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Analysis of Stroke Occurring in the SYNTAX Trial Comparing Coronary Artery Bypass Surgery and Percutaneous Coronary Intervention in the Treatment of Complex Coronary Artery Disease

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Objectives This study sought to analyze stroke rates in the SYNTAX (Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery) trial's randomized and registry cohorts of patients being treated with coronary artery bypass grafting (CABG) or percutaneous coronary intervention (PCI) for treatment of complex coronary artery disease.

Background The SYNTAX trial compared PCI to CABG in patients with de novo 3-vessel and/or left main coronary disease.

Methods The SYNTAX randomized trial was conducted at 85 U.S. and European sites (n = 1,800). All strokes (up to 4 years) were independently adjudicated by a clinical events committee that included a neurologist. An additional 1,077 (of which 644 were followed for 5 years) and 198 patients were included in the CABG and PCI registries, respectively.

Results In the randomized cohort, 31 CABG and 19 PCI patients experienced 33 and 20 strokes post-randomization at 4-year follow-up, respectively (p = 0.062). Three strokes occurred pre-procedurally but following randomization in CABG-treated patients. After CABG, a large proportion of strokes occurred acutely (0 to 30 days: 9 of 33), whereas in the PCI arm, most strokes occurred >30 days after the procedure (18 of 20). Stroke resulted in death in 3 patients in both the PCI and CABG groups. Of the patients who developed stroke, 68% (21 of 31) in the CABG group had residual deficits at discharge; in the PCI group, 47% (9 of 19) had residual deficits. In a multivariate analysis, treatment with CABG was not significantly associated with increased stroke rates (odds ratio: 1.67, 95% confidence interval: 0.93 to 3.01, p = 0.089). The incidence and outcomes of stroke were similar in the randomized trial and registries.

Conclusions There is a higher risk of periprocedural stroke in patients undergoing CABG versus PCI; however, the risk converges over the first 4 years of follow-up. (SYNTAX Study: TAXUS Drug-Eluting Stent Versus Coronary Artery Bypass Surgery for the Treatment of Narrowed Arteries; NCT00114972) (J Am Coll Cardiol Intv 2013;6:344–54) © 2013 by the American College of Cardiology Foundation

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In the past few decades, differences in the rates of adverse cardiac events, including death and myocardial infarction after percutaneous coronary intervention (PCI) have converged with coronary artery bypass grafting (CABG), predominantly because PCI techniques and technology as well as adjuvant medical therapy have improved (1–5). Though CABG is the established method of revascularization in patients with left main (LM) and 3-vessel disease (3VD), PCI has become an increasingly used alternative in this group of high-risk patients.

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Stroke, especially early post-operative stroke, is considered a serious risk for patients undergoing CABG but not as much for patients receiving PCI (4–7). The causes of stroke following CABG are multifactorial and the impact of newer surgical revascularization techniques—no touch off-pump CABG—on the incidence of stroke is uncertain. With the improved outcomes for PCI using drug-eluting stents, the increase in the risk of stroke with CABG needs to be weighed against the increased likelihood of repeated revascularization.

Few randomized studies comparing CABG and PCI have focused on stroke, and especially stroke during follow-up has been an underrepresented analysis (8). The objective of this post hoc analysis was to assess stroke in the large, complex patient population enrolled in both the SYNTAX (Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery) randomized trial and nested registries and to define the risk factors and outcomes of patients who experienced a stroke within the first 4 years of follow-up.

Methods

Study design and treatment description. SYNTAX is a prospective, multinational, randomized clinical trial (RCT) (N = 1,800: CABG: n = 897; PCI: n = 903) with parallel nested registries (CABG registry: n = 1,077 of which n = 644 were followed for 5 years; PCI registry: n = 198) designed to assess clinical outcomes after PCI with Taxus Express stents (Boston Scientific, Natick, Massachusetts) compared with outcomes after CABG for the treatment of de novo LM and/or 3VD. By consensus of the heart team, consisting of at least 1 interventional cardiologist and cardiac surgeon, CABG-ineligible patients were enrolled in a PCI registry and PCI-ineligible patients were enrolled in a CABG registry (9,10). Trial design and detailed methods of this study have been previously published (5,11). Analysis of the subset of patients in the RCT with stroke was not pre-specified. Additionally, as the primary endpoint of the overall SYNTAX study was not met (5), the results of these subgroup analyses are intended to be observational and hypothesis-generating and, therefore, should be interpreted with caution.

The institutional review board at each participating site approved the study and all subjects provided written informed consent before enrollment. The protocol and consent forms were consistent with the International Conference on Harmonisation Guidance for Industry E6 Good Clinical Practice, the Declaration of Helsinki, and all local regulations, as appropriate. The study is registered as identifier NCT00114972 on the National Institute of Heath's Clinicaltrials.gov website.

Abbreviations and Acronyms

3VD = 3-vessel disease
AF = atrial fibrillation
AFL = atrial flutter
CABG = coronary artery bypass grafting
CEC = Clinical Events Committee
CI = confidence interval
IQR = interquartile range
LM = left main
OR = odds ratio
PCI = percutaneous coronary intervention
RCT = randomized controlled trial

Definitions. A cerebrovascular event, or stroke, was characterized by a focal neurological deficit lasting >72 h, resulting in irreversible brain damage or permanent impairment. Confirmation of neurological injury by head computed tomography scan or magnetic resonance imaging was recommended. Strokes were also classified as ischemic or hemorrhagic. In the randomized controlled cohort of SYNTAX, all strokes were confirmed by a local neurologist and adjudicated by an independent clinical events committee (CEC) that included a neurologist. In the CABG and PCI registries, strokes were

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site-reported but not adjudicated by a CEC. Atrial fibrillation (AF) and atrial flutter (AFL) were reported by the investigative sites as serious adverse events and were not adjudicated by the CEC. Stroke was assumed to be directly correlated with AF/AFL whenever the timing of events was interlinked and/or when this association was confirmed in the patient chart narratives.

Statistical methods. Analysis was based on the intention-to-treat principle and was conducted using SAS System software (version 8.0 or higher, SAS Institute, Cary, North Carolina). Data are summarized using descriptive statistics, presented as percentage, count of sample size, or mean ± SD. The Student *t* test was used to compare continuous variables; differences in discrete variables were assessed by means of the chi-square or Fisher exact test, as appropriate.

The cumulative incidence of stroke was analyzed using the Kaplan-Meier method. The binary rate of stroke was analyzed in pre-specified subgroups by lesion subsets (3VD and LM), sex, age (≤70 and >70 years), and the presence of diabetes. Post hoc analyses according to prior stroke and/or TIA, peripheral vascular disease, carotid artery disease, and SYNTAX score tertiles were furthermore performed (low: ≤22, intermediate: 23 to 32, high: ≥33) (5). In-hospital outcome comparisons between treatments and stroke rates within these subgroups do not seem appropriate because of the low stroke rate at this 30-day time point. Landmark analyses after 1-year follow-up were performed.

Univariate analysis, including a combination of pre-operative and intraoperative variables believed to be clinically relevant (Appendix), was used to identify potential predictors of 4-year stroke. Subsequently, multivariate predictors were identified using stepwise selection with a significance level of <0.10 for entry and exit in a logistic regression model in the overall and the CABG, and PCI cohorts separately; medically treated diabetes and LM/3VD were forced into the model based on previous findings. Predictors are expressed as odds ratio (OR) ± 95% confidence interval (CI).

Results

Randomized arms. INCIDENCE OF STROKE. The 30-day stroke rate was 1% (9 of 897) after CABG and 0.2% (2 of 903) after PCI (p = 0.037). At 4 years of follow-up, 3.7% of CABG-randomized patients experienced stroke (n = 31 patients, n = 33 strokes) compared with 2.3% of PCI-randomized patients (n = 19 patients, n = 20 strokes; p = 0.062) (Fig. 1). The majority of strokes were ischemic (CABG: 29 of 33; PCI: 13 of 20).

Three patients in the CABG arm of the RCT suffered a stroke before the index procedure (Fig. 2); 47 days before treatment in 1 patient and on the day of randomization (3 days before surgery) in a second patient. One patient had a stroke the day before the index procedure, 7 days after allocation; this patient ultimately received medical therapy and not CABG but was counted in the CABG group by intention-to-treat. No pre-procedural strokes occurred in the PCI arm. In those patients who experienced stroke, the

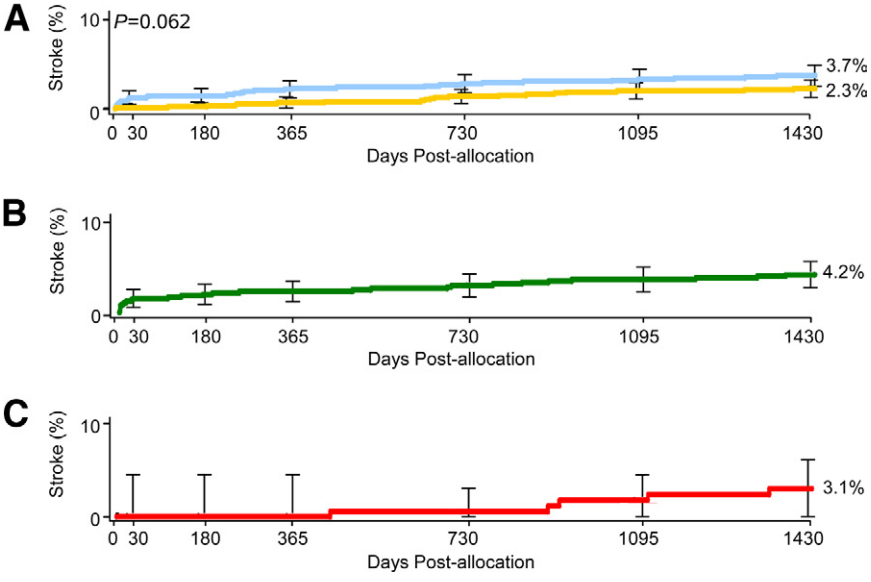

Figure 1. Unadjusted Cumulative Stroke Rate to 4 Years Post-Allocation

Kaplan-Meier estimates (±1.5 × SE) for stroke in randomized patients treated with coronary artery bypass grafting (CABG) **(blue line)** or percutaneous coronary intervention (PCI) **(yellow line) (A),** CABG registry patients **(green line) (B)** or PCI registry **(red line)** patients **(C)**. p value in **A** from log-rank test. SE = standard error.

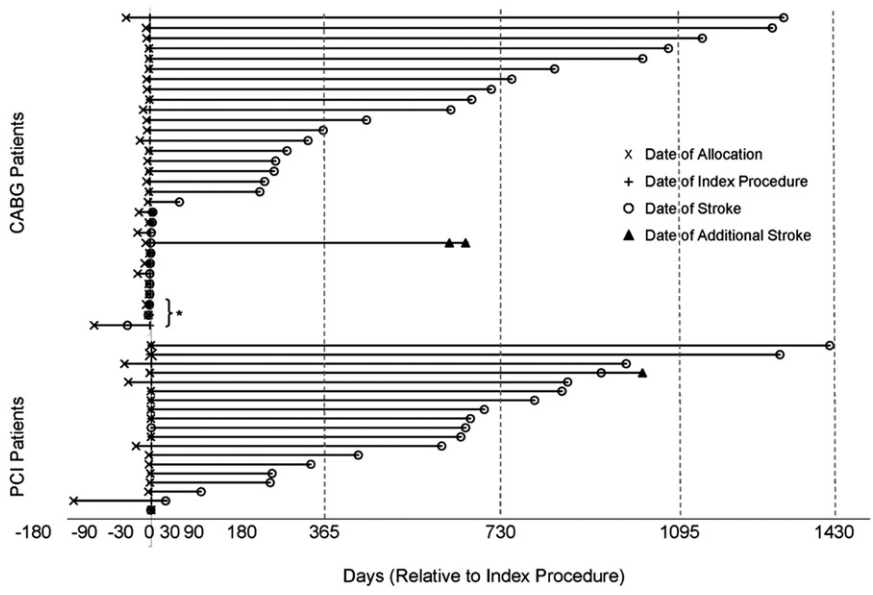

Figure 2. Timing of Stroke Relative to Treatment Group Allocation and Index Procedure in the Randomized Controlled Trial

The date of allocation (×), index procedure (+), first stroke (○), and second stroke, if applicable (▲), in each patient are represented on a **single line**. The **dotted gray lines** indicate yearly follow-up intervals and the (*) indicates those strokes that occurred before the index procedure. Abbreviations as in Figure 1.

length of time between randomization and index procedure was similar between treatment arms (CABG: 12.6 ± 22.4 days [median: 6 (interquartile range [IQR]: 2 to 11 days)] vs. PCI 17.5 ± 38.8 days [median: 2 (IQR: 1 to 6 days)]).

BASELINE AND PROCEDURAL CHARACTERISTICS. Baseline characteristics of the randomized cohort of SYNTAX are presented in Table 1. Patients who experienced stroke were older and had more severe cardiovascular disease as defined by increased incidences of prior cerebrovascular events, peripheral vascular disease, hypertension, and a higher mean logistic EuroSCORE (European System for Cardiac Operative Risk Evaluation).

Table 1. Baseline Characteristics of RCT Stroke Patients

		CABG		PCI	
	All Patients (N = 1,800)	Stroke Patients (n = 31)	Nonstroke Patients (n = 866)	Stroke Patients (n = 19)	Nonstroke Patients (n = 884)
Age, yrs	65.1 ± 9.7 (1,800)	67.7 ± 9.2 (31)	64.9 ± 9.8 (866)	71.5 ± 8.0 (19)	65.1 ± 9.7 (884)
Female	22.3 (402/1,800)	29.0 (9/31)	20.8 (180/866)	26.3 (5/19)	23.5 (208/884)
Prior stroke	4.4 (78/1,789)	0 (0/30)	5.0 (43/860)	10.5 (2/19)	3.8 (33/880)
Prior TIA	4.7 (84/1,789)	10.0 (3/30)	4.9 (42/858)	10.5 (2/19)	4.2 (37/882)
Carotid artery disease	8.2 (148/1,800)	16.1 (5/31)	8.1 (70/866)	0 (0/19)	8.3 (73/884)
Peripheral artery disease	9.8 (177/1,800)	22.6 (7/31)	10.2 (88/866)	15.8 (3/19)	8.9 (79/884)
History of smoking	64.7 (1,160/1,793)	74.2 (23/31)	68.9 (592/859)	63.2 (12/19)	60.3 (533/884)
Current smoker	20.2 (363/1,793)	29.0 (9/31)	21.8 (187/859)	15.8 (3/19)	18.6 (164/884)
Medically treated diabetes	25.1 (452/1,800)	29.0 (9/31)	24.5 (212/866)	26.3 (5/19)	25.6 (226/884)
Hypertension	75.5 (1,349/1,787)	93.5 (29/31)	76.4 (657/860)	89.5 (17/19)	73.7 (646/877)
Logistic EuroSCORE	3.8 ± 4.5 (1,800)	4.6 ± 3.3 (31)	3.9 ± 4.4 (866)	6.1 ± 5.9 (19)	3.7 ± 4.5 (884)
Mean SYNTAX score	28.7 ± 11.4 (1,789)	29.1 ± 11.2 (31)	29.1 ± 11.4 (859)	31.8 ± 10.4 (19)	28.3 ± 11.5 (880)

Values are mean ± SD (N) or % (n/N).

CABG = coronary artery bypass grafting; EuroSCORE = European System for Cardiac Operative Risk Evaluation; PCI = percutaneous coronary intervention; RCT = randomized controlled trial; SYNTAX = Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery; TIA = transient ischemic attack.

The rate of off-pump bypass surgery was 15% (128 of 853) in the randomized CABG patient population, with a similar cumulative 4-year stroke rate of 3.6% in the off-pump group compared with 3.5% in patients that underwent on-pump surgery (p = 0.98 by log rank).

AF and/or AFL during follow-up were reported in 3.4% (31 of 903) after PCI and in 7.9% (71 of 897) after CABG. The rate of stroke in patients with versus without arrhythmia was 9.7% (3 of 31) versus 1.8% (16 of 872) after PCI and 5.6% (4 of 71) versus 3.3% (27 of 826) after CABG.

In general, patients in the PCI cohort received dual antiplatelet therapy at greater rates before, during, and after the index procedure compared with CABG patients up to 3 years following randomization (4-year data not available) (12).

OUTCOMES AFTER STROKE. Of the RCT patients who had strokes, 3 in each treatment arm died because of the event (PCI vs. CABG, p = 0.66) (Fig. 3). The median length of stay in the hospital—whether this was the index hospitalization or readmission—in patients experiencing stroke was 8 days in the CABG arm (IQR: 7 to 14 days) and 7 days (IQR: 2 to 21 days) in the PCI arm. Overall, after the stroke, patients were discharged equally to home or to a rehabilitation facility.

There were 7 patients (23%) in the CABG group and 7 patients (37%) in the PCI group that were alive with no long-term residual deficits after stroke (p = 0.28) (Fig. 3). The remaining 21 (68%) and 9 (47%) surviving CABG and PCI patients, respectively, had residual deficits that included though not limited to: hypoesthesia/numbness; motor deficits; language deficits; visual deficits; muscle weakness; muscle spasms; paresis/paralysis; and dysphasia. The most common residual symptoms were language deficit and paresis/paralysis.

SUBGROUPS. In the subgroup of RCT patients with LM disease, stroke was significantly increased in CABG-treated patients (CABG: 4.3% [n = 14] vs. PCI: 1.5% [n = 5]; p = 0.03); whereas, in patients with 3VD, no significant difference was found (3.4% [n = 17] vs. 2.8% [n = 14]; p = 0.53). No significant differences in stroke were found between pre-specified subgroups of sex, age, or the presence of diabetes, nor in post-hoc analyses according to prior stroke and/or TIA, or the presence of carotid artery disease (Fig. 4).

Although no statistical comparisons were made because of the low number of events, it was noted that the stroke rate in the CABG and PCI arms of the RCT was differentially affected by complexity of coronary artery disease as measured by the SYNTAX score. In CABG-randomized patients, the stroke rate was similar in each SYNTAX score

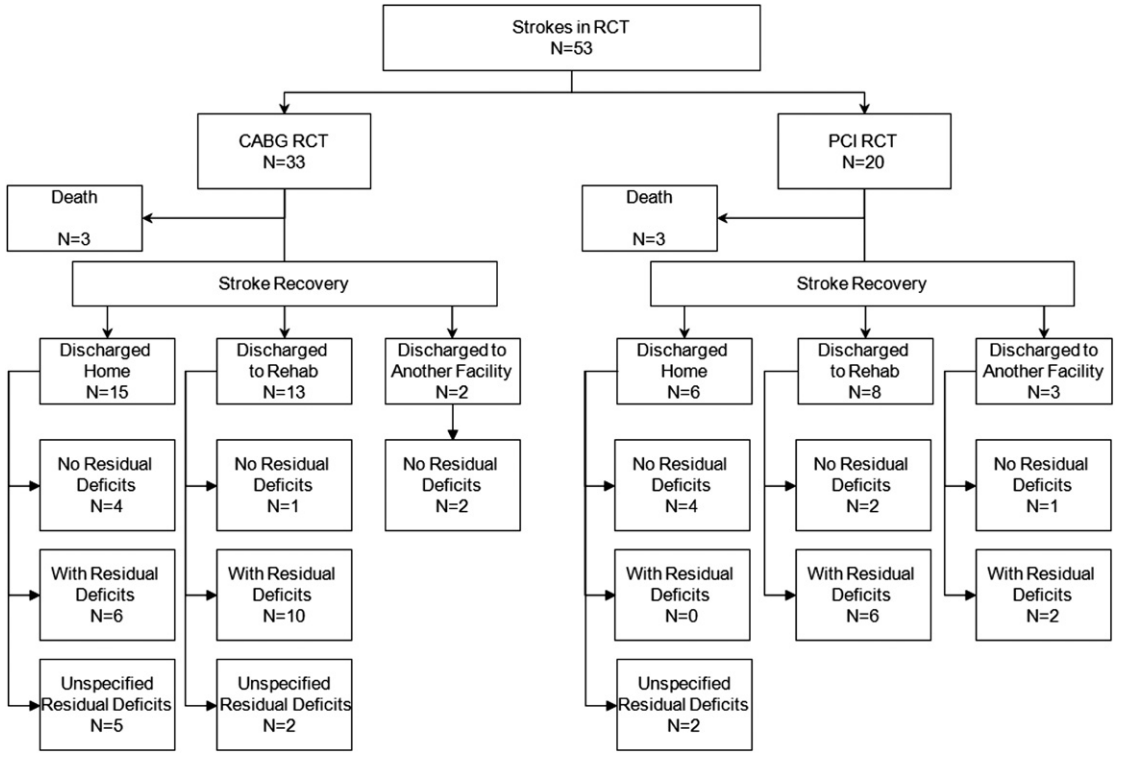

Figure 3. Outcomes After Stroke

Nearly all patients who experienced a stroke were discharged either to home or to a rehabilitation center. Abbreviations as in Figures 1 and 2.

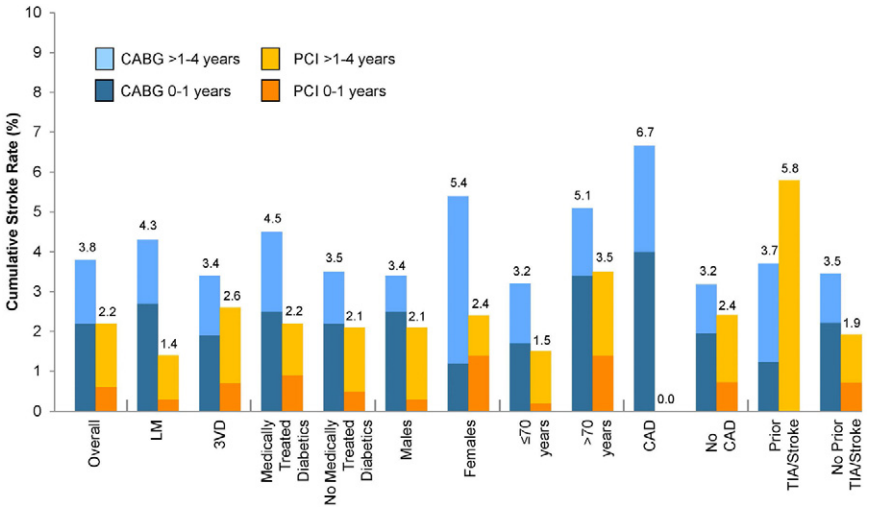

Figure 4. Rate of Stroke at 4 Years in Pre-Defined and Post Hoc Subgroups

The percentage of patients experiencing a stroke within 4 years of follow-up (CABG = **blue;** PCI = **orange/yellow**) in the overall patient population, patients with left main (LM) or 3-vessel disease (3VD) (without LM disease), patients with or without medically treated diabetes, men and women, patients younger or older than 70 years of age, patients with or without carotid artery disease (CAD), and patients with or without prior transient ischemic attack (TIA) and/or stroke. Abbreviations as Figure 1.

tertile (low SYNTAX score: 4% [n = 10], intermediate: 3.6% [n = 10], and high: 3.7% [n = 11]). A stepwise increase in the risk of stroke was found within SYNTAX score tertiles in PCI-treated patients (low: 1.4% [n = 4], intermediate: 2% [n = 6], and high: 3.5% [n = 9]).

PREDICTORS OF STROKE. By multivariate analysis, the predictors with the greatest impact on likelihood of stroke within 4 years in all randomized patients were age per 10 years, hypertension, moderate or poor left ventricular ejection fraction, and Canadian Cardiovascular Society angina class 3/4 (Table 2). Treatment with CABG was not significantly associated with increased stroke rates (OR: 1.67, 95% CI: 0.93 to 3.01; p = 0.089).

In the PCI arm, several markers of the severity of cardiovascular disease (e.g., previous myocardial infarction, peripheral vascular disease, moderate or poor left ventricular ejection fraction, and Canadian Cardiovascular Society angina class 3/4) were found to be predictors of stroke within 4 years. In the CABG arm, patients had an increased risk of stroke if they were older and had previously experienced a TIA or stroke.

Nested registries. The CABG registry (n = 644 followed for 5 years) predominantly included patients in whom PCI was not considered technically feasible by the heart team, and the PCI registry (n = 198) included patients in whom it was felt that the outcome of CABG would be unfavorable (10). As a result, patients in the CABG registry are comparable to the randomized trial except on SYNTAX score (37.8 ± 13.3 vs. 29.1 ± 11.4 in the trial). In contrast, patients in the PCI registry had similar lesion complexity but higher logistic EuroSCORE (7.7 ± 9.0 vs. 3.8 ± 4.5 in the trial).

The rate of stroke in the CABG registry was 4.2% (n = 26 patients, n = 29 strokes) at 4 years of follow-up; there were 3 patients that had 2 strokes. The rate was 3.1% (n = 5 patients, n = 5 strokes) in the PCI registry (Figs. 1B and 1C). Baseline characteristics of the PCI and CABG registries are presented in Table 3. Similar to randomized cohorts, patients who experienced stroke more often had prior cerebrovascular events, peripheral vascular disease, or hypertension.

Off-pump CABG was performed in 120 patients, of which 6 patients had a stroke. Twenty patients suffered a stroke after on-pump CABG. The cumulative rate of stroke was 5.3% and 4% in patients that underwent off-pump and on-pump surgery, respectively (p = 0.57 by log rank).

In the CABG registry, 3 patients suffered strokes that led to death. There were 26 discharges of which 14 were to home, 8 were to a rehabilitation center, and 4 to another facility. Seven (27%) CABG registry patients recovered from the stroke without residual deficits. The median post-stroke hospital stay was 11 days (range 6 to 21 days). In the PCI registry, 1 patient died as the result of a stroke. Three patients were discharged with residual deficits; 1 was discharged home and 2 to another facility. One patient recovered from the stroke without residual deficits. The median hospital stay after the stroke in PCI registry patients was 12 days (range 7 to 14 days).

Table 2. Univariate and Multivariate Predictors of Stroke

	Univariate OR (95% CI)	p Value	Multivariate OR (95% CI)	p Value
Overall cohort (N = 1,800)				
Age per 10 yrs	1.65 (1.21–2.25)	0.001	1.56 (1.14–2.14)	0.006
Hypertension	4.02 (1.44–11.24)	0.008	3.47 (1.23–9.80)	0.019
Peripheral vascular disease	2.37 (1.16–4.84)	0.017	1.96 (0.94–4.10)	0.071
Moderate or poor LVEF	2.02 (1.10–3.71)	0.023	2.06 (1.08–3.95)	0.029
Angina class CSS 3/4	1.79 (0.99–3.22)	0.052	1.84 (1.01–3.35)	0.048
CABG treatment group	1.78 (1.00–3.18)	0.051	1.67 (0.93–3.01)	0.089
Medically treated diabetes*	—	—	0.91 (0.47–1.77)	0.790
Left main disease*	—	—	0.83 (0.46–1.53)	0.559
PCI cohort (n = 903)				
Previous MI	0.29 (0.10–0.84)	0.023	0.18 (0.05–0.62)	0.007
Hypertension	4.67 (1.10–19.76)	0.036	4.10 (0.95–17.62)	0.058
Peripheral vascular disease	2.58 (1.08–6.18)	0.033	2.73 (1.09–6.83)	0.031
Moderate or poor LVEF	1.99 (0.92–4.32)	0.081	2.62 (1.12–6.14)	0.027
Angina class CSS 3/4	2.27 (1.09–4.73)	0.028	2.54 (1.18–5.46)	0.017
Medically treated diabetes*	—	—	0.88 (0.37–2.06)	0.762
Left main disease*	—	—	1.04 (0.49–2.23)	0.915
CABG cohort (n = 897)				
Age per 10 yrs	2.41 (1.38–4.20)	0.002	2.57 (1.43–4.63)	0.002
Prior TIA or stroke	3.43 (1.11–10.66)	0.033	3.58 (1.13–11.38)	0.031
Medically treated diabetes*	—	—	1.03 (0.36–2.94)	0.956
Left main disease*	—	—	0.49 (0.17–1.40)	0.186

*Forced into the model.

CI = confidence interval; CSS = Canadian Cardiovascular Society; LVEF = left ventricular ejection fraction; MI = myocardial infarction; OR = odds ratio; other abbreviations as in Table 1.

Discussion

The overall incidence of stroke was low at 4 years in the SYNTAX trial and was not significantly different between PCI and CABG. In the short term after treatment, patients that underwent CABG were more likely to experience a stroke than were PCI-treated patients. After this procedure-related risk, a similar stroke hazard was found in PCI and CABG patients during follow-up.

Whereas large registries and randomized trials comparing PCI and CABG have mainly focused on survival, myocardial infarction, and repeat revascularization, stroke is par-

Table 3. Baseline Characteristics of Registry Stroke Patients

	CABG Registry			PCI Registry		
	Overall (N = 644)	Stroke Patients (n = 26)	Nonstroke Patients (n = 618)	Overall (N = 192)	Stroke Patients (n = 5)	Nonstroke Patients (n = 187)
Age, yrs	65.7 ± 9.4 (644)	67.0 ± 9.7 (26)	65.6 ± 9.3 (618)	71.2 ± 10.4 (192)	74.4 ± 7.2 (5)	71.1 ± 10.5 (187)
Female	19 (124/644)	35 (9/26)	18.6 (115/618)	30 (57/192)	40 (2/5)	29.4 (55/187)
Prior stroke	6 (35/639)	12 (3/25)	5.2 (32/614)	8 (15/192)	40 (2/5)	7.0 (13/187)
Prior TIA	6 (36/638)	19 (5/26)	5.1 (31/612)	8 (15/191)	20 (1/5)	7.5 (14/186)
Carotid artery disease	12 (79/644)	19 (5/26)	12.0 (74/618)	10 (20/192)	0 (0/5)	10.7 (20/187)
Peripheral artery disease	14 (89/644)	19 (5/26)	13.6 (84/618)	16 (31/192)	60 (3/5)	15.0 (28/187)
History of smoking	64 (411/639)	65 (17/26)	64.3 (394/613)	57 (108/188)	40 (2/5)	57.9 (106/183)
Current smoker	22 (140/639)	19 (5/26)	22.0 (135/613)	11 (21/188)	0 (0/5)	11.5 (21/183)
Medically treated diabetes	26 (170/644)	35 (9/26)	26.1 (161/618)	30 (58/192)	80 (4/5)	28.9 (54/187)
Hypertension	74 (465/633)	88 (23/26)	72.8 (442/607)	76 (145/191)	80 (4/5)	75.8 (141/186)
Logistic EuroSCORE	4.0 ± 4.4 (644)	5.2 ± 5.2 (26)	4.0 ± 4.4 (618)	7.7 ± 9.0 (192)	10.3 ± 12.4 (5)	7.7 ± 8.9 (187)
SYNTAX score	37.8 ± 13.3 (632)	35.8 ± 12.8 (25)	37.9 ± 13.3 (607)	31.6 ± 12.3 (189)	36.0 ± 11.2 (5)	31.5 ± 12.4 (184)

Values are mean ± SD (N) or % (n/N).

Abbreviations as in Tables 1 and 2.

ticularly underrepresented from such studies (13–15). Especially assessments of stroke over long-term follow-up have been limited. Yet, in-depth analysis of stroke is crucial to determine the true risk/benefit ratio of PCI and CABG, weighing the risk of stroke versus the risk of repeat revascularization (16). In our report, the hazard of stroke during follow-up was low and there was a similar incidence of stroke after PCI and CABG, providing reassuring information especially for the surgical perspective. Nevertheless, the outcome of patients in this cohort was poor; stroke led to death in 6 patients (CABG: n = 3, PCI: n = 3) and a significant amount of surviving patients experienced long-term residual impairment after the stroke (CABG: 68%, PCI: 47%).

Procedure-related stroke remains a serious complication after isolated CABG occurring in as many as 1% to 4% of patients (5,8,17,18). Previous nonrandomized studies of CABG versus PCI in LM or multivessel-disease patient populations have found either an increase in stroke in CABG-treated patients (6,7) or no difference in stroke rate (19–21). However, data from randomized trials are limited and, like SYNTAX's data, are not powered to detect a significant difference in stroke rate. A meta-analysis of 7 randomized trials comparing PCI (with balloon angioplasty of bare-metal stents) with CABG for multivessel disease showed that the 90-day stroke rate after randomization to PCI was significantly lower (0.5% vs. 1.1%, p = 0.02) (8). Moreover, Daemen et al. (22) reported in a meta-analysis of 5 randomized trials using bare-metal stents that rates appear to be comparable at 5-year follow-up: 3.6% versus 3.1% for CABG and PCI, respectively. After adjustment for several clinical characteristics, there was little evidence of a benefit for either treatment, with an adjusted hazard ratio of 1.16 (95% CI: 0.73 to 1.83). Considering these data, the results presented here of the SYNTAX trial are comparable to other trials comparing PCI with CABG. However, the recent results from the FREEDOM (Future Revascularization Evaluation in Patients With Diabetes Mellitus: Optimal Management of Multivessel Disease) trial showed a significant increase in stroke at 5-year follow-up after CABG as compared with PCI in 1,900 randomized diabetic patients (23).

Attempts to improve outcomes after surgical coronary revascularization should be directed toward reducing the rate of stroke. Indeed, some studies have shown a stroke benefit with off-pump surgery due to avoidance of cardiopulmonary bypass and indirectly by reducing the rate of AF/AFL (24). In SYNTAX, 15% of randomized and 18.6% of registry CABG patients underwent off-pump surgery. No differences in rates of stroke in the trial (3.6% vs. 3.5% with on-pump) nor in the registry (5.3% vs. 4.0% with on-pump) were found, suggesting no benefit of off-pump CABG in reducing the rate of stroke. However, no data were available on manipulation of the ascending aorta or the use of epiaortic scanning, so whether off-pump surgery would truly be beneficial cannot be evaluated. Furthermore, the numbers treated with the off-pump technique were small, and no firm conclusions should be based on these data. It should not be expected that off-pump surgery is useful in all patients undergoing isolated CABG, but it could be more beneficial to consider it merely for subgroups of patients with, for example, severe aortic calcification (25,26). Further efforts should be directed in screening the aorta and in the use of "no touch" off-pump CABG.

New-onset AF occurs in up to 40% of patients shortly after cardiac surgery and has clearly been associated with an increase in the incidence of stroke (27). Very limited data are available on AF during follow-up after revascularization. One study reported AF during follow-up in 11.4% of patients after CABG, but it did not find that this was related to stroke (28). In the SYNTAX trial, we found a low rate of AF/AFL during follow-up (PCI: 3.4%, CABG: 7.9%). The low incidence of AF and the smaller fraction of AF patients who experienced stroke make it difficult to draw any meaningful conclusions regarding the relationship between AF/AFL and stroke, especially when considering that the arrhythmia event was not adjudicated by the CEC. In this regard, the correlation between AF/AFL and stroke was only based on chart narratives, whereas the rate of stroke was clearly higher in patients with late arrhythmia. Unfortunately, AF could not be added to the univariate and multivariate analyses because it was considered an adverse event by itself, occurring late during follow-up.

Despite technical improvements, the cause of stroke after revascularization is multifactorial and depends on many more factors, which are also relevant for patients treated with PCI. The presence of multivessel disease has been shown to independently predict stroke after both PCI and CABG (29,30). In SYNTAX, the incidence of stroke in the PCI arm, but not the CABG arm, increased with SYNTAX score tertile, suggesting that stroke occurs more frequently in complex disease. Looking more specifically to LM or 3VD subgroups, LM disease has been shown to be a correlate of carotid artery disease, which may increase stroke in LM CABG patients (30–32). Additionally, aortic manipulation may be more prevalent in the LM subgroup than in the 3VD subgroup, suggesting that the likelihood of stroke is higher in the LM subgroup. Nevertheless, LM and 3VD were not significantly associated with stroke in the overall, PCI, or CABG multivariate models.

There is significant variation in the incidence of stroke among different subgroups of patients. Diabetes, female sex, prior TIA or stroke, and advanced age may influence the risk of stroke potentially because of widespread cerebrovascular disease, impaired cerebral blood flow, and/or increased susceptibility to atheroembolism or thromboembolism (29,30,33–37). Examining these subgroups in the SYNTAX patient population, there is a nonsignificant difference in the timing of stroke events in

these subgroups that could affect potential preventive or treatment strategies. The timing of strokes in the PCI arm of these subgroups occurs throughout follow-up, whereas in CABG-treated patients, most strokes occur in the first year. In the multivariate analysis, we found that advanced age emerged as a significant independent predictor of stroke in the overall patient population as well as in the CABG-treated cohort. Furthermore, several factors (e.g., hypertension or moderate or poor left ventricular ejection fraction) that have been shown to predict stroke (38) indeed emerged as independent predictors in our analysis. Patients in the randomized trial and nested registries that suffered a stroke more often had prior cerebrovascular events. Clearly, this factor is related to an increased risk of stroke after revascularization, although we were only able to confirm this through multivariate analyses in the CABG cohort. Furthermore, female sex and diabetes did not emerge as significant predictors of stroke, but these results may be the consequence of the low number of events.

The length of time between randomization and treatment was similar in those CABG and PCI patients who suffered a stroke, suggesting the numeric increase in pre-procedural stroke in the CABG arm was not related to a delay in surgical therapy. Nevertheless, patients randomized to CABG would have been less likely to receive antiplatelet therapy while awaiting their index revascularization. This may have influenced the pre-procedure stroke rate as dual antiplatelet therapy has been shown to reduce the risk of a major vascular event compared with aspirin alone (though it is less effective than oral anticoagulant therapy) (39,40). There were 3 pre-procedure strokes in the CABG arm; 1 stroke may have been the result of pre-operatively discontinuing antiplatelet medications, because the stroke occurred on the day before the procedure when the platelet count would have been relatively high. The other 2 strokes were unlikely to be related to discontinued medications due to the timing of the stroke.

As dual antiplatelet therapy is not the accepted standard of care for post-CABG patients, the overall increase in stroke could have been influenced by the reduced use of aspirin or other antiplatelet agents in the CABG arm. However, the cause of stroke in PCI and CABG cohorts could be different, and even if medication use was comparable, this may only have a limited affect on stroke rates. Still, establishing clinical directives for aggressive medical therapy in CABG patients might result in a decrease in stroke risk and is worthy of further study.

Study limitations. Although this analysis provides contemporary insights into the incidence of stroke in a complex PCI- and CABG-treated patient population, it is underpowered to detect a difference in stroke rate. Furthermore, more patients withdrew consent (or were lost to follow-up) in the CABG treatment arm, which may have affected our findings, although this is unlikely (12).

Data on pre-operative AF or new AF during index revascularization admission was not recorded in the SYNTAX trial and, therefore, such analyses could not be included. Follow-up data on AF or AFL were reported by investigation sites as adverse events and were not adjudicated by an independent CEC; therefore, the conclusions derived from these data are limited. Furthermore, patient-level details concerning the level of aortic manipulation and the presence of asymptomatic carotid stenosis and mild neuropsychological disturbance pre- and post-revascularization were not captured.

Finally, a rule of thumb regarding multivariate analyses is to include 1 covariate per ~10 events. We have limited the inclusion of covariates strictly to those deemed clinically relevant, but still we have overfitted the model to include more covariates. Therefore, these data from the multivariate analyses should be interpreted with caution. However, the limited number of stroke comparisons from randomized PCI versus CABG trials was an incentive to overfit the model, as this may provide novel hypothesis-generating data as to the multifactorial cause of stroke after myocardial revascularization.

Conclusions

The overall incidence of stroke was low at 4 years in the SYNTAX trial in both CABG- and PCI-treated patients. Though more strokes occurred in the CABG arm than in the PCI arm early in the study, no significant differences were found at 4 years and the outcome of stroke after PCI and CABG was similar.

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Key Words: coronary artery bypass graft ■ drug-eluting stent(s) ■ percutaneous coronary intervention ■ stroke ■ SYNTAX ■ Taxus.

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Appendix
Variables included in univariate and multivariate logistic regression analyses

In the overall model: age per 10 years increase, sex, previous MI, prior transient ischemic attack (TIA) or stroke, medically treated diabetes, angina class, cigarette use, hypertension, hyperlipidemia, carotid artery disease, 3VD/left main (LM), moderate or poor LVEF, renal failure (creatinine $\geq$200 μmol/L), peripheral vascular disease, overall SYNTAX score, number of vessels treated, treatment group.

In addition for the percutaneous coronary intervention (PCI) model: antiplatelet medication compliance.

In addition for the coronary artery bypass grafting (CABG) model: off-pump.