (n = 292)	BMS (n = 305)
Target graft recipient vessel	301	315
Left anterior descending, n (%)	9 (3%)	13 (4%)
Diagonal artery, n (%)	51 (17%)	60 (20%)
Circumflex/obtuse marginal, n (%)	122 (41%)	129 (41%)
Right coronary artery/posterior descending artery, n (%)	117 (39%)	111 (35%)
SVG target lesion location	330	359
Ostial, n (%)	68 (21%)	88 (25%)
Body, n (%)	234 (71%)	240 (67%)
Distal anastomosis, n (%)	28 (8%)	31 (9%)
Pre-stenting target SVG lesion flow		
0, n (%)	2 (1%)	3 (1%)
1, n (%)	10 (3%)	14 (4%)
2, n (%)	54 (16%)	42 (12%)
3, n (%)	264 (80%)	300 (84%)
Post-stenting target SVG lesion flow		
0, n (%)	1 (0%)	1 (0%)
1, n (%)	1 (0%)	0 (0%)

Table 1. Baseline clinical and angiographic characteristics of the study patients and lesions, procedural techniques, and outcomes.

	DES (n = 292)	BMS (n = 305)
2, n (%)	7 (2%)	4 (1%)
3, n (%)	321 (97%)	354 (99%)
Index procedure characteristics		
Arterial access		
Femoral, n (%)	267 (91%)	279 (91%)
Radial, n (%)	20 (7%)	23 (8%)
Anticoagulant		
Unfractionated heparin, n (%)	166 (57%)	177 (58%)
Bivalirudin, n (%)	123 (42%)	137 (45%)
Glycoprotein IIb/IIIa inhibitor, n (%)	44 (15%)	43 (14%)
Staged PCI, n (%)	30 (10%)	35 (11%)
Hemodynamic support during PCI, n (%)	1 (0%)	3 (1%)
Embolic protection device used, n (%)	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 1 target SVG lesion	49 (17%)	46 (15%)
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

Table 1. Baseline clinical and angiographic characteristics of the study patients and lesions, procedural techniques, and outcomes.

	DES (n = 292)	BMS (n = 305)
Number of non-target lesions intervened per patient	1.4 ± 0.6	1.4 ± 0.7
Type of DES used in target lesions		
First generation, n (%)	21 (7%)	0 (0%)
Second generation, n (%)	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, n (%)	64 (22%)	57 (19%)
Angiographic success, n (%)	274 (94%)	291 (95%)
Any procedural complication, n (%)	15 (5%)	22 (7%)
Periprocedural myocardial infarction, n (%)	9 (3%)	23 (8%)*

* defined as >3x upper limit of normal increase in patients with normal baseline CK-MB and >50% increase in patients with elevated baseline CK-MB; $p = 0.0156$.

Note: Summary statistics in all tables are based on the number of participants who provided a response for each given characteristic.

Table 2. Clinical events during 12-month follow-up and medications administered during follow-up.

	DES (n = 292)	BMS (n = 305)	Unadjusted Hazard Ratio (95% Confidence Interval)	P-Value*
Clinical Event	Number of patients (cumulative rate)			
Primary endpoint: target vessel failure at one year	51 (17%)	58 (19%)	0.92 (0.63, 1.34)	0.670
Death from any cause	23 (8%)	21 (7%)	1.17 (0.65, 2.12)	0.634
Cardiac or unknown cause of death (component of TVF)	17 (6%)	16 (5%)	1.15 (0.58, 2.27)	0.725
Cardiac	15 (5%)	11 (4%)	1.47 (0.68, 3.20)	0.356
Noncardiac	6 (2%)	5 (2%)	1.23 (0.37, 4.05)	0.731
Unknown cause	2 (1%)	5 (2%)	0.43 (0.08, 2.24)	0.3045
Any myocardial infarction during follow-up	28 (10%)	31 (10%)	0.94 (0.56, 1.57)	0.7580
Target vessel or indeterminate myocardial infarction during follow-up (component of TVF)	16 (5%)	20 (7%)	0.83 (0.43, 1.60)	0.549
Non-target vessel myocardial infarction during follow-up	13 (4%)	13 (4%)	1.05 (0.49, 2.27)	0.961
Any revascularization	56 (19%)	53 (17%)	1.11 (0.76, 1.61)	0.4457
Any PCI	55 (19%)	53 (17%)	1.09 (0.74, 1.58)	0.51
Any CABG	2 (1%)	0 (0%)		
Target vessel revascularization (component of TVF)	34 (12%)	34 (11%)	1.04 (0.65, 1.67)	0.7482
With PCI	33 (11%)	34 (11%)	1.01 (0.62, 1.63)	0.85

Table 2. Clinical events during 12-month follow-up and medications administered during follow-up.

With CABG	2 (1%)	0 (0%)		
<u>Non-target vessel revascularization</u>	<u>33 (11%)</u>	<u>26 (9%)</u>	<u>1.34 (0.80, 2.24)</u>	<u>0.260</u>
With PCI	32 (11%)	26 (9%)	1.30 (0.77, 2.18)	0.25
With CABG	2 (1%)	0 (0%)		
Target lesion revascularization	26 (9%)	25 (8%)	1.09 (0.63, 1.88)	0.6274
With PCI	25 (9%)	25 (8%)	1.04 (0.60, 1.82)	0.73
With CABG	2 (1%)	0 (0%)		
Patient-oriented composite endpoint (composite of all-cause death, any MI, and target lesion revascularization)	62 (21%)	68 (22%)	0.94 (0.67, 1.33)	0.8175
	DES (n = 292)	BMS (n = 305)	Unadjusted Hazard Ratio (95% Confidence Interval)	P-Value*
Target lesion failure (composite of cardiac or unknown death, target vessel MI, and target lesion revascularization)	45 (15%)	51 (17%)	0.93 (0.62, 1.38)	0.7669
Definite stent thrombosis	6 (2%)	7 (2%)	0.85 (0.28, 2.53)	0.814
Definite or probable stent thrombosis	14 (5%)	17 (6%)	0.87 (0.43, 1.76)	0.7068
Stroke	2 (1%)	3 (1%)	0.72 (0.12, 4.32)	0.71400
Post-Procedural bleed	0 (0%)	2 (1%)		0.50
TVF or SVG occlusion that did not undergo intervention	51 (17%)	59 (19%)	0.90 (0.62, 1.31)	0.640
	DES (n = 292)	BMS (n = 305)		P-Value*
Medications during follow-up				
Aspirin at 12 months, n (%)	241 (93%)	249 (92%)		0.58
P2Y12 inhibitor at 12 months, n (%)	230 (89%)	240 (89%)		0.92
Clopidogrel at 12 months, n (%)	220 (85%)	217 (80%)		0.13
Ticlopidine at 12 months, n (%)	0 (0%)	1 (0%)		1.00
Prasugrel at 12 months, n (%)	6 (2%)	16 (6%)		0.03485
Ticagrelor at 12 months, n (%)	4 (2%)	7 (3%)		0.40

Table 2. Clinical events during 12-month follow-up and medications administered during follow-up.

Statin at 12 months, n (%)	240 (93%)	251 (93%)	0.97
Aspirin at 24 months, n (%)	179 (90%)	192 (91%)	0.84
P2Y12 inhibitor at 24 months, n (%)	110 (56%)	131 (62%)	0.18
Clopidogrel at 24 months, n (%)	103 (52%)	118 (56%)	0.43
Ticlopidine at 24 months, n (%)	0 (0%)	0 (0%)	
Prasugrel at 24 months, n (%)	4 (2%)	6 (3%)	0.75
Ticagrelor at 24 months, n (%)	3 (2%)	7 (3%)	0.34
Statin at 24 months, n (%)	184 (93%)	192 (91%)	0.47
Aspirin at 36 months, n (%)	110 (85%)	111 (83%)	0.73
P2Y12 inhibitor at 36 months, n (%)	62 (48%)	58 (44%)	0.66
Clopidogrel at 36 months, n (%)	51 (39%)	55 (41%)	0.57
Ticlopidine at 36 months, n (%)	0 (0%)	0 (0%)	
Prasugrel at 36 months, n (%)	7 (5%)	1 (1%)	0.07
Ticagrelor at 36 months, n (%)	4 (3%)	2 (2%)	0.68
Statin at 36 months, n (%)	115 (88%)	118 (89%)	0.38

*P-value is from the log-rank test if the ~~un~~adjusted hazard ratio ([which accounts for randomization being stratified by diabetes status and number of target SVG lesions](#)) is shown; otherwise it is from the chi-square or Fisher's exact test.

Table 3. Clinical events during entire duration of follow-up (median 2.7 years).

	DES (n = 292)	BMS (n = 305)	Unadjusted Hazard Ratio (95% Confidence Interval)	P-Value*
Clinical Event	Number of patients (cumulative rate)			
Target vessel failure (TVF)	108 (37%)	105 (34%)	1.10 (0.84, 1.43) 1.11 (0.85, 1.45)	0.446
Death from any cause	55 (19%)	51 (17%)	1.14 (0.78, 1.67) 1.13 (0.77, 1.65)	0.514
Cardiac or unknown cause of death (component of TVF)	41 (14%)	41 (13%)	1.08 (0.70, 1.66) 1.05 (0.68, 1.62)	0.7583
Cardiac	25 (9%)	21 (7%)	1.28 (0.72, 2.29) 1.25 (0.70, 2.23)	0.415
Noncardiac	14 (5%)	10 (3%)	1.39 (0.61, 3.14) 1.45 (0.64, 3.26)	0.4237
Unknown cause	16 (5%)	20 (7%)	0.86 (0.44, 1.66) 0.84 (0.43, 1.61)	0.659
Any myocardial infarction during follow-up	53 (18%)	62 (20%)	0.89 (0.61, 1.28) 0.88 (0.61, 1.28)	0.521
Target vessel or indeterminate myocardial infarction during follow-up (component of TVF)	35 (12%)	40 (13%)	0.90 (0.57, 1.42) 0.91 (0.58, 1.43)	0.667
Non-target vessel myocardial infarction during follow-up	25 (9%)	31 (10%)	0.85 (0.50, 1.43) 0.84 (0.49, 1.42)	0.531
Any revascularization	107 (37%)	96 (31%)	1.20 (0.91, 1.59) 1.22 (0.93, 1.61)	0.115
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

Table 3. Clinical events during entire duration of follow-up (median 2.7 years).

Target vessel revascularization (component of TVF)	68 (23%)	58 (19%)	<u>1.23 (0.87, 1.75)</u> 1.27 (0.90, 1.81)	0.158
With PCI	64 (22%)	56 (18%)	<u>1.19 (0.83, 1.71)</u>	0.24
With CABG	5 (2%)	4 (1%)	<u>1.27 (0.34, 4.78)</u>	0.56
<u>Non-target vessel revascularization</u>	<u>69 (24%)</u>	<u>60 (20%)</u>	<u>1.25 (0.89, 1.77)</u> 1.24 (0.88, 1.76)	<u>0.142</u> 0.142
<u>With PCI</u>	<u>64 (22%)</u>	<u>59 (19%)</u>	<u>1.17 (0.82, 1.67)</u>	0.30
<u>With CABG</u>	<u>6 (2%)</u>	<u>1 (0%)</u>	<u>6.33 (0.76, 52.71)</u>	0.0355
Target lesion revascularization	47 (16%)	40 (13%)	<u>1.23 (0.80, 1.87)</u> 1.25 (0.82, 1.91)	0.229
With PCI	44 (15%)	39 (13%)	<u>1.17 (0.76, 1.81)</u>	0.33
With CABG	4 (1%)	1 (0%)	<u>4.20 (0.47, 37.78)</u>	0.13
Patient-oriented composite endpoint (composite of all-cause death, any MI, and target lesion revascularization)	127 (43%)	127 (42%)	<u>1.06 (0.83, 1.36)</u> 1.07 (0.84, 1.37)	0.559

	DES (n = 292)	BMS (n = 305)	<u>Unadjusted</u> Hazard Ratio (95% Confidence Interval)	P-Value*
Target lesion failure (composite of cardiac or unknown death, target vessel MI, and target lesion revascularization)	94 (32%)	95 (31%)	<u>1.05 (0.79, 1.39)</u> 1.05 (0.79, 1.40)	0.6573
Definite stent thrombosis	9 (3%)	10 (3%)	<u>0.90 (0.36, 2.22)</u>	0.889
Definite or probable stent thrombosis	26 (9%)	30 (10%)	<u>0.90 (0.53, 1.52)</u> 0.90 (0.53, 1.52)	0.7469
Stroke	10 (3%)	12 (4%)	<u>0.88 (0.38, 2.03)</u> 0.86 (0.37, 1.99)	0.8473
TVF or SVG occlusion that did not undergo intervention	112 (38%)	110 (36%)	<u>1.09 (0.84, 1.42)</u> 1.10 (0.85, 1.43)	0.447

*P-value is ~~the~~ from the log-rank test if the ~~un~~adjusted hazard ratio (which accounts for randomization being stratified by diabetes status and number of target SVG lesions) is shown; otherwise it is from the chi-square or Fisher's exact test.

Supplementary figures

Figure S1. Additional clinical outcomes at 12 months.

Cumulative incidence curves for patients who received drug-eluting stents and those who received bare metal stents for all-cause death (panel A), any myocardial infarction (panel B), target lesion revascularization (panel C), and definite or probable stent thrombosis (panel D).

Figure S2. Clinical outcomes during the entire duration of follow-up.

Cumulative incidence curves for patients who received drug-eluting stents and those who received bare metal stents for target vessel failure (composite outcome of cardiac death, target vessel myocardial infarction, or target vessel revascularization, panel A), cardiac death (panel B), target vessel myocardial infarction (panel C), and target vessel revascularization (panel D).

Figure S3. Additional clinical outcomes during the entire duration of follow-up.

Cumulative incidence curves for patients who received drug-eluting stents and those who received bare metal stents for all-cause death (panel A), any myocardial infarction (panel B), target lesion revascularization (panel C), and definite or probable stent thrombosis (panel D).

Supplementary Tables

Supplementary Table S1. Types of stents used in study patients.

Stent	DES (n = 292)	BMS (n = 305)
Drug-eluting stent		
Everolimus-eluting, n (%)		
Absorb, n (%)	0 (0%)	0 (0%)
Promus, n (%)	66 (23%)	1 (0%)
Synergy, n (%)	0 (0%)	0 (0%)
Xience, n (%)	121 (41%)	4 (1%)
Zotarolimus-eluting, n (%)		
Endeavor, n (%)	14 (5%)	0 (0%)
Resolute, n (%)	77 (26%)	3 (1%)
Sirolimus-eluting, n (%)		
Cypher, n (%)	0 (0%)	0 (0%)
Paclitaxel-eluting, n (%)		
Ion, n (%)	5 (2%)	0 (0%)
Taxus, n (%)	2 (1%)	0 (0%)
Name Unknown, n (%)	1 (0%)	0 (0%)
Bare metal stent		
Driver, n (%)	0 (0%)	3 (1%)
Integrity, n (%)	1 (0%)	152 (50%)
Multilink Vision, Ultra, or 8, n (%)	0 (0%)	123 (40%)
Rebel, n (%)	1 (0%)	6 (2%)
Veriflex (formerly Liberte), n (%)	0 (0%)	11 (4%)
Type unknown, n (%)	0 (0%)	7 (2%)

Supplementary Table S2. Target vessel failure by treatment group at 12 months and over the entire duration of follow-up for various subgroups.*

Length of Follow-up and Subgroup	DES (n = 292)	BMS (n = 305)	<u>Adjusted</u> Hazard Ratio (95% Confidence Interval)	P- Value^	Log- Rank Statistic	Number of Events	Interaction P-Value
12 MONTHS							
Diabetes : No	17/120 (14%)	22/119 (18%)	<u>0.72 (0.38, 1.37)</u> 0.75 (0.40, 1.42)	<u>0.36</u> 0.38	<u>0.91</u> 0.88	39	0.35 <u>42</u>
Yes	34/172 (20%)	36/186 (19%)	<u>1.05 (0.66, 1.67)</u> 1.04 (0.65, 1.66)	<u>0.19</u> 0.88	<u>0.85</u> 0.16	70	
Number of target SVG lesions: 1	42/243 (17%)	45/259 (17%)	<u>1.01 (0.67, 1.54)</u> 1.01 (0.67, 1.54)	<u>0.96</u> 0.95	<u>0.05</u> 0.06	87	0.31 <u>27</u>
2	9/49 (18%)	13/46 (28%)	<u>0.61 (0.25, 1.48)</u> 0.60 (0.26, 1.41)	<u>0.32</u> 0.24	<u>0.99</u> 1.18	22	
Most recent graft age (years): <13.5	23/135 (17%)	28/164 (17%)	<u>0.99 (0.57, 1.72)</u> 1.02 (0.59, 1.77)	<u>0.97</u> 0.94	<u>0.04</u> 0.07	51	0.68 <u>2</u>
≥13.5	28/156 (18%)	29/139 (21%)	<u>0.85 (0.50, 1.43)</u> 0.84 (0.50, 1.42)	<u>0.55</u> 0.51	<u>0.60</u> 0.65	57	
Minimum stent diameter (mm): 2.25 to < 3.0	12/50 (24%)	10/63 (16%)	<u>1.68 (0.72, 3.93)</u> 1.51 (0.65, 3.50)	<u>0.21</u> 0.33	<u>1.26</u> 0.97	22	0.71

Length of Follow-up and Subgroup	DES (n = 292)	BMS (n = 305)	<u>Adjusted</u> Hazard Ratio (95% Confidence Interval)	P- Value^	Log- Rank Statistic	Number of Events	Interaction P-Value
3.0 to < 3.5	13/71 (18%)	17/65 (26%)	<u>0.72 (0.35, 1.48)</u> 0.69 (0.33, 1.42)	<u>0.58</u> 0.31	<u>0.56</u> 1.02	30	
3.5 to < 4.0	13/89 (15%)	17/92 (18%)	<u>0.80 (0.39, 1.64)</u> 0.79 (0.38, 1.63)	<u>0.56</u> 0.52	<u>0.58</u> 0.64	30	
4.0 or more	13/78 (17%)	13/83 (16%)	<u>1.06 (0.49, 2.29)</u> 1.10 (0.51, 2.38)	<u>0.88</u> 0.80	<u>0.15</u> 0.25	26	
Total stent length (mm): <20	21/137 (15%)	20/156 (13%)	<u>1.23 (0.67, 2.27)</u> 1.23 (0.67, 2.26)	<u>0.38</u> 0.51	<u>0.87</u> 0.65	41	0.265
≥20	30/151 (20%)	37/147 (25%)	<u>0.79 (0.49, 1.28)</u> 0.77 (0.48, 1.25)	<u>0.37</u> 0.30	<u>0.89</u> 1.05	67	
Recipient vessel: LAD	17/60 (28%)	15/69 (22%)	<u>1.42 (0.71, 2.85)</u> 1.38 (0.69, 2.76)	<u>0.33</u> 0.36	<u>0.98</u> 0.91	32	0.46
Circumflex	19/112 (17%)	27/124 (22%)	<u>0.78 (0.43, 1.41)</u> 0.77 (0.43, 1.38)	<u>0.41</u> 0.38	<u>0.83</u> 0.89	46	
RCA	15/117 (13%)	15/111 (14%)	<u>0.87 (0.42, 1.81)</u> 0.95 (0.46, 1.94)	<u>0.82</u> 0.88	<u>0.22</u> 0.14	30	
Target lesion location: Aortic/Ostial	14/64 (22%)	20/81 (25%)	<u>0.88 (0.44, 1.74)</u> 0.92 (0.46, 1.81)	<u>0.74</u> 0.80	<u>0.33</u> 0.26	34	0.98

Length of Follow-up and Subgroup	DES (n = 292)	BMS (n = 305)	<u>Adjusted</u> Hazard Ratio (95% Confidence Interval)	P- Value^	Log- Rank Statistic	Number of Events	Interaction P-Value
Body	34/195 (17%)	33/193 (17%)	<u>0.99</u> (0.61, 1.60) 1.02 (0.63, 1.64)	<u>0.96</u> 0.95	<u>0.05</u> 0.06	67	
Distal Anastomosis	3/30 (10%)	4/30 (13%)	<u>0.61</u> (0.13, 2.79) 0.73 (0.16, 3.28)	<u>0.59</u> 0.69	<u>0.53</u> 0.41	7	
Baseline use of antiplatelet medications: No	20/121 (17%)	27/137 (20%)	<u>0.84</u> (0.47, 1.51) 0.84 (0.47, 1.50)	<u>0.62</u> 0.56	<u>0.49</u> 0.59	47	0.78 0
Yes	31/171 (18%)	31/168 (18%)	<u>0.99</u> (0.60, 1.63) 0.98 (0.60, 1.62)	<u>0.98</u> .95	<u>0.03</u> 0.07	62	
ACS status: No	21/137 (15%)	25/136 (18%)	<u>0.80</u> (0.45, 1.43) 0.83 (0.47, 1.49)	<u>0.56</u> .54	<u>0.58</u> 0.62	46	0.63 4
Yes	30/155 (19%)	33/169 (20%)	<u>1.00</u> (0.61, 1.64) 1.00 (0.61, 1.63)	<u>0.99</u> .99	<u>0.01</u> 0.01	63	
ALL FOLLOW-UP							
Diabetes: No	43/120 (36%)	38/119 (32%)	<u>1.13</u> (0.73, 1.77) 1.16 (0.75, 1.79)	<u>0.54</u> .51	<u>0.62</u> 0.65	81	0.99 82
Yes	65/172 (38%)	67/186 (36%)	<u>1.09</u> (0.78, 1.54) 1.08 (0.77, 1.52)	<u>0.62</u> .66	<u>0.50</u> 0.43	132	
Number of target SVG lesions: 1	89/243 (37%)	83/259 (32%)	<u>1.20</u> (0.89, 1.62) 1.20 (0.89, 1.61)	<u>0.25</u> .24	<u>1.15</u> 1.18	172	0.19 6
2	19/49 (39%)	22/46 (48%)	<u>0.78</u> (0.41, 1.48) 0.74 (0.40, 1.36)	<u>0.53</u> .33	<u>0.63</u> 0.98	41	
Most recent graft age (years): <13.5	51/135 (38%)	54/164 (33%)	<u>1.21</u> (0.82, 1.77) 1.24 (0.85, 1.82)	<u>0.28</u> .26	<u>1.08</u> 1.11	105	0.40 35

Length of Follow-up and Subgroup	DES (n = 292)	BMS (n = 305)	Adjusted Hazard Ratio (95% Confidence Interval)	P- Value^	Log- Rank Statistic	Number of Events	Interaction P-Value
≥13.5	56/156 (36%)	49/139 (35%)	0.96 (0.65, 1.41) 0.95 (0.65, 1.39)	0.82 .79	0.23 0.27	105	0.88
Minimum stent diameter (mm): 2.25 to < 3.0	21/50 (42%)	22/63 (35%)	1.37 (0.75, 2.50) 1.38 (0.76, 2.51)	0.31 .30	1.01 1.04	43	
3.0 to < 3.5	24/71 (34%)	26/65 (40%)	0.87 (0.50, 1.51) 0.85 (0.49, 1.47)	0.80 .55	0.25 0.59	50	
3.5 to < 4.0	33/89 (37%)	30/92 (33%)	1.14 (0.70, 1.87) 1.14 (0.69, 1.87)	0.52 .61	0.65 0.51	63	
4.0 or more	29/78 (37%)	25/83 (30%)	1.23 (0.72, 2.11) 1.29 (0.75, 2.20)	0.56 .36	0.59 0.92	54	
Total stent length (mm) : <20	44/137 (32%)	42/156 (27%)	1.26 (0.83, 1.93) 1.26 (0.83, 1.92)	0.18 .29	1.35 1.07	86	0.435
≥20	63/151 (42%)	61/147 (41%)	1.03 (0.73, 1.47) 1.01 (0.71, 1.44)	0.73 .95	0.34 0.06	124	
Recipient vessel: LAD	25/60 (42%)	22/69 (32%)	1.34 (0.75, 2.38) 1.31 (0.74, 2.33)	0.38 .36	0.88 0.92	47	0.90
Circumflex	39/112 (35%)	48/124 (39%)	0.96 (0.63, 1.47) 0.94 (0.62, 1.44)	0.97 .78	0.04 0.28	87	
RCA	44/117 (38%)	34/111 (31%)	1.21 (0.76, 1.90) 1.29 (0.82, 2.01)	0.36 .27	0.91 1.11	78	
Target lesion location: Aortic/Ostial	22/64 (34%)	28/81 (35%)	0.95 (0.54, 1.68) 0.98 (0.56, 1.72)	0.97 .96	0.04 0.05	50	0.29
Body	75/195 (38%)	70/193 (36%)	1.12 (0.81, 1.56) 1.15 (0.83, 1.59)	0.37 .41	0.90 0.82	145	
Distal Anastomosis	11/30 (37%)	6/30 (20%)	1.73 (0.63, 4.71) 1.96 (0.72, 5.29)	0.29 .19	1.05 1.35	17	
Baseline use of antiplatelet medications: No	38/121 (31%)	43/137 (31%)	0.99 (0.64, 1.54) 1.01 (0.66, 1.57)	0.998 .95	0.002 0.06	81	0.764

Length of Follow-up and Subgroup	DES (n = 292)	BMS (n = 305)	Adjusted Hazard Ratio (95% Confidence Interval)	P-Value [^]	Log-Rank Statistic	Number of Events	Interaction P-Value
Yes	70/171 (41%)	62/168 (37%)	1.13 (0.80, 1.59) 1.16 (0.82, 1.63)	0.53 .40	0.63 0.85	132	0.315
ACS status: No	43/137 (31%)	44/136 (32%)	0.87 (0.57, 1.33) .95 (0.63, 1.45)	0.63 .82	0.49 0.23	87	
Yes	65/155 (42%)	61/169 (36%)	1.23 (0.87, 1.75) 1.00 (0.61, 1.63)	0.26 .99	1.12 0.01	126	

Formatted Table

*All subgroup analyses except age of most recent SVG were prespecified in the protocol.

[^] P-value ~~and adjusted hazard ratio statistics are~~ from the stratified log-rank test which accounts for randomization being stratified by both diabetes status and number of target SVG lesions for all subgroups except diabetes status (stratified only by number of target SVG lesions) and number of target SVG lesion (stratified only by diabetes status)

ACS, acute coronary syndrome; BMS, bare metal stent; DES, drug-eluting stent; LAD, left anterior descending artery; RCA, right coronary artery; SVG, saphenous vein graft

Supplementary Table S3. Serious Adverse Events: tallies of participants and events.

Outcome	DES	BMS	P-value
Number of participants with SAEs (N, %)	231 (79%)	244 (80%)	NS0.79
Number of SAEs	1066	1110	
SAEs attribution to stent			
Not attributed	906	959	
Possibly attributed	102	90	
Yes, attributed	56	54	
SAEs attribution to thienopyridine			
Not attributed	1014	1051	
Possibly attributed	49	53	
Yes, attributed	1	5	

BMS, bare metal stent; DES, drug-eluting stent; SAE, serious adverse event.

Supplementary Table S4. Counts of participants with one or more serious adverse event by MedDRA classification experienced by at least 5% of participants in one or both treatment arms. Serious adverse events were reported regardless of attribution to stent or P2Y12 inhibitor use.

MedDRA System Organ Class	MedDRA Higher Level Term Group (HLTG)	DES	%	BMS	%
Cardiac disorders	Cardiac arrhythmias	36	12%	38	12%
Cardiac disorders	Coronary artery disorders	134	46%	140	46%
Cardiac disorders	Heart failures	52	18%	58	19%
General disorders and administration site conditions	Complications associated with device	25	9%	28	9%
General disorders and administration site conditions	General system disorders NEC	35	12%	34	11%
Infections and infestations	Bacterial infectious disorders	19	7%	13	4%
Infections and infestations	Infections - pathogen unspecified	51	17%	51	17%
Injury, poisoning and procedural complications	Procedural related injuries and complications NEC	15	5%	14	5%
Metabolism and nutrition disorders	Electrolyte and fluid balance conditions	14	5%	18	6%
Nervous system disorders	Central nervous system vascular disorders	20	7%	23	8%
Renal and urinary disorders	Renal disorders (excl nephropathies)	28	10%	30	10%
Respiratory, thoracic and mediastinal disorders	Bronchial disorders (excl neoplasms)	15	5%	8	3%
Vascular disorders	Decreased and nonspecific blood pressure disorders and shock	11	4%	16	5%

*Comparison of % of participants by group was not significant for any HLTG.