JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY VOL. 72, NO. 4, 2018

PUBLISHED BY ELSEVIER

Stroke Rates Following Surgical Versus Percutaneous Coronary Revascularization

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ABSTRACT

BACKGROUND Coronary artery bypass grafting (CABG) and percutaneous coronary intervention (PCI) are used for coronary revascularization in patients with multivessel and left main coronary artery disease. Stroke is among the most feared complications of revascularization. Due to its infrequency, studies with large numbers of patients are required to detect differences in stroke rates between CABG and PCI.

OBJECTIVES This study sought to compare rates of stroke after CABG and PCI and the impact of procedural stroke on long-term mortality.

METHODS We performed a collaborative individual patient-data pooled analysis of 11 randomized clinical trials comparing CABG with PCI using stents; ERACI II (Argentine Randomized Study: Coronary Angioplasty With Stenting Versus Coronary Bypass Surgery in Patients With Multiple Vessel Disease) (n = 450), ARTS (Arterial Revascularization Therapy Study) (n = 1,205), MASS II (Medicine, Angioplasty, or Surgery Study) (n = 408), SoS (Stent or Surgery) trial (n = 988), SYNTAX (Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery) trial (n = 1,800), PRECOMBAT (Bypass Surgery Versus Angioplasty Using Sirolimus-Eluting Stent in Patients With Left Main Coronary Artery Disease) trial (n = 600), FREEDOM (Comparison of Two Treatments for Multivessel Coronary Artery Disease in Individuals With Diabetes) trial (n = 1,900), VA CARDS (Coronary Artery Revascularization in Diabetes) (n = 198), BEST (Bypass Surgery Versus Everolimus-Eluting Stent Implantation for Multivessel Coronary Artery Disease) (n = 880), NOBLE (Percutaneous Coronary Angioplasty Versus Coronary Artery Bypass Grafting in Treatment of Unprotected Left Main Stenosis) trial (n = 1,184), and EXCEL (Evaluation of Xience Versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization) trial (n = 1,905). The 30-day and 5-year stroke rates were compared between CABG and PCI using a random effects Cox proportional hazards model, stratified by trial. The impact of stroke on 5-year mortality was explored.

RESULTS The analysis included 11,518 patients randomly assigned to PCI (n = 5,753) or CABG (n = 5,765) with a mean follow-up of 3.8 ± 1.4 years during which a total of 293 strokes occurred. At 30 days, the rate of stroke was 0.4% after PCI and 1.1% after CABG (hazard ratio [HR]: 0.33; 95% confidence interval [CI]: 0.20 to 0.53; $p < 0.001$). At 5-year follow-up, stroke remained significantly lower after PCI than after CABG (2.6% vs. 3.2%; HR: 0.77; 95% CI: 0.61 to 0.97; $p = 0.027$). Rates of stroke between 31 days and 5 years were comparable: 2.2% after PCI versus 2.1% after CABG (HR: 1.05; 95% CI: 0.80 to 1.38; $p = 0.72$). No significant interactions between treatment and baseline clinical or angiographic variables for the 5-year rate of stroke were present, except for diabetic patients (PCI: 2.6% vs. CABG: 4.9%) and nondiabetic patients (PCI: 2.6% vs. CABG: 2.4%) (p for interaction = 0.004). Patients who experienced a stroke within 30 days of the procedure had significantly higher 5-year mortality versus those without a stroke, both after PCI (45.7% vs. 11.1%, $p < 0.001$) and CABG (41.5% vs. 8.9%, $p < 0.001$).

CONCLUSIONS This individual patient-data pooled analysis demonstrates that 5-year stroke rates are significantly lower after PCI compared with CABG, driven by a reduced risk of stroke in the 30-day post-procedural period but a similar risk of stroke between 31 days and 5 years. The greater risk of stroke after CABG compared with PCI was confined to patients with multivessel disease and diabetes. Five-year mortality was markedly higher for patients experiencing a stroke within 30 days after revascularization. (J Am Coll Cardiol 2018;72:386–98) © 2018 by the American College of Cardiology Foundation.

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ISSN 0735-1097/$36.00 https://doi.org/10.1016/j.jacc.2018.04.071

Numerous randomized clinical trials have compared coronary artery bypass grafting (CABG) and percutaneous coronary intervention (PCI) for treating coronary artery disease; first in the era of balloon angioplasty, subsequently with the use of bare-metal stents (BMS) (1,2), and most recently with use of drug-eluting stents (DES) (3). With improving technology and techniques of PCI, trials have increasingly focused on more complex patients with multivessel disease (MVD), left main (LM) disease, and diabetes.

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Several studies have suggested that CABG versus PCI is associated with a significant increase of procedural stroke (1), a devastating outcome with substantial mortality, morbidity, and reduced quality of life. To date, there is a lack of conclusive evidence on the exact incidence and consequences of stroke following either CABG or PCI because individual randomized trials lacked sufficient power to detect small but meaningful differences between CABG and PCI (4). In a recent collaborative analysis of 11 randomized trials of patients with multivessel or LM coronary artery disease who were randomly assigned to CABG or PCI, we found significant differences in 5-year all-cause mortality in favor of CABG over PCI in patients with MVD and diabetes, whereas no differences were seen among patients with MVD without diabetes and in those with LM disease (5). Beyond mortality, it is important to consider endpoints that significantly impact quality of life, including stroke.

We therefore performed an analysis from the individual patient data from 11 randomized clinical trials of CABG versus PCI to compare procedural and long-term rates of stroke and the impact of stroke on survival.

METHODS

STUDY SELECTION AND DATA COLLECTION. Details of this pooled analysis have been previously published (5). In summary, a systematic search was performed on July 19, 2017, to identify randomized clinical trials comparing CABG with PCI for the treatment of multivessel or LM disease. Studies were selected if: 1) patients were randomly assigned to undergo CABG or PCI treatment; 2) patients had multivessel or LM disease; 3) patients did not present with an acute myocardial infarction; 4) PCI was performed using stents (BMS or DES) and not balloon angioplasty; 5) the occurrence of stroke was collected beyond 30 days of follow-up; and 6) >1-year follow-up for all-cause mortality was available. The study was performed according to PRISMA (Preferred Reporting Items for Systematic Review and Meta-Analyses) guidelines (6).

ABBREVIATIONS AND ACRONYMS

BMS = bare-metal stent(s)

CABG = coronary artery bypass grafting

CI = confidence interval

DAPT = dual antiplatelet therapy

DES = drug-eluting stent(s)

HR = hazard ratio

LM = left main

MVD = multivessel disease

PCI = percutaneous coronary intervention

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Investigators from 11 individual trials provided the data for the current pooled analysis: ERACI II (Argentine Randomized Study: Coronary Angioplasty With Stenting Versus Coronary Bypass Surgery in Patients With Multiple Vessel Disease) (7), ARTS (Arterial Revascularization Therapy Study) (8), MASS II (Medicine, Angioplasty, or Surgery Study) (9), SoS (Stent or Surgery) trial (10), SYNTAX (Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery) trial (11), PRECOMBAT (Bypass Surgery Versus Angioplasty Using Sirolimus-Eluting Stent in Patients With Left Main Coronary Artery Disease) trial (12), FREEDOM (Comparison of Two Treatments for Multivessel Coronary Artery Disease in Individuals With Diabetes) trial (13), VA CARDS (Coronary Artery Revascularization in Diabetes) (14), BEST (Bypass Surgery Versus Everolimus-Eluting Stent Implantation for Multivessel Coronary Artery Disease) (15), EXCEL (Evaluation of Xience Versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization) trial (16), and NOBLE (Percutaneous Coronary Angioplasty Versus Coronary Artery Bypass Grafting in Treatment of Unprotected Left Main Stenosis) trial (17) (Online Figure 1). Only the data from the LE MANS (Study of Unprotected Left Main Stenting Versus Bypass Surgery) trial ($n = 105$) could not be obtained (18). Baseline and procedural characteristics of individual trials are presented in Online Table 1.

Local medical ethics committees approved each trial at the time of study execution. Patients in each of the 11 trials provided written informed consent.

OUTCOMES, DEFINITIONS, AND FOLLOW-UP. Follow-up time was calculated from the time of the procedure to allow a universal definition of follow-up among trials. Follow-up time was calculated from randomization if patients experienced a stroke or died before the procedure took place or if patients did not undergo revascularization but only received medical treatment. The primary endpoint of this study was stroke. A procedural stroke was defined as stroke occurring in the first 30 days after the procedure. All trials, except the SoS trial, collected stroke during the entire duration of follow-up; the SoS trial collected stroke only up to 1 year after revascularization (10). Stroke was defined using the criteria applied in each study and consisted mainly of: 1) a focal neurological deficit of central origin lasting >24 h with or without confirmation with neuroimaging; or 2) a deficit lasting >72 h without the need for confirmation with neuroimaging. Secondary endpoints of the present study were all-cause mortality after stroke and a composite of all-cause mortality or stroke. In all trials, a clinical events committee adjudicated the events.

Patients with MVD were defined as having 2- or 3-vessel disease without LM disease. Patients with LM disease were defined as having LM disease, either isolated or in combination with single-vessel disease or MVD.

STATISTICAL ANALYSIS. The main analyses were performed according to the intention-to-treat principle. Outcome data were also analyzed on an as-treated basis to determine more accurately the impact of the specific procedure on stroke rate. Continuous variables are expressed as a mean ± SD and compared using Student's *t*-tests, and discrete data are presented as frequencies and compared using chi-square tests. We pooled the individual patient data from 11 trials to provide descriptive statistics and unadjusted Kaplan-Meier curves. Hazard ratios (HR) of CABG versus PCI for stroke were estimated using random effects Cox proportional

Pythagoras Medical, and ReCor. Dr. Farkouh has received research support from Amgen and Novo Nordisk. Dr. Holm has received institutional research grants from Abbott, Biosensors, Biotronik, and Boston Scientific; and has received speaking honoraria from Abbott, Biotronik, and Terumo. Dr. Sabik has served on the Cardiac Surgery Advisory Board of Medtronic; and is the North American surgical principal investigator for the EXCEL trial, sponsored by Abbott. Dr. Stone has received grant support from the Cardiovascular Research Foundation during the conduct of the study; has received personal fees from Velomedix, Toray, Matrizyme, Miracor, TherOx, Reva, V-wave, Vascular Dynamics, Ablative Solutions, Neovasc, and Medical Development Technologies; has received other support from the MedFocus family of funds, Guided Delivery Systems, Micardia, Vascular Nontransfer Technologies, Cagent, Qool Therapeutics, Caliber, Aria, and the Biostar family of funds outside the submitted work; has served as a consultant on prasugrel patent litigation paid for by Lupin Pharmaceuticals; and his institution, Columbia University, receives royalties from Abbott Vascular for sale of the MitraClip. Dr. Serruys has served as a consultant for Abbott Laboratories, AstraZeneca Pharmaceuticals, Biotronik, Cardialysis B.V., GLG Research, Medtronic, Sino Medical Sciences Technology Inc. Tianjin China, Stentys France, Svelte Medical Systems Inc., Volcano/Philips Europe, Q3Medical Devices Limited, and St. Jude Medical; and has served as a member of the corporate advisory board for Xeltis. Dr. Kappetein is an employee of Medtronic. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose. Amar Krishnaswarmy, MD, served as Guest Editor for this paper.

Manuscript received March 17, 2018; accepted April 23, 2018.

hazards models that were stratified by trial, using a gamma frailty term to account for heterogeneity among trials. Frailties are unobserved factors, distributed as γ random variables with a mean of 1 and variance ϑ. Hence, the variance of the frailty terms represents heterogeneity in baseline risk among trials. The statistical significance of the variance parameter was assessed using the likelihood ratio test. The rate of stroke was estimated at 30 days and 5 years, and landmark analyses were performed after 30 days follow-up to assess the long-term risk of stroke after CABG versus PCI. Prespecified subgroup analyses of 30-day and 5-year stroke rates were performed according to baseline clinical and anatomical characteristics and multivessel or LM disease. The p values for interaction were calculated in the random effects Cox proportional hazards models. Due to a limited number of events in several of the subgroup analyses of 30-day stroke, no frailty model could be built; in these specific analyses, the HR and interaction terms were analyzed through standard Cox proportional hazards models. We did not perform interaction analyses on stratification according to LM/MVD, because the LM and MVD groups are not mutually exclusive. Moreover, we explored the impact of off-pump CABG as opposed to on-pump CABG among trials that provided information on the use of cardiopulmonary bypass, the impact of PCI being performed with BMS or DES, and the impact of single versus dual antiplatelet therapy (DAPT) at hospital discharge on stroke. Multivariable Cox proportional hazards models that included baseline and procedural characteristics were constructed to predict 30-day and 5-year stroke. Variables were included in the multivariable model if $p < 0.15$ at univariable analyses, with the variable CABG versus PCI being forced into the model. The impact of stroke within 30 days of the procedure on mortality was explored using the Kaplan-Meier method comparing patients with and without 30-day stroke. The composite rate of all-cause mortality or stroke was explored at 30 days and 5 years in the overall group of patients, and according to status of diabetes, SYNTAX score tertiles, and MVD or LM disease. Two-sided $p < 0.05$ was considered to indicate statistical significance. Statistical analyses were performed using SPSS software version 21 (IBM Corporation, Armonk, New York) or R software version 3.2.4 (Institute for Statistics and Mathematics of Wirtschaftsuniversität, Wien, Austria).

ROLE OF THE FUNDING SOURCE. Whereas several of the individual studies were funded by industry, this collaborative analysis had no external funding and did not involve any of the original study sponsors.

TABLE 1 Baseline, Procedural, and Discharge Data of Randomized Cohorts

	PCI (n = 5,753)	CABG (n = 5,765)
Age, yrs	63.6 ± 9.8 (5,753)	63.7 ± 9.9 (5,765)
Female	23.9 (1,373/5,753)	23.8 (1,371/5,765)
BMI >30 kg/m^2	28.1 (1,548/5,506)	28.3 (1,558/5,511)
Smoking, current	22.3 (1,274/5,701)	22.3 (1,273/5,703)
Diabetes	38.5 (2,215/5,753)	37.7 (2,171/5,765)
Insulin treatment	12.9 (545/4,234)	11.9 (504/4,245)
Hypertension	67.6 (3,880/5,739)	68.1 (3,913/5,748)
Hypercholesterolemia	69.5 (3,982/5,726)	67.3 (3,862/5,735)
Peripheral vascular disease	8.2 (424/5,158)	8.5 (440/5,164)
Carotid artery disease	7.8 (161/2,072)	8.1 (168/2,074)
Previous TIA or CVA	5.4 (218/4,052)	6.2 (253/4,054)
Previous MI	28.0 (1,438/5,138)	27.5 (1,417/5,156)
LV dysfunction, <30%	0.9 (49/5,303)	1.0 (54/5,430)
Unstable disease	34.6 (1,786/5,158)	34.2 (1,767/5,160)
3-vessel disease*	58.6 (2,460/4,201)	61.8 (2,594/4,197)
Left main disease	38.8 (2,233/5,753)	38.9 (2,245/5,765)
SYNTAX score	26.0 ± 9.3 (4,081)	26.0 ± 9.8 (4,057)
PCI-DES used†	73.4 (4,120/5,610)	–
PCI-number of stents	3.1 ± 2.0 (4,935)	–
CABG-LIMA use	–	96.2 (4,574/4,753)
CABG-BIMA use	–	18.7 (771/4,122)
CABG-off-pump	–	27.5 (1,085/3,945)
Aspirin at discharge	97.3 (4,487/4,612)	95.5 (3,814/3,994)
Thienopyridine at discharge	96.7 (4,479/4,630)	45.1 (1,815/4,026)
DAPT at discharge	95.1 (4,384/4,612)	44.0 (1,759/3,994)

Values are mean ± SD (N) or % (n/N). *Of the group of patients with multivessel disease. †Data only for patients who were randomized to PCI and indeed underwent PCI. The type of stent used was not available for 1 patient enrolled in the VA CARDS trial.

BIMA = bilateral internal mammary artery; BMI = body mass index; CABG = coronary artery bypass grafting; CVA = cerebrovascular accident; DAPT = dual antiplatelet therapy; DES = drug-eluting stents; LIMA = left internal mammary artery; LV = left ventricular; MI = myocardial infarction; PCI = percutaneous coronary intervention; SYNTAX = Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery; TIA = transitory ischemic attack; VA CARDS = Coronary Artery Revascularization in Diabetes.

RESULTS

STUDY POPULATION. Eleven trials randomized 11,518 patients; 5,765 patients were randomly assigned to CABG and 5,753 to PCI. Of the 5,765 patients assigned to CABG, 5,421 underwent CABG (94%), 233 underwent PCI (4%), and 111 underwent neither procedure (2%). Of the 5,753 patients assigned to PCI, 5,610 underwent PCI (98%), 101 underwent CABG (2%), and 42 underwent neither procedure (1%). In the as-treated analysis, 5,522 patients underwent CABG and 5,843 patients underwent PCI. Data on crossovers in each study are presented in Online Table 2.

Patient enrollment was between 1995 and 2015 (Online Table 1). PCI was performed in 4 trials

exclusively with BMS (MASS II, ERACI II, SoS, and ARTS; n = 1,518 PCI patients), in 3 trials with first-generation DES (PRECOMBAT, SYNTAX, and FREEDOM; n = 2,156 PCI patients), in 3 trials with second-generation DES (BEST, EXCEL, and NOBLE; n = 1,978 PCI patients), and in 1 trial with a mix of stent generations (VA CARDS; n = 101 PCI patients).

There were no clinically significant differences in baseline characteristics between patients randomly assigned to either CABG or PCI (Table 1). The pooled patient population had a mean age of 63.6 ± 9.8 years, and 24% were female. Diabetes was present in 38% of patients, with 12% on insulin. LM disease was present in 39% of patients. At discharge, antiplatelet therapy was prescribed significantly more often after PCI than after CABG ($p < 0.001$ for all analyses). The mean follow-up was 3.8 ± 1.4 years.

FREQUENCY AND PREDICTORS OF STROKE. A total of 293 strokes occurred during follow-up. The cumulative stroke rate at 5-year follow-up was 2.6% (129 strokes) in patients randomized to PCI and 3.2% (164 strokes) in patients randomized to CABG (HR: 0.77; 95% confidence interval [CI]: 0.61 to 0.97; $p = 0.027$) (Central Illustration, panel A). At 30 days, stroke occurred in 21 patients (0.4%) randomized to PCI and 64 patients (1.1%) randomized to CABG (HR: 0.33; 95% CI: 0.20 to 0.53; $p < 0.001$) (Central Illustration, panel B). The rate of stroke between 31 days up to 5 years was comparable between PCI (2.2%; 108 strokes) and CABG (2.1%; 100 strokes) (HR: 1.05; 95% CI: 0.80 to 1.38; $p = 0.72$) (Central Illustration, panel B). Results were similar in the as-treated analysis. The value of the frailty parameter theta (θ) for heterogeneity was $\theta = 0.09$ ($p < 0.001$). In a multivariable analysis, the only independent predictor of 30-day stroke was CABG (HR: 8.33; 95% CI: 1.06 to 62.5; $p = 0.043$). In multivariable analysis of 5-year stroke, CABG was not an independent predictor (HR: 1.43; 95% CI: 0.94 to 2.13; $p = 0.089$).

In 7 trials that provided data on on-pump or off-pump CABG (n = 3,945), 28% of patients underwent off-pump CABG surgery. Rates of stroke at 30 days were 0.6% (6 of 1,085) after off-pump CABG and 1.4% (40 of 2,860) after on-pump CABG ($p = 0.13$), with 5-year rates of 2.9% (25 of 1,085) versus 3.5% (84 of 2,860), respectively ($p = 0.60$). After CABG, 44% of patients were discharged on DAPT. The rate of stroke at 5 years was comparable between patients on DAPT or single antiplatelet therapy (3.1% [48 of 1,759] vs. 3.8% [67 of 2,109], respectively; $p = 0.84$).

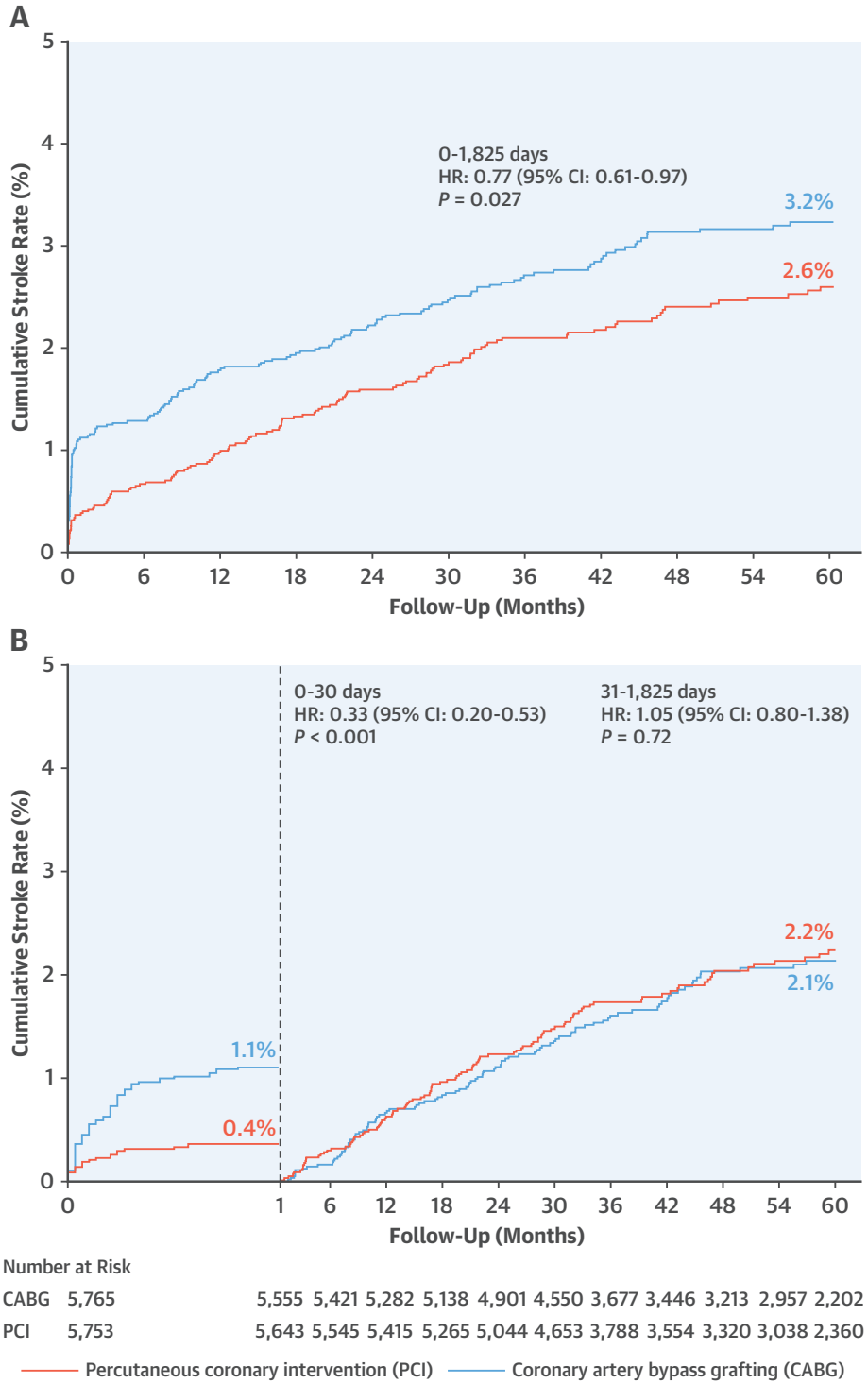
Whether PCI was performed with BMS or DES did not have an impact on the rate of stroke at 30 days (0.5% [7 of 1,518] vs. 0.3% [14 of 4,235]; $p = 0.89$) or 5 years (2.6% [39 of 1,518] vs. 2.7% [90 of 4,235]; $p = 0.83$). When analyzing BMS and DES trials separately, the difference between PCI and CABG in 5-year stroke was similar among trials that used exclusively BMS (2.6% vs. 3.2%, respectively; $p = 0.39$) or DES (2.7% vs. 3.3%, respectively; $p = 0.038$) (p for interaction = 0.78). Only 190 patients were discharged on single antiplatelet therapy after PCI, with the rates of stroke at 5 years being 2.5% (91 of 4,384) for patients on DAPT and 4.0% (5 of 190) for patients on single antiplatelet therapy ($p = 0.41$).

SUBGROUP ANALYSES. There were no significant interactions between any the treatment effects of PCI versus CABG in the rate of stroke at 30 days except for the presence of hypercholesterolemia (p for interaction = 0.023) (Figure 1). There were no significant interactions between PCI and CABG and baseline characteristics on the rate of stroke at 5 years, except for diabetes (Figures 2 and 3). As shown in Figure 3A, the 5-year rate of stroke was lower in patients with diabetes randomized to PCI versus CABG (2.6% [n = 47 of 2,215] vs. 4.9% [n = 86 of 2,171], respectively; HR: 0.52; 95% CI: 0.37 to 0.75; $p < 0.001$) but not in patients without diabetes (2.6% [n = 82 of 3,538] vs. 2.4% [n = 78 of 3,594], respectively; HR: 1.04; 95% CI: 0.77 to 1.42; $p = 0.78$) (p for interaction = 0.004).

In 4,478 randomized patients with LM disease, treatment with PCI compared with CABG resulted in a lower rate of stroke at 30 days (0.3% [6 of 2,233] vs. 1.0% [23 of 2,245], respectively; HR: 0.26; 95% CI: 0.11 to 0.64; $p = 0.003$), a difference that was no longer present at 5 years (2.6% [43 of 2,233] vs. 2.6% [51 of 2,245], respectively; HR: 0.83; 95% CI: 0.55 to 1.24; $p = 0.36$) (Figure 3B). In 7,040 randomized patients with MVD, the rate of stroke was significantly lower after PCI than after CABG at 30 days (0.4% [15 of 3,520] vs. 1.2% [41 of 3,520], respectively; HR: 0.36; 95% CI: 0.20 to 0.65; $p < 0.001$) and 5 years (2.7% [86 of 3,520] vs. 3.6% [n = 113 of 3,520], respectively; HR: 0.74; 95% CI: 0.56 to 0.99; $p = 0.039$).

IMPACT OF STROKE ON MORTALITY. A total of 976 deaths occurred during follow-up. Patients who experienced a stroke within 30 days after revascularization had significantly higher 5-year mortality compared with patients who did not experience a stroke within 30 days after both CABG (41.5% [23 of 64] vs. 8.9% [414 of 5,701]; $p < 0.001$) and after PCI (45.7% [9 of 21] vs. 11.1% [530 of 5,732], respectively; $p < 0.001$) (Figure 4).

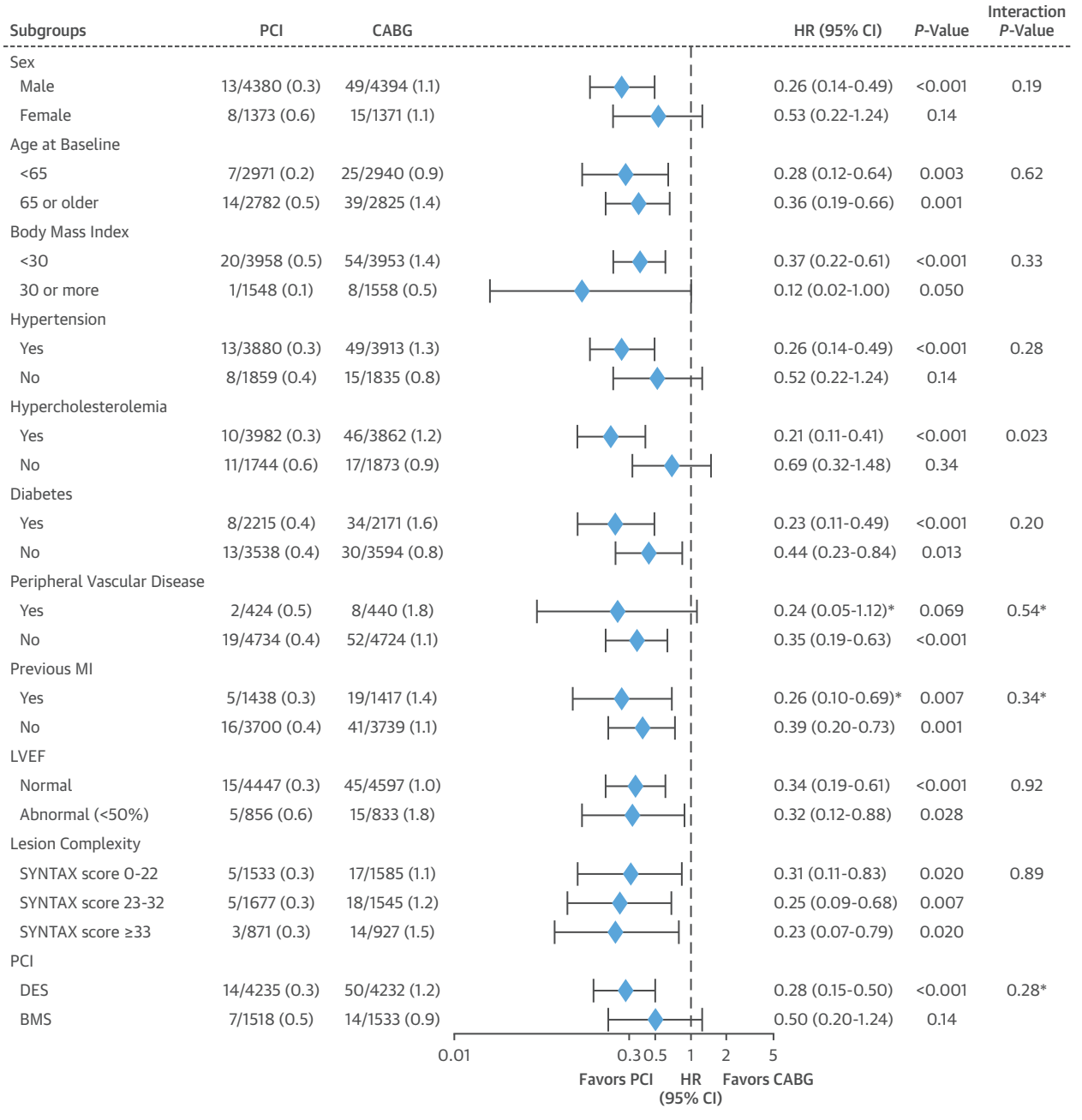
CENTRAL ILLUSTRATION **Stroke After Percutaneous Coronary Intervention Versus Coronary Artery Bypass Grafting**



Head, S.J. et al. J Am Coll Cardiol. 2018;72(4):386–98.

This figure illustrates the comparison of coronary artery bypass grafting (CABG) and percutaneous coronary intervention (PCI) on stroke during 5-year follow-up **(A)** and in landmark analyses of stroke at 30 days and beyond 30 days **(B)**. Hazard ratios (HR) are for PCI versus CABG. CI = confidence interval.

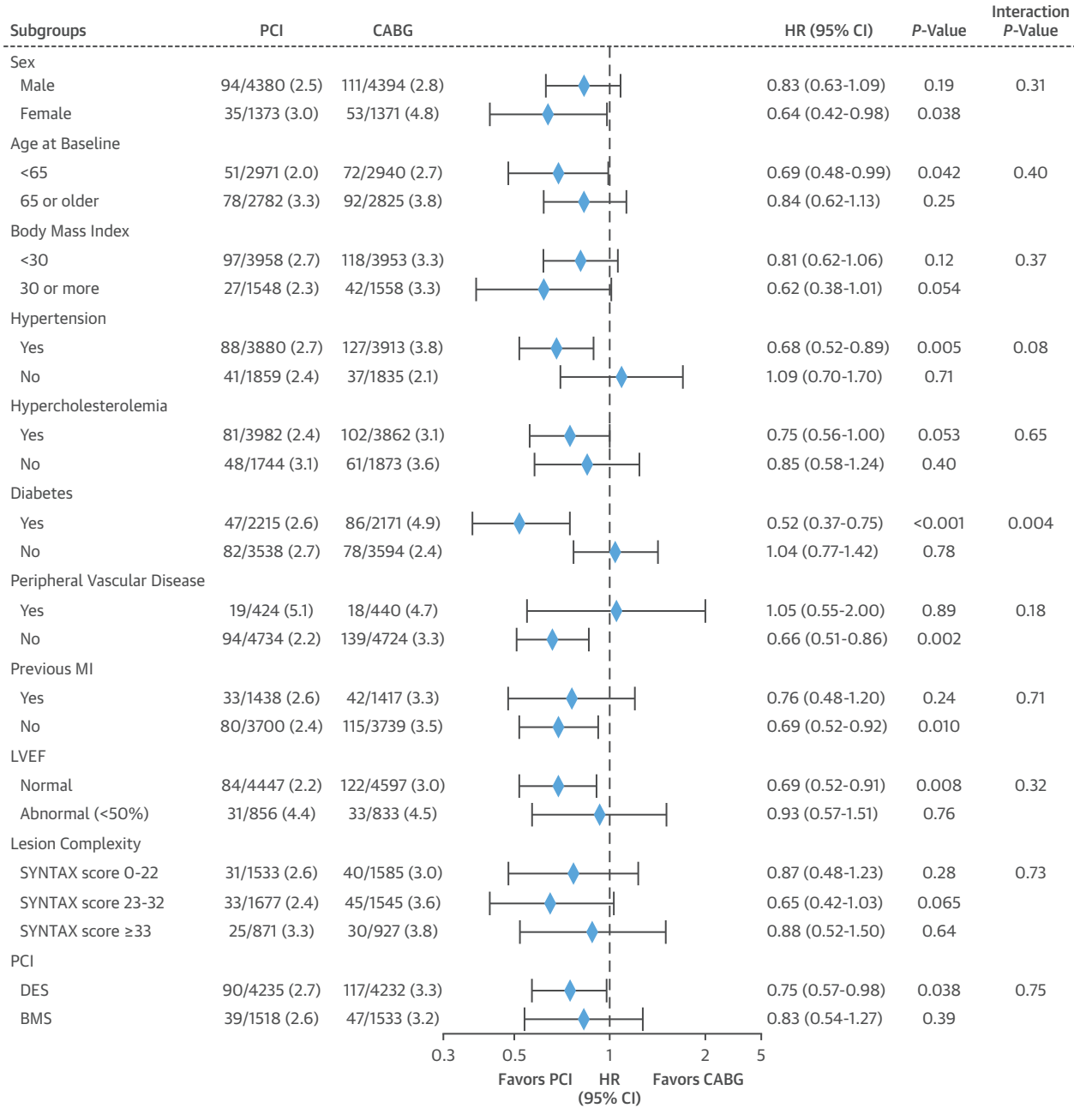
FIGURE 1 Stroke After PCI Versus CABG at 30 Days in Subgroup Analyses According to Baseline and Procedural Characteristics



*Due to the low number of events, the interaction term was derived from Cox proportional hazards models and not the random effects Cox proportional hazards models that included a frailty term. BMS = bare-metal stents; CI = confidence interval; DES = drug-eluting stents; HR = hazard ratio; LVEF = left ventricular ejection fraction; MI = myocardial infarction; SYNTAX = Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery.

COMPOSITE ENDPOINT OF ALL-CAUSE MORTALITY OR STROKE. As shown in Table 2, the rate of all-cause mortality or stroke at 30 days was 1.6% (91 of 5,753) after PCI versus 2.4% (135 of 5,765) after CABG ($p = 0.003$). The composite of all-cause mortality or stroke between 31 days and 5 years was higher after PCI compared with CABG (11.6% vs. 9.3%, respectively; HR: 1.26; 95% CI: 1.11 to 1.32; $p < 0.001$). Finally, the overall difference in the composite of all-cause mortality or stroke after PCI versus CABG at 5 years did not

FIGURE 2 Stroke After PCI Versus CABG During 5-Year Follow-Up in Subgroup Analyses According to Baseline and Procedural Characteristics

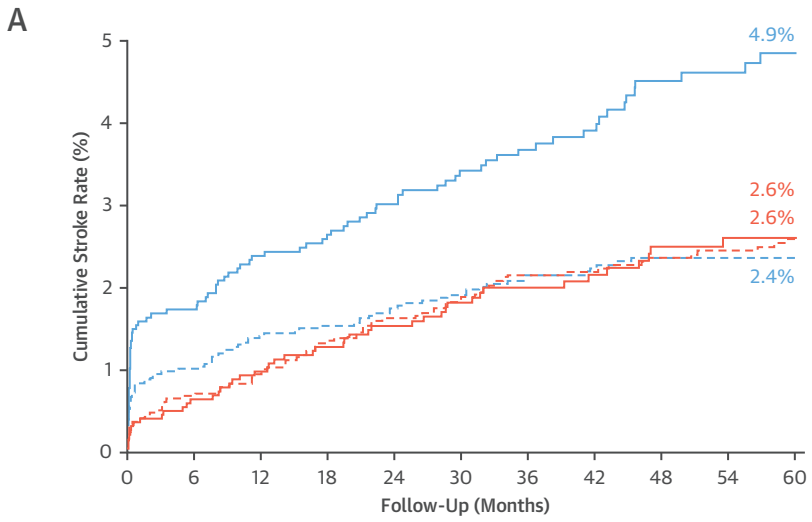


Abbreviations as in Figure 1.

reach statistical significance (13.0% vs. 11.4%, respectively; HR: 1.11; 95% CI: 0.99 to 1.24; p = 0.069). Although there were no significant interactions, the benefit of CABG over PCI was generally seen in patients with diabetes and higher SYNTAX scores.

The difference between PCI and CABG in rates of the composite of all-cause death or stroke at 30 days was similar in patients with MVD (1.8% [n = 62] vs. 2.6% [n = 90]; HR: 0.68; 95% CI: 0.49 to 0.94; p = 0.020) and LM disease (1.3% [n = 29] vs. 2.0%

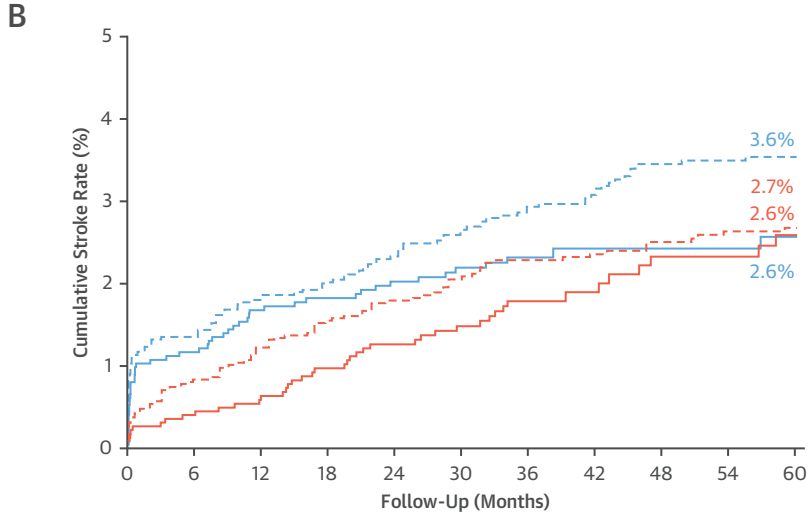
FIGURE 3 Stroke After PCI Versus CABG During 5-Year Follow-Up of Patients With and Without DM, LM, or MVD



Number at Risk

CABG	(DM)	2,171	1,986	1,921	1,862	1,744	1,579	1,287	1,141	1,007	846	604
PCI	(DM)	2,215	2,097	2,025	1,955	1,842	1,647	1,354	1,209	1,068	890	671
CABG	(Non-DM)	3,594	3,435	3,361	3,276	3,157	2,971	2,390	2,305	2,206	2,111	1,599
PCI	(Non-DM)	3,538	3,448	3,390	3,310	3,202	3,006	2,434	2,345	2,252	2,148	1,690

PCI-DM
CABG-DM
> HR: 0.52 (95% CI: 0.37-0.75, *P* < 0.001)
PCI-Non DM
CABG-Non DM
> HR: 1.04 (95% CI: 0.77-1.42, *P* = 0.78)



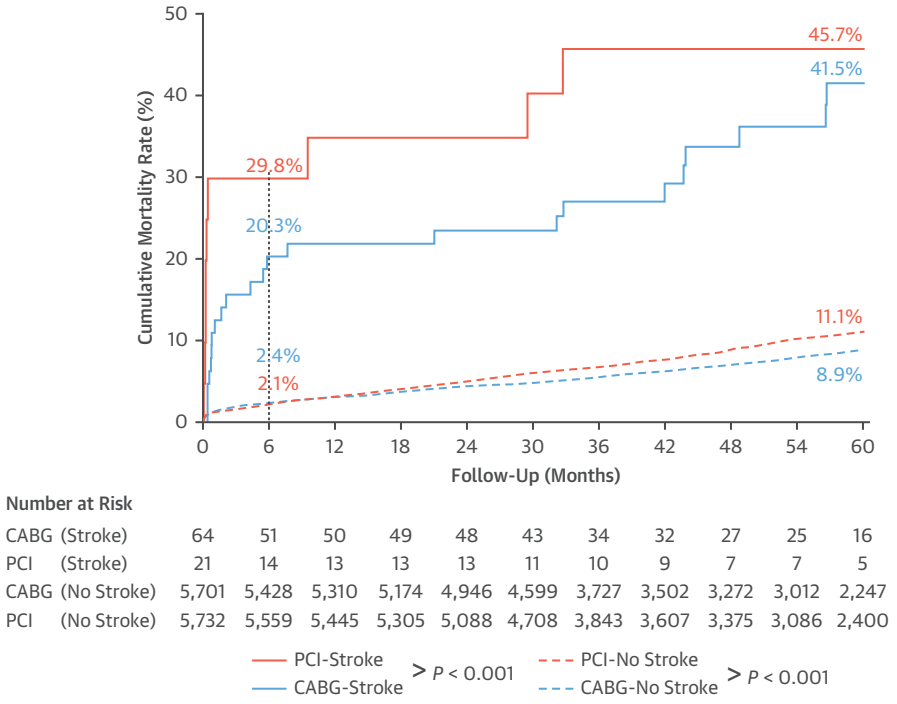
Number at Risk

CABG	(LM)	2,245	2,132	2,061	1,985	1,875	1,659	917	856	788	714	398
PCI	(LM)	2,233	2,175	2,111	2,033	1,938	1,700	968	903	838	769	476
CABG	(MVD)	3,520	3,289	3,221	3,153	3,026	2,891	2,760	2,590	2,425	2,243	1,805
PCI	(MVD)	3,520	3,370	3,304	3,232	3,106	2,953	2,820	2,651	2,482	2,269	1,885

PCI-LM
CABG-LM
> HR: 0.83 (95% CI: 0.55-1.24, *P* = 0.36)
PCI-MVD
CABG-MVD
> HR: 0.74 (95% CI: 0.56-0.99, *P* = 0.039)

Stroke after PCI (percutaneous coronary intervention) versus CABG (coronary artery bypass grafting) during 5-year follow-up of patients with and without diabetes mellitus (DM) **(A)** and patients with left main (LM) or multivessel disease (MVD) **(B).** There was significant diabetes-by-treatment interaction (p for interaction = 0.004). No interaction was explored for LM and MVD, because these groups are not mutually exclusive. Abbreviations as in Figure 1.

FIGURE 4 Mortality After PCI Versus CABG of Patients With and Without Stroke Within 30 Days After Revascularization



Solid lines indicate patients who experienced a stroke within the first 30 days of follow-up, and **dotted lines** indicate patients without a stroke. Follow-up starts at 30 days, indicated here as time 0. Abbreviations as in **Figures 1 and 3**.

[n = 45]; HR: 0.64; 95% CI: 0.40 to 1.02; p = 0.062). Between 31 days and 5 years, the rate of the composite of all-cause death or stroke after PCI versus CABG was 11.9% (n = 371) versus 9.1% (n = 274) in patients with MVD (HR: 1.31; 95% CI: 1.12 to 1.53; p < 0.001) and 11.3% (n = 174) versus 10.2% (n = 147) in patients with LM disease (HR: 1.16; 95% CI: 0.93 to 1.44; p = 0.20). At 5 years, there was a difference between PCI and CABG in patients with MVD (13.5% [n = 433] vs. 11.4% [n = 364]; HR: 1.16; 95% CI: 1.01 to 1.33; p = 0.041) but not in patients with LM disease (12.4% [n = 203] vs. 12.0% [n = 192]; HR: 1.02; 95% CI: 0.84 to 1.25; p = 0.81).

DISCUSSION

In this individual patient-data pooled analysis based on 11 randomized clinical trials comparing CABG with PCI for multivessel or LM disease, CABG resulted in significantly higher rates of 5-year stroke. A higher rate of stroke in the first 30 days after the procedure drove the difference. Rates of stroke between 31-day and 5-year follow-ups were similar between CABG and PCI. The increased 5-year risk of stroke with CABG compared with PCI was confined to patients with MVD and diabetes. Strokes occurring within 30 days after the procedure were strongly associated with increased long-term mortality, with a rate approaching 50% at 5 years. The composite of all-cause mortality or stroke was lower after PCI compared with CABG at 30 days, but higher after PCI at 5 years, especially in patients with diabetes, MVD, and in those with high SYNTAX scores.

Periprocedural strokes are more common after CABG, with an absolute incremental risk of ~0.7% observed in the present large-scale study. The mechanisms underlying the increased risk of stroke with surgery are likely multifactorial. First, most CABG procedures are performed on-pump with cannulation and clamping of the aorta; even if they are performed off-pump, the aorta is often manipulated for construction of the proximal anastomosis (19–21). Data from cohort studies suggests that limiting, if not completely avoiding, aortic manipulation by performing an anaortic off-pump CABG procedure reduces stroke rates substantially (22,23). The use of

TABLE 2 Composite Endpoint of All-Cause Mortality or Stroke

	30 Days				31 Days–5 Years				5 Years			
	PCI vs. CABG	HR (95% CI)	p Value	Interaction p Value	PCI vs. CABG	HR (95% CI)	p Value	Interaction p Value	PCI vs. CABG	HR (95% CI)	p Value	Interaction p Value
All	1.6 (91) vs. 2.4 (135)	0.67 (0.51–0.87)	0.003	–	11.6 (545) vs. 9.3 (421)	1.26 (1.11–1.43)	<0.001	–	13.0 (636) vs. 11.4 (556)	1.11 (0.99–1.24)	0.069	–
Diabetes												
Yes	2.2 (48) vs. 3.1 (66)	0.70 (0.48–1.02)	0.063	0.68	15.4 (263) vs. 11.2 (180)	1.39 (1.15–1.68)	<0.001	0.14	17.2 (311) vs. 13.9 (246)	1.20 (1.02–1.42)	0.031	0.19
No	1.2 (43) vs. 1.9 (69)	0.63 (0.43–0.92)	0.016		9.5 (282) vs. 8.3 (241)	1.15 (0.97–1.37)	0.11		10.6 (325) vs. 10.0 (310)	1.03 (0.88–1.21)	0.69	
SYNTAX score												
0–22	0.9 (14) vs. 2.2 (34)	0.42 (0.23–0.79)	0.007	0.15	10.3 (116) vs. 8.0 (94)	1.19 (0.91–1.57)	0.20	0.22	11.1 (130) vs. 10.0 (128)	0.98 (0.77–1.26)	0.89	0.09
23–32	1.4 (23) vs. 2.1 (32)	0.65 (0.38–1.12)	0.12		12.8 (162) vs. 11.4 (123)	1.18 (0.93–1.49)	0.16		14.0 (185) vs. 13.3 (155)	1.07 (0.86–1.32)	0.56	
≥33	2.6 (23) vs. 2.7 (25)	0.97 (0.55–1.71)	0.92		16.3 (111) vs. 11.1 (75)	1.61 (1.20–2.16)	0.001		18.5 (134) vs. 13.6 (100)	1.45 (1.12–1.88)	0.005	

Event rates were based on Kaplan-Meier estimates in time-to-first-event analyses expressed as % (n).
CI = confidence interval; HR = hazard ratio; other abbreviations as in Table 1.

bilateral internal mammary arteries avoids the need for proximal anastomoses and side-clamping of the aorta and has been associated with lower stroke rates (24). In the current study, the rate of bilateral internal mammary arteries use was relatively low. Second, strategies to reduce post-operative bleeding that are often required after CABG (but not after PCI), such as usage of tranexamic acid, lead to a hypercoagulable state that may increase the risk of stroke (25). Third, post-operative atrial fibrillation is frequent after CABG and increases the risk of stroke in the early post-operative period (26,27). Fourth, periods of hypoperfusion during surgery and early post-operative low cardiac output syndrome may impair brain perfusion, leading to ischemia and watershed strokes (28). Another hypothesis is that strokes may be lower after PCI due to the routine use of DAPT after stent implantation (29). However, in the current study, we did not find this to be associated with a lower rate of stroke after CABG.

Our landmark analysis demonstrated a low rate of stroke beyond 30 days that was similar between CABG and PCI. The need for more repeat revascularizations after PCI than after CABG, as shown in these individual trials (30), did not result in a higher stroke rate during follow-up after PCI. Moreover, subgroup analyses demonstrated no significant heterogeneity according to baseline characteristics, with the important exception of diabetes: stroke rates were nearly doubled after CABG compared with PCI in patients with diabetes, but nearly identical in patients without diabetes (p for interaction = 0.004). This finding should be considered hypothesis-generating and requires confirmation in future studies.

Whereas PCI was associated with lower periprocedural rates of stroke compared with CABG in patients with MVD and patients with LM disease, the long-term risk of stroke was higher after PCI than CABG in those with LM disease. This finding is likely the result of inclusion of the NOBLE trial in which long-term rates of strokes were inexplicably higher after PCI than after CABG (17), a finding not confirmed in any other randomized trial.

When the endpoints of all-cause mortality and stroke were combined in a composite endpoint, there was no significant difference in the 5-year rates of death or stroke between PCI and CABG. However, CABG was associated with superior outcomes in patients with MVD, diabetes, and higher SYNTAX scores, but not in patients with LM disease.

It remains unclear whether there is a difference in the severity of stroke occurring after CABG and PCI. In the FREEDOM trial, severely disabling strokes accounted for 55% of all strokes after CABG but only 27% of all strokes after PCI (13). An in-depth analysis of strokes occurring in the SYNTAX trial showed that residual defects were present at discharge in 68% of patients after CABG and in 47% after PCI (31). It is evident that quality of life of patients who experienced a stroke is impaired, although no studies have compared quality of life of patients experiencing a stroke after CABG or PCI to determine whether the higher rate of residual deficits after CABG is translated into significantly lower long-term quality of life. We did, however, find that 5-year mortality was markedly higher among patients who experienced a 30-day stroke versus those

who did not experience a stroke, regardless of whether stroke occurred after CABG or PCI.

The present analysis has several strengths. Sharing of trial data among investigators is crucial to compare low-frequency outcomes such as stroke and to assess safety and efficacy in patient subgroups (32). This collaborative analysis from 11 randomized clinical trials had sufficient power to analyze the occurrence of stroke after CABG versus PCI. Moreover, the inclusion of patients from different geographic areas increases the external validity of our results. All trials prospectively enrolled patients and had a clinical events committee to adjudicate events, confirming the diagnosis of stroke.

STUDY LIMITATIONS. First, techniques for both CABG and PCI have evolved during the patient inclusion period that ranged from 1995 to 2015. Although we showed consistent stroke rates after PCI with BMS and DES and for off-pump and on-pump CABG, it is unclear whether other unmeasured factors may have played a role. Second, there was some heterogeneity in baseline characteristics between trials, with more recent trials enrolling patients with more complex coronary artery disease and with a greater frequency of diabetes. Third, several variables potentially related to stroke after CABG were not collected in many of the included trials (e.g., aortic manipulation, post-operative atrial fibrillation), and therefore our multivariable models could not include factors that may have predicted periprocedural stroke. Fourth, rates of stroke may have been underestimated because independent neurological evaluation was not routinely performed nor required for the diagnosis of stroke. Involvement of a stroke neurologist has been shown to increase the number of strokes found after aortic valve procedures and is now mandatory in trials of transcatheter and surgical aortic valve replacement (33). Fifth, data on the severity of stroke and residual deficits after stroke could not be evaluated because only 2 trials collected such data and definitions varied. Finally, antiplatelet therapy may reduce the occurrence of stroke, but we lacked data of medication regimens during follow-up. Nevertheless, most patients receive at least 1 antiplatelet agent after CABG or PCI, which is generally considered to be sufficient for stroke prevention.

CONCLUSIONS

In this large-scale, individual patient-data pooled analysis of randomized trials including patients with multivessel or LM coronary artery disease who underwent coronary revascularization, PCI resulted in significantly lower 30-day and 5-year rates of stroke than CABG, with similar rates of stroke between 31 days and 5 years. The increased 5-year risk of stroke with CABG was confined to patients with MVD and diabetes. Five-year mortality was high in patients experiencing a stroke within 30 days after both CABG and PCI. The differential risks of stroke after PCI and CABG should be considered in the comprehensive assessment of the long-term risk-benefit ratio of these alternative revascularization options.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: In patients undergoing coronary revascularization for multivessel or LM disease, rates of stroke were lower after PCI than CABG during the first 30 days but comparable thereafter during the next 5 years.

TRANSLATIONAL OUTLOOK: More studies are needed on strategies to prevent perioperative stroke in patients undergoing CABG surgery.

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KEY WORDS coronary artery bypass graft, left main, mortality, multivessel, percutaneous coronary intervention, stenting, stroke

APPENDIX For supplemental tables and a figure, please see the online version of this paper.