Stroke following coronary revascularization: a patient-level pooled analysis of 11 randomised trials comparing coronary artery bypass grafting versus percutaneous coronary intervention

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CONFLICTS OF INTEREST

Head: none
Milojevic: none
Daemen:
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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 (LM) coronary artery disease. Stroke is amongst the most feared outcomes after revascularization. As it occurs infrequently, studies with large numbers of patients are required to detect differences in stroke rates between CABG and PCI.

Methods: We performed a collaborative individual patient-level pooled analysis of 11 randomized clinical trials comparing CABG with PCI using stents; ERACI II (n=450), ARTS (n=1205), MASS II (n=408), SoS (n=988), SYNTAX (n=1800), PRECOMBAT (n=600), FREEDOM (n=1900), VA CARDS (n=198), BEST (n=880), NOBLE (n=1184) and EXCEL (n=1905). Thirty-day and 5-year stroke events 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 CABG (n=5765) or PCI (n=5753) 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 1.1% after CABG and 0.4% after PCI (*P*<0.001). At 5-year follow-up, stroke remained significantly higher after CABG than after PCI (3.2% versus 2.6%, *P*=0.027). Rates of stroke between 30 days and 5 year were comparable: 2.1% after CABG versus 2.2% after PCI (*P*=0.72). Treatment effect of PCI versus CABG on 5-year stroke was not modified by using bare-metal stents or drug-eluting stents, the coronary complexity, or by clinical characteristics except for a significant interaction among diabetics (CABG: 4.9% versus PCI: 2.6%) and non-diabetics (CABG: 2.4% versus PCI: 2.6%) (P_{int}=0.004). Patients who suffered a stroke versus those without a stroke within 30 days of the procedure had a high 5-year mortality after CABG (41.5% versus 8.9%, *P*<0.001) and PCI (45.7% versus 11.1%, *P*<0.001).

Conclusions: In this large-scale individual patient-level pooled analysis, CABG resulted in significantly higher 30-day and 5-year rates of stroke than PCI, but rates of stroke between 30 days and 5 years were similar. Five-year mortality was higher for patients suffering a stroke within 30 days of the CABG or PCI procedure.

Keywords: Coronary artery bypass grafting; CABG; Percutaneous coronary intervention; PCI; Stenting; Left main; Multivessel; Stroke

INTRODUCTION

Coronary artery bypass grafting (CABG) and percutaneous coronary intervention (PCI) are treatment options for patients with coronary artery disease who require coronary revascularization. Numerous randomized clinical trials have compared these two treatments; 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 three-vessel disease (3VD), left main (LM) disease, and diabetes.

A pooled analysis of individual data from 10 randomized trials showed that CABG, as compared with PCI using balloon angioplasty or BMS, had similar long-term rates of mortality, but higher complication rates at 90 days after the procedure (1). Several studies suggest that CABG is associated with a significant increase of procedural stroke, a devastating outcome with substantial mortality, morbidity and reduced quality of life. It is uncertain whether advances in PCI and CABG have led to a decrease in the number of strokes, but since stroke occurs infrequently, individual randomized trials do not have enough power to detect meaningful small differences between PCI and CABG. Moreover, it is unclear to what degree long-term survival is impacted by the occurrence of stroke (4).

We performed a collaborative analysis with individual patient data from 11 randomized clinical trials of patients with multivessel or LM coronary artery disease who were randomly assigned to CABG or PCI to compare procedural and long-term rates of stroke and the impact of stroke on survival.

METHODS

Study Selection and Data Collection

On the 19th of July, 2017, the PubMed, Embase, and Cochrane databases were searched without limits to identify randomized clinical trials comparing CABG with PCI for the treatment of multivessel or LM coronary artery disease. The search was performed with the following combination of keywords: “coronary artery bypass”, “percutaneous coronary intervention”, “stent” and “random*”. Reference lists of retrieved articles were also hand-searched. Conference abstracts were not considered.

Studies were selected if (i) patients were randomly assigned to undergo CABG or PCI treatment, (ii) patients had multivessel or left main coronary artery disease, (iii) patients did not present with a myocardial infarction, (iv) PCI was performed using stents (BMS or DES) and not balloon angioplasty, (v) the occurrence of stroke was collected beyond 30 days of follow-up, and (vi) more than one-year follow-up for all-cause mortality was available.

After study selection, principal investigators were contacted and invited to supply data for a collaborative, pooled analysis based on individual patient data. Participating studies completed a prespecified spreadsheet that included baseline characteristics and outcome measures (Supplementary Appendix 1). The provided data were cross-checked against the primary publication and longer-term follow-up publications from each individual trial, and inconsistencies were resolved by contacting trial principal investigators. Investigators from 11 individual trials provided the data for the current pooled analysis: ERACI II (5), ARTS (6), MASS-II (7), SoS (8), SYNTAX (9), PRECOMBAT (10), FREEDOM (11), VA CARDS (12), BEST (13), EXCEL (14), and NOBLE (15). Only the data from the LE MANS trial (n=105) could not be obtained (16). Baseline and procedural characteristics of individual trials are presented in Supplementary Appendix 2.

Local Medical Ethics Committees approved all these trials at the time of study execution. Patients in each of the 11 trials provided written informed consent.

Outcomes and Follow-up

Follow-up time was calculated from the time of the procedure. Follow-up time was calculated from randomization if patients suffered 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 occurred during the first 30 days after the procedure. All trials, but the SoS trial, collected stroke during the entire duration of follow-up; the SoS trial collected stroke only up to 1 year after revascularization (8). The definition of stroke was a focal neurological deficit of central origin lasting more than 24 hours either confirmed by neuroimaging or a deficit lasting longer than 72 hours without the need for confirmation with neuroimaging. The secondary endpoint of this study was all-cause death. In all trials, a Clinical Events Committee (CEC) adjudicated the events.

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 ± standard deviation and compared using 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 survival curves. Hazard ratios of CABG versus PCI for stroke were estimated using a Cox proportional hazards model that was 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. Since several trials

enrolled patients with specific characteristics, subgroup analyses were performed according to diabetes status and multivessel or LM disease. The impact of baseline characteristics on treatment estimates of 5-year stroke was also explored in subgroup analyses with *P*-values for interaction calculated in a Cox proportional hazards model. Moreover, the impact of off-pump CABG as opposed to on-pump CABG was explored among trials that provided information on the use of cardiopulmonary bypass. 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. A two-sided $P<0.05$ was considered to indicate statistical significance. All statistical analyses were performed using SPSS software, version 21 (IBM Corporation, Armonk, NY, USA) or R software version 3.2.4 (Institute for Statistics and Mathematics of WU, Wien, Austria).

Role of the Funding Source

While 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. The corresponding author had full access to the data. The entire group of investigators decided to submit the manuscript, which was executed by the corresponding author, who takes final responsibility for the content.

RESULTS

Study Population

Eleven trials randomized 11,518 patients; 5765 patients were randomly assigned to CABG and 5753 to PCI. Of the 5765 patients assigned to CABG, 5421 underwent CABG (94%), 233 underwent PCI (4%), and 111 underwent neither procedure (2%). Of the 5753 patients assigned to PCI, 5610 underwent PCI (98%), 101 underwent CABG (2%), and 42 underwent neither procedure (1%). In the as-treated analysis 5522 patients underwent CABG and 5843 patients underwent PCI. Data on cross-overs in each study are presented in Supplementary Appendix 3.

Patient enrollment was conducted between 1995 and 2015. PCI was performed in four trials exclusively with bare-metal stents (MASS 2, ERACI 2, SoS, and ARTS; n=1518 PCI patients), in three trials with first-generation drug-eluting stents (PRECOMBAT, SYNTAX, and FREEDOM; n=2156 PCI patients), in three trials with second-generation drug-eluting stents (BEST, EXCEL, and NOBLE; n=1978 PCI patients), and in one 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 CABG and 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. Left main 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, with follow-up among survivors being 4.0 ± 1.3 years.

Stroke

A total of 293 strokes occurred during follow-up. The cumulative stroke rate at 5-year follow-up was 3.2% (n=164) in patients randomized to CABG and 2.6% (n=129) in patients randomized to PCI (P=0.027) (Figure 1A). At 30 days, stroke occurred in 64 patients (1.1%) randomized to CABG and in 21 patients (0.4%) randomized to PCI (P<0.001) (Figure 1B). The rate of stroke after 30 days up to 5 years was comparable between CABG (2.1%; n=100) and PCI (2.2%; n=108) (P=0.72) (Figure 1B). Results were similar in the as-treated analysis. The value of the frailty parameter theta (θ) for

heterogeneity was θ=0.09 (*P*<0.001). In a multivariable analysis, the only independent predictor of 30-day stroke was CABG as a method of revascularization (HR=8.33, 95% CI 1.06-62.5; *P*=0.043). In multivariable analysis of 5-year stroke, CABG versus PCI failed to be an independent predictor.

Within the 7 trials that provided data on on- or off-pump CABG (n=3945), 28% of patients underwent off-pump CABG surgery. Rates of stroke at 30 days were 0.6% [6/1085] after off-pump and 1.4% [40/2860] after on-pump CABG (*P*=0.13), with 5-year rates of 2.9% [25/1085] versus 3.5% [84/2860], respectively (*P*=0.60). After CABG, 44% of patients were discharged on dual antiplatelet therapy. The rate of stroke at 5 years was comparable between patients on DAPT or single antiplatelet therapy (3.1% [48/1759] versus 3.8% [67/2109], respectively; *P*=0.84).

Whether PCI was performed with BMS or DES did not have an impact on the rate of stroke at 5 years (2.6% [39/1518] versus 2.7% [90/4235], *P*=0.83). When analyzing BMS and DES trials separately, the difference between PCI and CABG was similar among trials that used exclusively BMS (2.6% versus 3.2% after CABG, *P*=0.39) or DES (2.7% versus 3.3% after CABG, *P*=0.038). Only 190 patients were discharged on single antiplatelet therapy after PCI. The rates of stroke at 5 years were 2.5% (91/4384) for patients on DAPT and 4.0% (5/190) for patients on single antiplatelet therapy (*P*=0.41).

Subgroup Analyses

Analyses of patients with LM disease showed that there was no difference in the 5-year rate of stroke between CABG and PCI (2.6% [51/2245] versus 2.6% [43/2233], respectively; *P*=0.36). In patients with multivessel disease, the rate of stroke was significantly higher after CABG than after PCI (3.6% [n=113/3520] versus 2.7% [86/3520], respectively; *P*=0.039). There was no significant interaction between the treatment effect of CABG versus PCI and baseline characteristics for the occurrence of 5-year stroke, except for diabetes (Figures 2 and 3). The difference in stroke was significantly higher in diabetic patients randomized to CABG versus PCI (4.9% [n=86/2171] versus 2.6% [n=47/2215],

respectively; *P*<0.001) but not in non-diabetics (2.4% [n=78/3594] versus 2.6% [n=82/3538], respectively; *P*=0.78) (*P* for interaction = 0.004)(Figure 2).

Impact of Stroke on Death

A total of 976 deaths occurred during follow-up. Patients who suffered a stroke within 30 days after CABG had significantly higher 5-year mortality compared to patients that did not suffer a stroke within 30 days of CABG (41.5% [23/64] versus 8.9% [414/5701]; *P*<0.001). Mortality was also significantly higher in PCI patients that suffered a stroke within 30 days versus those who did not (45.7% [9/21] versus 11.1% [530/5732], respectively; *P*<0.001). Mortality among patients that suffered a stroke any time during follow-up is depicted in Figure 4.

DISCUSSION

In this individual patient-level pooled analysis with data from 11 randomized clinical trials comparing CABG with PCI for multivessel or left main coronary artery disease, CABG resulted in significantly higher rates of 5-year stroke. This was driven by a higher rate of stroke in the first 30 days after the procedure. However, rates of stroke between 30 days and 5-year follow-up were similar between CABG and PCI. Strokes occurring within 30 days after the procedure significantly increased mortality, with a rate approaching 50% at 5 years.

Procedural strokes are more common after CABG for several reasons. First, most CABG procedures are performed with some extend of aortic manipulation (17-19). Data from cohort studies suggests that limiting, if not completely avoiding aortic manipulation reduces stroke rates substantially (20). The use of bilateral internal mammary arteries (BIMA) avoids the need for proximal anastomoses and side-clamping of the aorta and has therefore been associated with lower stroke rates (21). In the current analysis the rate of BIMA use was low. Second, strategies to reduce postoperative bleeding that are often required after CABG but not PCI, such as usage of tranexamic acid, lead to a hypercoagulable state that potentially increase the risk of seizures and stroke (22).

Another reason might be postoperative atrial fibrillation that is frequent after CABG and increases the risk of stroke in the early postoperative period (23). Fourth, periods of hypoperfusion during surgery and low cardiac output syndrome in the early postoperative period may impair brain perfusion, leading to ischaemia and watershed strokes (24). Another hypothesis is that strokes are lower after PCI due to dual antiplatelet therapy immediately after stent implantation, while CABG patients generally only receive single antiplatelet therapy (25).

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 (26), did not result in a higher stroke rate after PCI. Moreover, our subgroup analyses demonstrate no significant heterogeneity according to baseline characteristics; therefore, PCI produces superior results to CABG in terms of 5-year stroke rates among diverse patients.

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% and 27% of all strokes occurring after CABG and PCI, respectively (11). An in-depth analysis of strokes occurring in the SYNTAX trial showed that 68% and 47% in the CABG and PCI groups, respectively, had residual deficits at discharge (27). It is evident that quality of life of patients that suffered a stroke is impaired, although no studies have compared quality of life of patients suffering 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 significantly higher among patients that suffered a 30-day stroke versus those that did not suffer a stroke.

Sharing of trial data among investigators is crucial to assess safety and efficacy in small patient subgroups (28). This collaborative analysis from 11 randomized clinical trials demonstrates that a pooled analysis is required to analyze events that occur infrequently, such as stroke. Moreover, the inclusion of patients from different geographic areas increases the external validity of

our results. All trials prospectively enrolled patients and had a CEC adjudicating events, confirming the diagnosis of stroke.

Our analysis also has some 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 DES and BMS and for off-pump and on-pump CABG, it is unclear whether other unmeasured factors may have played a role. Secondly, there was some heterogeneity in baseline characteristics among trials, which may have been caused by more recent trials focusing on patients with more complex coronary artery disease or with diabetes. Third, no data on the severity of stroke or on residual deficits after stroke could be pooled because only two trials collected such data and definitions varied. Fourth, antiplatelet therapy may reduce stroke incidences, but we lacked data of medication regimens during follow-up. Nevertheless, most patients receive at least one antiplatelet agent after CABG or PCI, which should be sufficient for stroke prevention.

CONCLUSION

In this individual patient-level pooled analysis of randomized trials including patients with multivessel or left main coronary artery disease who require coronary revascularization, CABG resulted in significantly higher 30-day and 5-year rates of stroke than PCI, but rates of stroke after 30 days up to 5 years were similar. Five-year mortality was high in patients suffering a stroke within 30 days after CABG and PCI.

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TABLES

Table 1. Baseline, procedural, and discharge data of randomized cohorts.

Characteristic	PCI (n=5753)	CABG (n=5765)
Age	63.6 ± 9.8 (5753)	63.7 ± 9.9 (5765)
Female gender	23.9% (1373/5753)	23.8% (1371/5765)
BMI>30	28.1% (1548/5506)	28.3% (1558/5511)
Smoking current	22.3% (1274/5701)	22.3% (1273/5703)
Diabetes	38.5% (2215/5753)	37.7% (2171/5765)
On Insulin	12.9% (545/4234)	11.9% (504/4245)
Hypertension	67.6% (3880/5739)	68.1% (3913/5748)
Hypercholesterolemia	69.5% (3982/5726)	67.3% (3862/5735)
Peripheral vascular disease	8.2% (424/5158)	8.5% (440/5164)
Carotid artery disease	7.8% (161/2072)	8.1% (168/2074)
Previous TIA or CVA	5.4% (218/4052)	6.2% (253/4054)
Previous MI	28.0% (1438/5138)	27.5% (1417/5156)
LV dysfunction (<30%)	0.9% (49/5303)	1.0% (54/5430)
Unstable disease	34.6% (1786/5158)	34.2% (1767/5160)
Three-vessel disease	58.6% (2460/4201)	60.1% (2594/4197)
Left main disease	38.8% (2233/5753)	38.9% (2245/5765)
SYNTAX score	24.5 ± 9.0 (4099)	24.7 ± 9.3 (4069)
PCI – DES used	73.5% (4121/5607)	-
PCI – number of stents	3.1 ± 2.0 (4935)	-
CABG – LIMA use	-	96.2% (4574/4753)
CABG – BIMA use	-	18.7% (771/4122)
CABG – off-pump	-	27.5% (1085/3945)
Aspirin at discharge	97.3% (4487/4612)	95.5% (3814/3994)
Thienopyridine at discharge	96.7% (4479/4630)	45.1% (1815/4026)
DAPT	95.1% (4384/4612)	44.0% (1759/3994)

Values are present as mean ± SD or n/N (%). PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; BMI, body mass index; TIA, transitory ischemic attack; CVA, cerebrovascular attack; MI, myocardial infarction; LV, left ventricular; DES, drug-eluting stents; LIMA, left internal mammary artery; BIMA, bilateral internal mammary artery; DAPT, dual antiplatelet therapy.

FIGURE LEGENDS

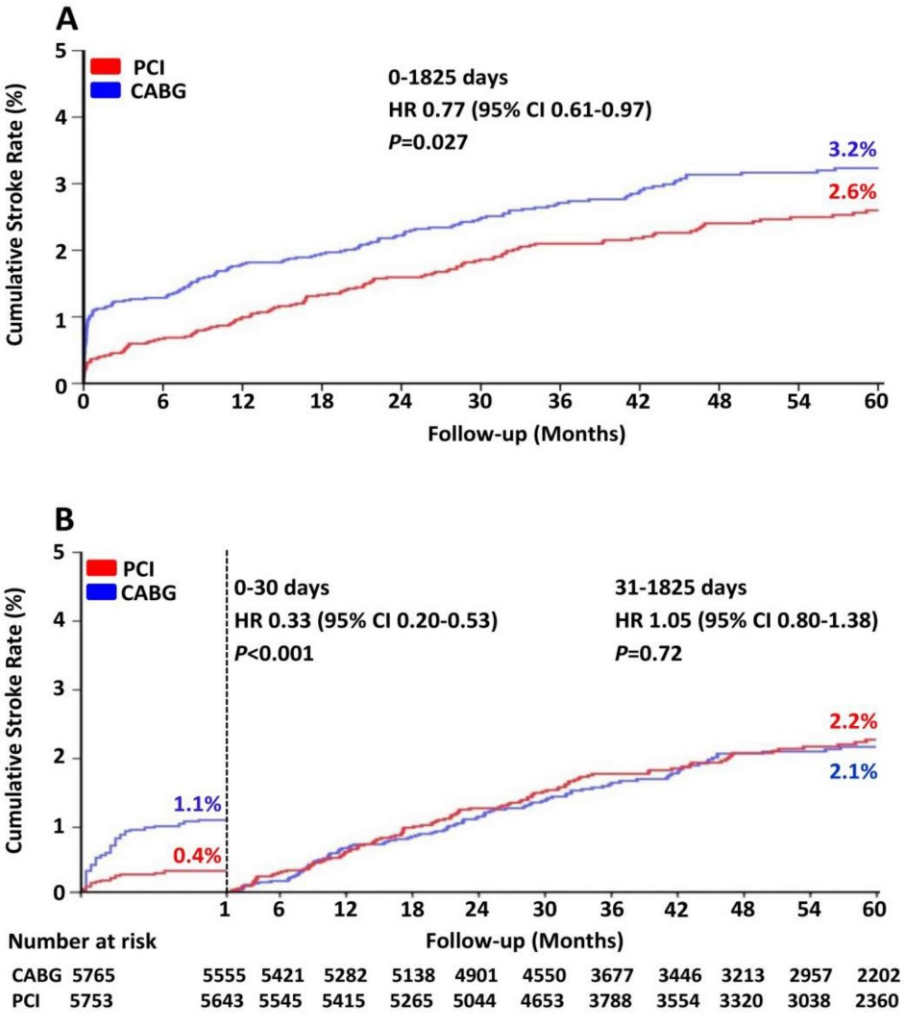
Figure 1. Stroke after percutaneous coronary intervention versus coronary artery bypass grafting during 5-year follow-up *(A)* and in landmark analyses of 30-day stroke and stroke beyond 30 days *(B)*. P-values are from log-rank test. CABG, coronary artery bypass grafting; CI, confidence interval; HR, hazard ratio; PCI, percutaneous coronary intervention

Figure 2. Stroke after percutaneous coronary intervention versus coronary artery bypass grafting during 5-year follow-up of patients with and without diabetes mellitus *(A)* and patients with left main or multivessel disease *(B)*. There was significant diabetes-by-treatment interaction (P_{int}=0.004), without significant interaction according to LM/MVD (P_{int}=0.68). CABG, coronary artery bypass grafting; PCI, percutaneous coronary intervention; DM, diabetes mellitus; LM, left main disease; MVD, multivessel disease

Figure 3. Stroke after percutaneous coronary intervention versus coronary artery bypass grafting during 5-year follow-up in subgroup analyses according to baseline and procedural characteristics. BMI, body mass index; BMS, bare-metal stents; CABG, coronary artery bypass grafting; DES, drug-eluting stents; DM, diabetes mellitus ; HTA, hypertension arterials; HLP, hyperlipidemia; LM, left main disease; LVEF, left ventricular ejection fraction; MVD, multivessel disease; PCI, percutaneous coronary intervention; PVD, peripheral vascular disease; PMI, prior myocardial infarction; HR, hazard ratio; CI, confidence interval

Figure 4. Death after percutaneous coronary intervention versus coronary artery bypass grafting during 5-year follow-up of patients with and without stroke. Solid lines indicate patients who developed stroke during follow-up period while dotted lines indicate patients without stroke during the 5-year of follow-up. CABG, coronary artery bypass grafting; PCI, percutaneous coronary intervention

FIGURES



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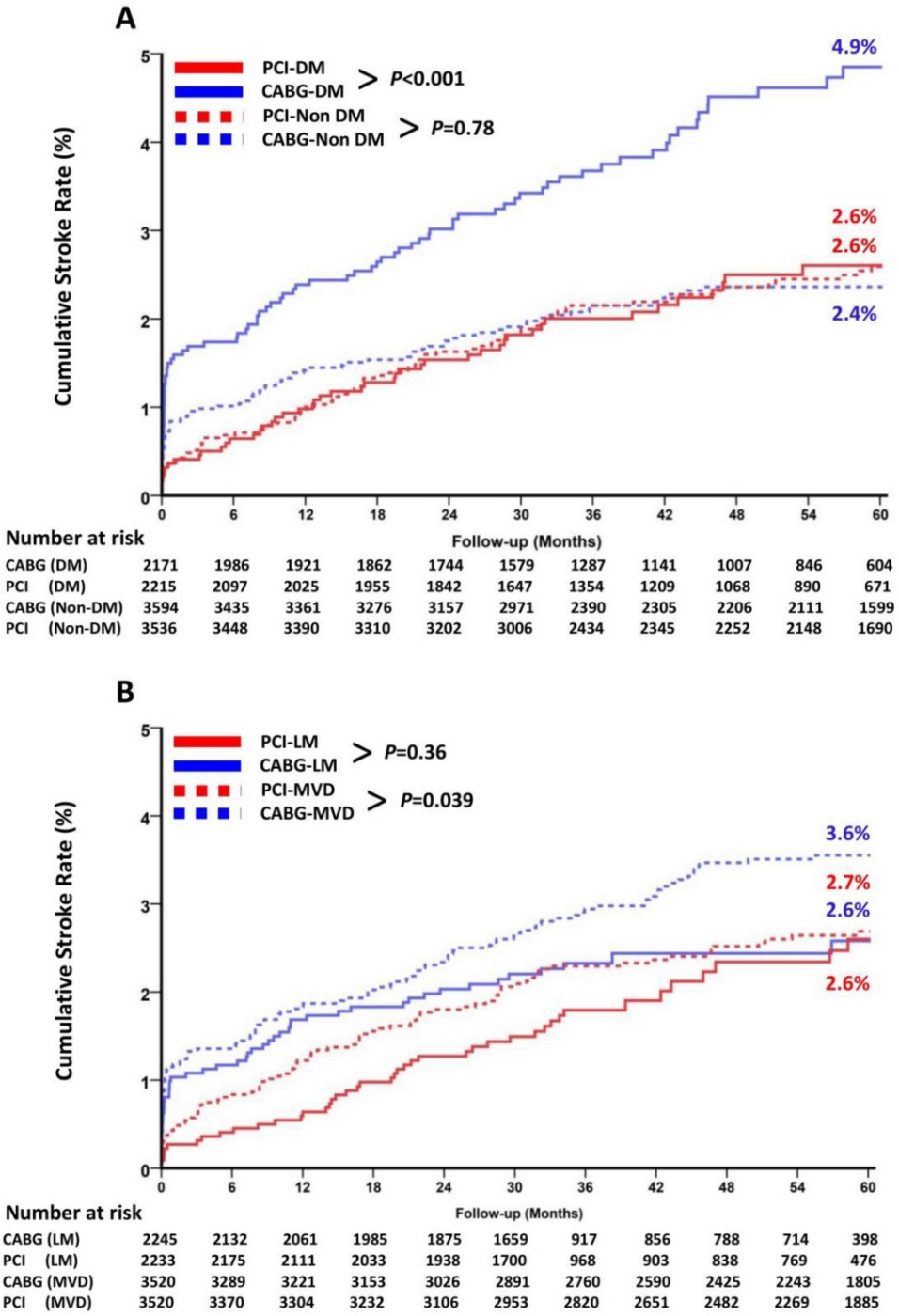

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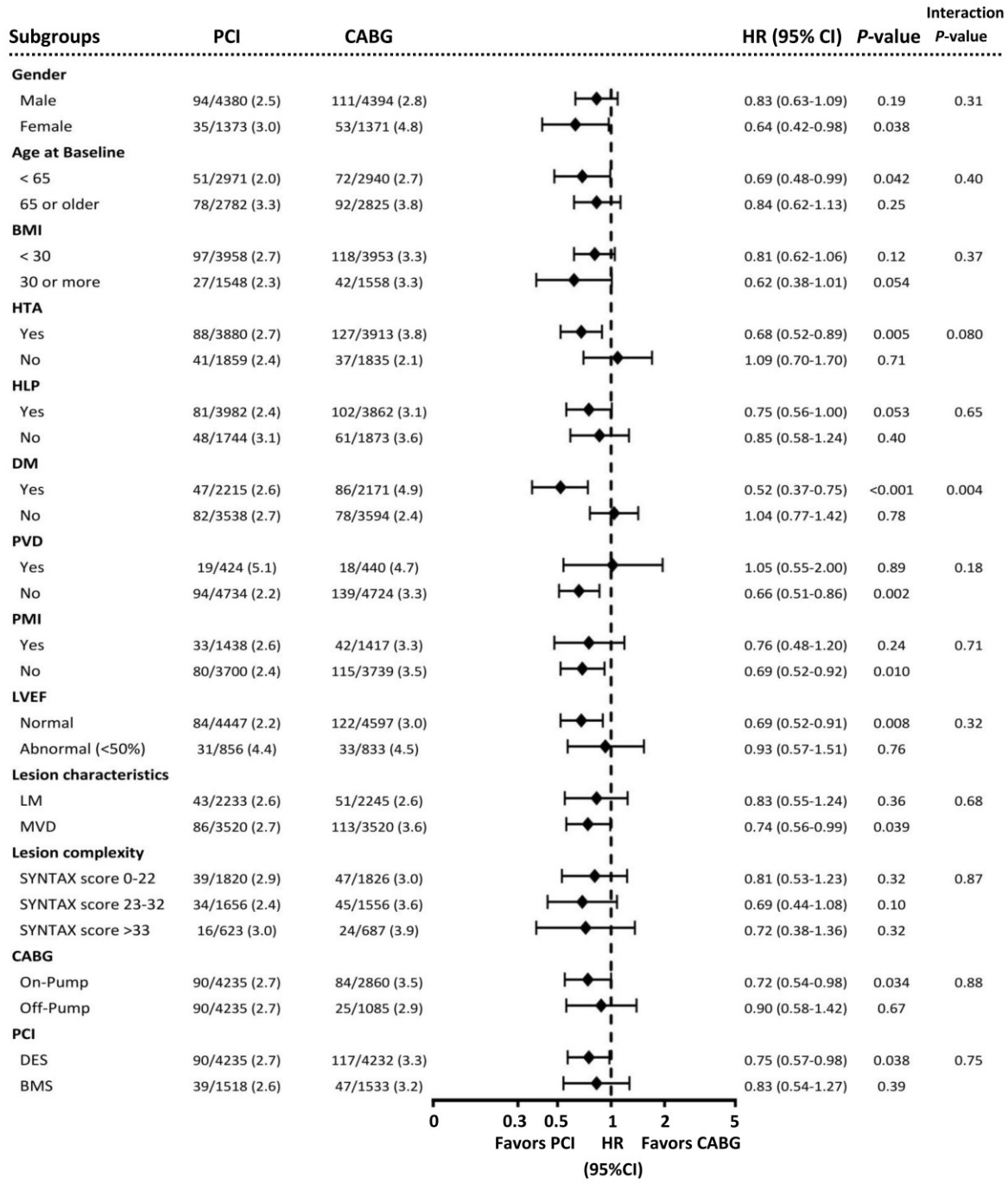

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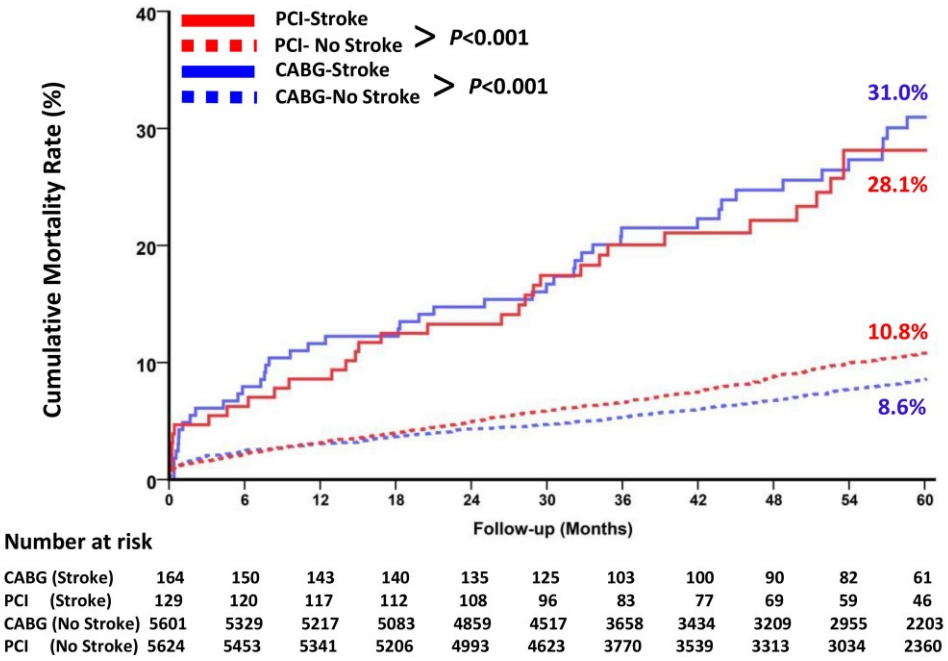

Number at risk

CABG (Stroke)	164	150	143	140	135	125	103	100	90	82	61
PCI (Stroke)	129	120	117	112	108	96	83	77	69	59	46
CABG (No Stroke)	5601	5329	5217	5083	4859	4517	3658	3434	3209	2955	2203
PCI (No Stroke)	5624	5453	5341	5206	4993	4623	3770	3539	3313	3034	2360

Figure 4. Death after percutaneous coronary intervention and coronary artery bypass grafting during 5-year follow-up of patients with and without stroke. Solid lines indicate patients who developed stroke during follow-up period while dotted lines indicate patients without stroke during the 5-year of follow-up. CABG, coronary artery bypass grafting; PCI, percutaneous coronary intervention.

SUPPLEMENTARY MATERIAL

APPENDIX 1. Data included in the prespecified extraction form.

Age, gender, body mass index, angina classification, hypertension, hypercholesterolemia, a family history of CAD, smoking status, diabetes, renal function, atrial fibrillation, peripheral vascular disease, carotid disease, previous transient ischemic attack or stroke, previous myocardial infarction, left ventricular function, previous myocardial revascularization, EuroSCORE, number of vessel disease, location of coronary lesions, medication use at baseline, treatment by PCI or CABG, completeness of revascularization, off-pump CABG, venous conduit use during CABG, internal mammary artery use during CABG, number of stents used during PCI, stent type used, postoperative hospital stay, postoperative atrial fibrillation, medication use at discharge, death during follow-up, stroke during follow-up, and medication use during follow-up.

APPENDIX 2. Baseline and procedural characteristics in individual trials.

Characteristic	ERACI-II (n=450)	ARTS (n=1205)	MASS-II (n=408)	SoS (n=988)	SYNTAX (n=1800)	PRECOMBAT (n=600)	FREEDOM (n=1900)	VA CARDS (n=198)	BEST (n=880)	NOBLE (n=1184)	EXCEL (n=1905)
Patient inclusion	1996-1998	1997-1998	1995-2000	1996-1999	2005-2007	2004-2009	2005-2010	2006-2010	2008-2013	2008-2015	2010-2014
Study location	Argentina	Europe, South America, Australasia	Brazil	Europe, Canada	Europe, US	Korea	North America, South America, Europe, India, Australasia	US	Asia	Europe	North America, South America, Europe, India, Australasia
Age	60.7 ± 10.2	60.6 ± 10.8	59.8 ± 9.0	61.4 ± 9.3	65.1 ± 9.7	62.2 ± 9.7	62.1 ± 9.1	62.4 ± 7.2	64.5 ± 9.4	66.2 ± 9.7	65.9 ± 9.6
Female gender	21% (93/450)	23% (283/1205)	31% (125/408)	21% (206/988)	22% (402/1800)	24% (141/600)	29% (544/1900)	1% (2/198)	29% (251/880)	22% (256/1184)	23% (441/1905)
BMI>30	NA	22% (260/1203)	25% (100/408)	22% (220/982)	32% (579/1799)	3% (20/595)	42% (789/1896)	68% (132/195)	4% (35/880)	29% (336/1155)	34% (639/1904)
Smoking current	52% (233/540)	27% (323/1203)	33% (134/408)	15% (149/988)	21% (363/1760)	29% (172/600)	16% (298/1900)	25% (48/195)	20% (177/880)	20% (235/1170)	22% (415/1850)
Diabetes	17% (78/450)	17% (208/1205)	28% (115/408)	14% (142/988)	25% (452/1800)	32% (192/600)	100% (1900/1900)	100% (198/198)	41% (363/880)	15% (184/1184)	29% (554/1905)
On insulin	NA	NA	5% (20/408)	3% (28/988)	10% (182/1800)	3% (19/600)	32% (615/1900)	NA	4% (38/880)	NA	8% (147/1905)
Hypertension	71% (318/450)	45% (540/1205)	62% (253/408)	45% (447/988)	75% (1349/1787)	53% (317/600)	85% (1612/1900)	96% (187/195)	67% (591/880)	66% (775/1182)	74% (1404/1892)
Hypercholesterolemia	61% (275/450)	58% (694/1201)	73% (298/408)	52% (509/988)	78% (1391/1785)	41% (247/600)	84% (1592/1900)	58% (111/191)	52% (461/880)	80% (946/1183)	70% (1320/1875)
Peripheral vascular disease	23% (103/450)	5% (64/1205)	0% (0/408)	7% (66/988)	10% (177/1800)	4% (22/600)	10% (197/1900)	14% (27/195)	3% (27/880)	NA	9% (181/1896)
Carotid artery disease	6% (25/450)	NA	NA	NA	8% (148/1800)	NA	NA	NA	NA	NA	8% (156/1896)
Previous TIA/stroke	2% (10/450)	NA	NA	4% (37/988)	8% (150/1788)	NA	3% (65/1900)	10% (20/198)	8% (70/879)	NA	6% (119/1903)
Previous MI	28% (126/450)	43% (520/1205)	47% (191/408)	45% (448/988)	33% (585/1780)	6% (33/567)	26% (487/1900)	42% (81/195)	6% (54/880)	NA	17% (330/1888)

LV dysfunction (<30%)	0% (0/446)	0% (0/1121)	0% (0/408)	1% (4/771)	2% (34/1800)	1% (5/542)	1% (27/1900)	7% (12/177)	1% (5/744)	1% (5/1020)	1% (11/1804)
Unstable disease	92% (412/450)	36% (438/1205)	0% (0/408)	0% (0/988)	29% (513/1800)	45% (272/600)	31% (584/1900)	NA	44% (384/880)	17% (206/1183)	39% (744/1892)
Number of lesions	2.6 ± 0.6	2.8 ± 1.0	2.8 ± 0.8	2.8 ± 1.1	4.0 ± 1.7	3.0 ± 1.0	NA	3.6 ± 1.5	3.4 ± 1.2	1.7 ± 1.0	NA
Three-vessel disease	49% (220/450)	33% (403/1205)	58% (238/408)	42% (419/988)	61% (1095/1800)	51% (308/600)	83.4% (1573/1887)	66% (120/181)	77% (679/880)	NA	NA
Left main disease	5% (21/450)	0.1% (1/1205)	0% (0/408)	1% (7/988)	39% (705/1800)	100% (600/600)	0.4% (8/1900)	0% (0/198)	5% (47/880)	100% (1184/1184)	100% (1905/1905)
SYNTAX score	NA	NA	NA	NA	28.7 ± 11.4	25.1 ± 10.0	26.2 ± 8.6	NA	24.4 ± 7.7	22.0 ± 7.3	20.6 ± 6.2
PCI – DES used	0% (0/222)	0% (0/593)	0% (0/205)	0% (0/488)	100% (885/885)	100% (276/276)	100% (939/939)	100% (93/93)	100% (413/413)	100% (580/580)	100% (935/935)
PCI – number of stents	1.4 ± 0.6	NA	1.2 ± 0.9	2.6 ± 1.4	4.6 ± 2.3	2.7 ± 1.4	4.1 ± 1.9	NA	3.4 ± 1.4	2.2 ± 1.2	2.4 ± 1.5
CABG – LIMA use	95% (198/209)	NA	95% (188/198)	93% (450/485)	97% (827/854)	94% (233/248)	94% (843/893)	NA	100% (382/382)	96% (545/565)	99% (908/923)
CABG – BIMA use	0.5% (1/209)	NA	32% (65/203)	10% (50/485)	28% (236/854)	NA	12% (110/893)	NA	NA	8% (44/549)	29% (265/923)
CABG – off-pump	NA	NA	NA	NA	15% (128/854)	63% (155/248)	18% (165/893)	32% (26/82)	66% (252/382)	16% (88/564)	29% (271/923)
Complete revascularization	68% (303/448)	82% (992/1205)	57% (224/408)	70% (693/988)	60% (1043/1741)	69% (416/600)	90% (1701/1900)	NA	61% (518/855)	94% (543/577)*	NA
Aspirin at discharge	100% (450/450)	NA	98% (391/397)	NA	92% (1633/1766)	99% (593/600)	98% (1826/1867)	98% (172/176)	97% (852/880)	93% (539/580)*	98% (1823/1867)
Thienopyridine at discharge	53% (238/450)	NA	48% (194/408)	NA	59% (1037/1766)	94% (565/600)	62% (1158/1867)	55% (96/176)	93% (818/880)	97% (566/580)*	66% (1227/1867)
DAPT	53% (238/450)	NA	47% (187/397)	NA	56% (987/1766)	93% (560/600)	81% (1513/1867)	54% (94/176)	92% (806/880)	92% (532/580)*	65% (1204/1867)

APPENDIX 3. Data on cross-overs in each trial.

	Randomized to CABG			Randomized to PCI		
	Actual CABG	**Actual PCI**	**No revasc.**	**Actual CABG**	**Actual PCI**	**No revasc.**
ARTS	579	19	7	6	593	1
ERACI-II	209	16	0	3	222	0
MASS-II	198	0	5	6	194	5
VA-CARDS	81	11	5	6	93	2
SoS	487	11	2	7	480	1
FREEDOM	893	18	36	5	939	9
SYNTAX	854	16	27	11	885	7
PRECOMBAT	248	51	1	24	276	0
BEST	382	51	9	19	413	6
EXCEL	567	23	2	7	580	5
NOBLE	923	17	17	7	935	6

CABG, coronary artery bypass grafting; PCI, percutaneous coronary intervention