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Risk Profile and 3-Year Outcomes From the SYNTAX Percutaneous Coronary Intervention and Coronary Artery Bypass Grafting Nested Registries

Stuart J. Head, MS,* David R. Holmes, Jr, MD,† Michael J. Mack, MD,‡ Patrick W. Serruys, MD, PhD,§ Friedrich W. Mohr, MD, PhD,‖ Marie-Claude Morice, MD,¶ Antonio Colombo, MD,# A. Pieter Kappetein, MD, PhD,* on behalf of the SYNTAX Investigators

Rotterdam, the Netherlands; Rochester, Minnesota; Plano, Texas; Leipzig, Germany; Massy, France; and Milan, Italy

Objectives The aim of this study was to evaluate the use of percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG) in "real-world" patients unsuitable for the alternative treatment.

Background No data are available on the risk profile and outcomes of patients that can only undergo PCI or CABG.

Methods In the SYNTAX (Synergy between PCI with TAXUS and Cardiac Surgery) trial, a multidisciplinary Heart Team reached a consensus on whether PCI and CABG could result in clinical equipoise; if so, the patient was randomized. If not, the patient was enrolled in a CABG-ineligible PCI registry or PCI-ineligible CABG registry. A proportion (60%) of patients in the CABG registry was randomly assigned to be followed up for 5 years. No statistical comparisons were performed between randomized and registry patients. Major adverse cardiac or cerebrovascular event (MACCE) rates are presented as observational only.

Results A total of 3,075 patients were treated in the SYNTAX trial; 198 (6.4%) and 1,077 (35.0%) patients were included in PCI and CABG registries, respectively. The main reason for inclusion in the CABG registry was too complex coronary anatomy (70.9%), and the main reason for inclusion in the PCI registry was too high-risk for surgery (70.7%). Three-year MACCE was 38.0% after PCI and 16.4% after CABG. Stratification by SYNTAX score terciles demonstrated a step-wise increase of MACCE rates in both PCI and CABG registries.

Conclusions The SYNTAX Heart Team concluded that PCI and CABG remained the only treatment options for 6.4% and 35.0% of patients, respectively. Inoperable patients with major comorbidities that underwent PCI had high MACCE rates. In patients not suitable for PCI, surgical results were excellent. (SYNTAX Study: TAXUS Drug-Eluting Stent Versus Coronary Artery Bypass Surgery for the Treatment of Narrowed Arteries, NCT00114972) (J Am Coll Cardiol Intv 2012;5:618–25) © 2012 by the American College of Cardiology Foundation

From the *Department of Cardiothoracic Surgery, Erasmus University Medical Center, Rotterdam, the Netherlands; †Department of Cardiovascular Disease, Mayo Clinic, Rochester, Minnesota; ‡Heart Hospital, Baylor Health Care System, Plano, Texas; §Department of Cardiology, Erasmus University Medical Center, Rotterdam, the Netherlands; ‖Department of Cardiac Surgery, Herzzentrum Universität Leipzig, Leipzig, Germany; ¶Department of Cardiology, Institut Cardiovasculaire Paris Sud, Massy, France; and the #Interventional Cardiology Unit, San Raffaele Scientific Institute, Milan, Italy. Boston Scientific was a sponsor of this study. The authors have reported that they have no relationships relevant to the contents of this paper to disclose. Michael Kutcher, MD, served as Guest Editor of this paper.

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Since the 1980s, coronary artery bypass graft surgery (CABG) is the treatment of choice for patients with multivessel and/or left main (LM) coronary artery disease. Numerous trials have compared CABG with percutaneous coronary intervention (PCI) but have not been able to produce favorable outcomes after PCI due to an excess in repeat revascularization (1).

The recent SYNTAX (Synergy between PCI with TAXUS and Cardiac Surgery) trial showed that CABG remains superior to PCI, even with the usage of drug-eluting stents (DES) (2). It has been demonstrated that PCI is as effective as CABG in subgroups of patients with less complex coronary artery disease and LM lesions (2–4). Other recent trials have confirmed more favorable outcomes with CABG (5,6).

Although CABG is still the gold standard, there are some patients who cannot undergo surgery. In addition, a proportion of patients are not eligible for PCI. The SYNTAX study was designed as an all-comers trial, but patients could be excluded if the Heart Team concluded that either PCI or CABG could not be performed (2,7). This decision was based on a team judgment and not on predefined criteria. Excluded patients were entered in a CABG registry to define the population at too high-risk for PCI and in a PCI registry to define the patients deemed unsuitable for surgery. Little is known of the characteristics and outcomes of these populations. Separate analysis is necessary to fully understand the strengths and limitations of PCI and CABG in the "real world" (8). This study presents characteristics and 3-year outcomes of patients that were deemed nonrandomizable and therefore were included in the SYNTAX PCI and CABG nested registries.

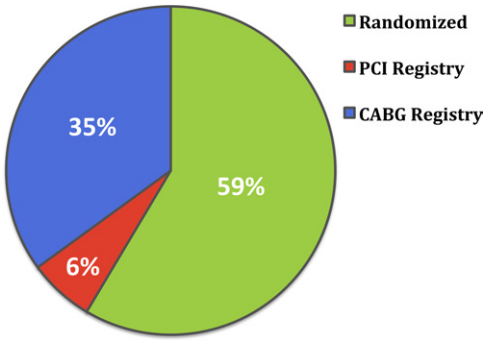

Figure 1. SYNTAX Patient Distribution

CABG = coronary artery bypass grafting; PCI = percutaneous coronary intervention; SYNTAX = Synergy Between PCI With TAXUS and Cardiac Surgery.

Methods

Study design. The SYNTAX trial design has been described previously (2,9). In brief, patients with 3-vessel or LM coronary artery disease were screened for enrollment in the randomized trial. During a multidisciplinary Heart Team discussion, including at least 1 surgeon and 1 interventional cardiologist, consensus was reached on whether both PCI and CABG would result in clinical equipoise (7). If a patient was not eligible for randomization, the patient was enrolled in the nested registry for CABG-ineligible patients (PCI registry) or PCI-ineligible patients (CABG registry).

Patients in the PCI registry were treated according to local practices with regard to technique and device preference, either with or without DES.

To compare the risk profile and outcomes of patients in the registries with the randomized arms, a randomly selected proportion of patients from the CABG registry and all PCI registry patients were scheduled to undergo clinical follow-up at 1, 6, 12, 36, and 60 months after treatment allocation (9).

The study protocol was approved by the institutional review board of all 85 enrollment sites and is consistent with the International Conference on Harmonisation Guidance of Industry E6 Good Clinical Practice, the Declaration of Helsinki, and all local regulations. Written consent was obtained from all participating patients. SYNTAX is registered at ClinicalTrials.gov (NCT00114972).

Abbreviations and Acronyms

CABG = coronary artery bypass grafting
DES = drug-eluting stent(s)
LM = left main
MACCE = major adverse cardiac or cerebrovascular event(s)
MI = myocardial infarction
PCI = percutaneous coronary intervention
SYNTAX = Synergy Between PCI With TAXUS and Cardiac Surgery

Definitions. The primary outcome of this study was the composite of major adverse cardiac or cerebrovascular events (MACCE) at 3 years of follow-up. MACCE included all-cause death, stroke, myocardial infarction (MI), and any repeat revascularization. The composite safety endpoint consisting of all-cause death, stroke, and MI, was also analyzed as well as individual outcomes. Adverse events were adjudicated by an independent Clinical Events Committee.

Definitions have been reported elsewhere (4). Briefly, stroke was defined as a focal neurological deficit of central origin lasting >72 h resulting in permanent brain damage or body impairment. Myocardial infarction was defined in relation to intervention status as follows: 1) after allocation but before treatment: Q-wave MI (new pathological Q waves in ≥2 leads lasting ≥0.04 s with creatine kinase-myocardial band [CK-MB] levels elevated above normal) and non–Q-wave MI [elevation of CK levels >2× the

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upper limit of normal [ULN] with positive CK-MB or elevation of CK levels to >2 × ULN without new Q waves if no baseline CK-MB was available); 2) <7 days after intervention: new Q waves and either peak CK-MB/total CK >10% or plasma level of CK-MB 5 × ULN; and 3) ≥7 days after intervention: new Q waves or peak CK-MB/total CK >10% or plasma level of CK-MB 5 × ULN or plasma level of CK 5 × ULN (4).

Table 1. Baseline Patient Demographic Data and Lesion Characteristics

Characteristics	PCI (n = 192)	CABG	
		With Follow-Up (n = 644)	All (n = 1,072)
Age, yrs	71.2 ± 10.4 (192)	65.7 ± 9.4 (644)	65.9 ± 9.4 (1,072)
Male	70.3% (135/192)	80.7% (520/644)	81.1% (869/1,072)
Comorbid risk factors			
Body mass index (kg/m^2)	28.0 ± 5.5 (191)	28.0 ± 4.6 (643)	28.0 ± 4.6 (1,069)
Medically treated diabetes			
Any	35.4% (68/192)	29.7% (191/644)	30.3% (325/1,072)
Requiring insulin	15.1% (29/192)	9.2% (59/644)	9.2% (99/1,072)
Triglycerides ≥150 mg/dl (1.7 mmol/l)	33.6% (37/110)	39.6% (114/288)	40.4% (182/451)
Blood pressure ≥130/85 mm Hg	69.8% (134/192)	68.5% (441/644)	68.9% (735/1,067)
Fasting glucose ≥110 mg/dl	47.2% (67/142)	49.8% (210/422)	49.7% (338/680)
Increased waist circumference	40.8% (58/142)	46.4% (245/528)	48.1% (414/861)
Hyperlipidemia	67.5% (129/191)	76.4% (480/628)	77.1% (809/1,049)
Cardiovascular history			
Current smoker	11.2% (21/188)	21.9% (140/639)	19.7% (209/1,062)
Previous myocardial infarction	40.4% (76/188)	33.5% (211/629)	32.5% (341/1,049)
Previous stroke	7.8% (15/192)	5.5% (35/639)	4.5% (48/1,065)
Previous transient ischemic attack	7.9% (15/191)	5.6% (36/638)	6.0% (64/1,062)
Previous cardiac surgery	1.6% (3/192)	0.0% (0/644)	0.0% (0/1,072)
Congestive heart failure	9.7% (18/186)	5.5% (35/633)	5.1% (54/1,057)
Peripheral vascular disease	16.1% (31/192)	13.8% (89/644)	12.5% (134/1,072)
Carotid artery disease	10.4% (20/192)	12.3% (79/644)	10.2% (109/1,072)
Creatinine >200 μmol/l	5.7% (11/192)	2.0% (13/644)	2.1% (23/1,072)
Chronic obstructive pulmonary disease	19.3% (37/192)	7.9% (51/644)	7.3% (78/1,072)
Angina			
Stable	46.4% (89/192)	62.9% (405/644)	63.3% (678/1,071)
Unstable	38.0% (73/192)	21.6% (139/644)	22.5% (241/1,071)
Ejection fraction <30%	5.7% (11/192)	4.5% (29/644)	3.9% (42/1,072)
Logistic EuroSCORE	7.7 ± 9.0 (192)	4.0 ± 4.4 (644)	4.0 ± 4.8 (1,072)
Additive EuroSCORE	5.8 ± 3.1 (192)	3.9 ± 2.7 (644)	3.9 ± 2.7 (1,072)
Parsonnet score	14.4 ± 9.5 (192)	9.0 ± 7.1 (644)	9.1 ± 7.2 (1,072)
Lesion complexity			
SYNTAX score	31.6 ± 12.3 (189)	37.8 ± 13.3 (632)	na
Diffuse disease or small vessels	18.5% (35/189)	13.6% (86/631)	na
Total occlusion	36.5% (69/189)	56.4% (356/631)	na
Bifurcation	74.6% (141/189)	80.8% (510/631)	na
Lesion characteristics			
Number of lesions	4.5 ± 1.8 (189)	4.6 ± 1.7 (632)	na
Left main, any	33.3% (63/189)	40.3% (254/631)	na
Left main only	2.6% (5/189)	1.6% (10/631)	na
Left main + 1 vessel	5.8% (11/189)	2.7% (17/631)	na
Left main + 2 vessel	11.6% (22/189)	8.4% (53/631)	na
Left main + 3 vessel	13.2% (25/189)	27.6% (174/631)	na
3-vessel disease only	66.7% (126/189)	59.7% (377/631)	na

Values are mean ± SD (N) or % (n/N).

CABG = coronary artery bypass grafting; na = not available; PCI = percutaneous coronary intervention; SYNTAX = Synergy between PCI with TAXUS and Cardiac Surgery.

Statistical analysis. Analyses were performed with SAS system software, version 8.0 or higher (SAS Institute, Cary, North Carolina). Outcomes are presented according to the as-treated-principle. The composite MACCE endpoint was analyzed as the time to the first event, whereas individual MACCE components are presented as proportions. Patient characteristics are presented as proportions (%, count/sample size) or mean ± SD.

We decided that no statistical comparisons between PCI and CABG should be performed, because entry into the registries depended on different variables specific for the corresponding registry. Thus, the patient characteristics and outcomes are only representative of patients ineligible to undergo PCI or CABG. Results are presented as observational only.

Subgroup analyses of separate SYNTAX score cohorts (low 0 to 22, intermediate 23 to 32, and high ≥33) were performed (10). The assessment of coronary anatomic complexity by SYNTAX score was based on tercile cohorts established in the randomized trial (2). Statistical comparison was performed by overall and pairwise log-rank testing, with a 2-sided p value <0.05 considered statistically significant.

Results

Inclusion. Between March 2005 and April 2007, a total of 4,337 patients were screened for eligibility of enrollment in the trial. After exclusion due to variable reasons (e.g., refusal of informed consent or concomitant valvular heart disease, among others), a total of 3,075 patients were treated within the SYNTAX trial. In the trial 1,800 patients were randomly assigned to undergo PCI (n = 903) and CABG (n = 897). Another 198 (6.4%) and 1,077 (35.0%) patients were included in the PCI and CABG registries, respectively (Fig. 1). From the 1,077 in the CABG registry, 649 were randomly selected to be followed-up for 5 years.

Of the 198 patients in the PCI registry, 192 were treated with PCI, 4 patients were treated medically, 1 underwent CABG, and 1 patient withdrew consent. Of the 649 CABG registry patients randomly assigned to 5-year follow-up, 644 were treated with CABG, 3 did not receive treatment, and 2 were managed medically. Another 9 patients were lost to follow-up, and 3 patients withdrew consent. Three-year MACCE rates were evaluable in 100% and 97.2% of the PCI and CABG patients, respectively.

Patients included in the PCI registry were considered too high-risk for CABG (70.7%), had no graft material for anastomosis (9.1%), refused CABG (5.6%), had small or poor quality of distal vessels (1.5%), or were excluded from randomization because of other reasons (13.1%). Reasons for inclusion in the CABG registry included too complex coronary anatomy to undergo PCI (70.9%), chronic total occlusion untreatable with PCI (22.0%), unable to take antiplatelet medication (0.9%), refusal to undergo PCI (0.5%), or other reasons (5.7%).

Patient characteristics. In general, compared with the patients that were randomized in the SYNTAX trial, the patients in the PCI registry were older (71.2 ± 10.4 years vs. 65.2 ± 9.7 years) and had a high-risk profile because of comorbidities and an eventful cardiovascular and noncardiovascular history; this was manifested in a higher Logistic EuroSCORE of 7.7 ± 9.0 (vs. 3.8 ± 4.5 in the randomized PCI group) and Parsonnet score of 14.4 ± 9.5 (vs. 8.5 ± 7.0 in the randomized PCI group) (Table 1). In addition, the lesion complexity by SYNTAX score was 31.6 ± 12.3 in the PCI registry, which was slightly higher than the 28.4 ± 11.5 in the randomized PCI group. A total occlusion was present in 36.5%, whereas this rate was only 24.2% in the trial.

Table 2. Perioperative Medication Use

	PCI (n = 192)	CABG (n = 644)
Aspirin		
Baseline	83.3% (160/192)	74.7% (481/644)
Discharge	92.7% (178/192)	88.4% (569/644)
Thienopyridine		
Baseline	71.9% (138/192)	16.1% (104/644)
Discharge	92.7% (178/192)	16.9% (109/644)
Nonthienopyridine antiplatelet		
Baseline	9.9% (19/192)	8.7% (56/644)
Discharge	6.8% (13/192)	6.1% (39/644)
Warfarin derivative		
Baseline	4.7% (9/192)	3.9% (25/644)
Discharge	3.6% (7/192)	9.6% (62/644)
Statin		
Baseline	64.1% (123/192)	70.0% (451/644)
Discharge	71.9% (138/192)	68.3% (440/644)
Beta-blocker		
Baseline	67.7% (130/192)	77.3% (498/644)
Discharge	70.3% (135/192)	79.3% (511/644)
ACE inhibitor		
Baseline	43.8% (84/192)	47.2% (304/644)
Discharge	54.2% (104/192)	45.2% (291/644)
Calcium-channel blocker		
Baseline	30.2% (58/192)	27.8% (179/644)
Discharge	27.1% (52/192)	21.9% (141/644)
Angiotensin II-receptor antagonist		
Baseline	16.1% (31/192)	11.3% (73/644)
Discharge	12.5% (24/192)	5.3% (34/644)
Antiarrythmic (amiodarone)		
Baseline	1.6% (3/192)	2.5% (16/644)
Discharge	2.6% (5/192)	12.3% (79/644)
H_2-receptor blocker		
Baseline	4.7% (9/192)	8.9% (57/644)
Discharge	8.9% (17/192)	19.9% (128/644)

Values are % (n/N).
ACE = angiotensin-converting enzyme; other abbreviations as in Table 1.

Table 3. Outcomes of Patients in PCI and CABG Registries

	PCI (n = 192)				CABG (n = 644)			
	30 Days (n = 192)	6 Months (n = 191)	1 Yr (n = 191)	3 Yrs (n = 192)	30 Days (n = 641)	6 Months (n = 639)	1 Yr (n = 633)	3 Yrs (n = 626)
Composite MACCE	7.3% (14)	14.1% (27)	20.4% (39)	38.0% (73)	3.4% (22)	6.7% (43)	8.8% (56)	16.4% (104)
Composite death/stroke/MI	6.3% (12)	8.4% (16)	10.5% (20)	24.6% (47)	3.3% (21)	5.8% (37)	6.6% (42)	12.6% (80)
Death	3.1% (6)	5.2% (10)	7.3% (14)	18.3% (35)	0.6% (4)	2.2% (14)	2.5% (16)	6.9% (44)
Cardiac death	2.6% (5)	3.7% (7)	4.7% (9)	7.0% (13)	0.5% (3)	1.4% (9)	1.4% (9)	2.5% (16)
Stroke	0.0% (0)	0.0% (0)	0.0% (0)	1.8% (3)	1.2% (8)	2.0% (13)	2.2% (14)	3.8% (24)
MI	3.6% (7)	3.7% (7)	4.2% (8)	8.4% (15)	1.6% (10)	2.2% (14)	2.5% (16)	3.7% (23)
Repeat revascularization, any	1.6% (3)	7.3% (14)	12.0% (23)	20.0% (36)	0.3% (2)	1.4% (9)	3.0% (19)	5.7% (35)
PCI	1.0% (2)	6.8% (13)	11.0% (21)	17.8% (32)	0.2% (1)	1.3% (8)	2.8% (18)	5.5% (34)
CABG	0.5% (1)	0.5% (1)	1.0% (2)	2.8% (5)	0.2% (1)	0.2% (1)	0.2% (1)	0.2% (1)

Values are % (n).
MACCE = major adverse cardiac and cardiovascular event(s); MI = myocardial infarction; other abbreviations as in Table 1.

Patients in the CABG registry had a Logistic EuroSCORE comparable to the CABG patients in the randomized trial (4.0 ± 4.4 vs. 3.9 ± 4.4 in the randomized trial) as well as a similar mean Parsonnet score (9.0 ± 7.1 vs. 8.4 ± 6.8 in the randomized CABG group) (Table 1). However, the lesions were more complex in the registry: the SYNTAX score was 37.8 ± 13.3 in the registry versus 29.1 ± 11.4 in the randomized trial. A total occlusion was present in 56.4% versus 22.2% in the randomized trial. More patients had LM and 3-vessel disease in the registry (27.6% vs. 13.0% in the trial).

Procedural characteristics. In the PCI registry, a mean of 2.5 ± 1.3 lesions were treated with 3.1 ± 1.8 stents and a mean total length of 58.5 ± 41.2 mm. This is much lower than in the randomized trial where 3.6 ± 1.6 lesions were treated with 4.6 ± 2.3 stents and a mean length of 86.1 ± 47.9 mm. In 76% of cases a DES stent (57% TAXUS) was used. Completeness or revascularization was only 36.5% in the registry compared with 56.7% in the trial.

A total of 3.0 ± 0.9 conduits were used per CABG patient (vs. 2.8 ± 0.7 in the randomized trial), of which 1.3 ± 0.7 were arterial and 1.7 ± 1.0 venous grafts. Complete arterial revascularization was performed in 11.2% compared with 18.9% in the randomized trial. In 96.7% at least 1 arterial graft was used; in the randomized trial this rate was 97.3%. Off-pump surgery was performed slightly more often in the registry (18.6% vs. 15.0% in the trial). Completeness of revascularization was 74.7% in the registry, compared with 63.2% in the trial.

Mean post-procedure hospital stay was 8.2 ± 5.5 days and 4.8 ± 12.0 days in the CABG and PCI registries, respectively. Perioperative medication use is displayed in Table 2.

PCI outcomes. Procedural 30-day MACCE occurred in 7.6% of the patients (Table 3). This was mainly driven by the 3.1% death rate and 3.6% MI rate. After 3 years of follow-up, the MACCE rate was 38.0% (Fig. 2, Table 3), with 18.3% death, 8.4% MI, 1.8% stroke, and 20.0% repeat revascularization (repeat PCI 17.8%, and repeat CABG 2.8%).

According to the SYNTAX score terciles, 44 patients had low lesion complexity (mean SYNTAX score 16.5 ± 5.1), 63 patients had intermediate complexity (mean SYNTAX score 27.7 ± 2.8), and 82 patients had high complexity (mean SYNTAX score 42.4 ± 9.2). Subgroup analyses revealed a MACCE rate of 29.5% in the cohort with a score ≤22 and increasing rates with intermediate (33.3%) and high (46.3%) scores (overall p = 0.09) (Fig. 3A). Difference in MACCE was not statistically significant between the low- and intermediate-score groups (p = 0.64) and intermediate- and high-score groups (p = 0.11). There was a trend toward a difference between the low- and high-score groups (p = 0.06). Breaking down MACCE into separate endpoints (Fig. 4A), there was a significant difference between the groups in terms of the composite safety endpoint of death, stroke, and MI (13.9% vs. 32.9% and 20.6% vs. 32.9%, p = 0.04), which was driven by increased rates of death in the high SYNTAX score group (24.4% vs. 9.3% in the low SYNTAX score group, p = 0.04). Other endpoints were comparable between groups (Fig. 4A).

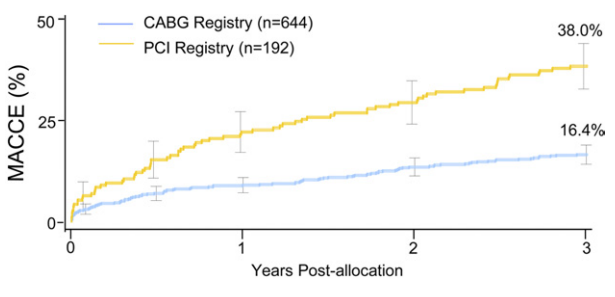

Figure 2. Cumulative Incidence of MACCE After PCI or CABG

CABG = coronary artery bypass grafting; MACCE = major adverse cardiac or cerebrovascular event(s); PCI = percutaneous coronary intervention.

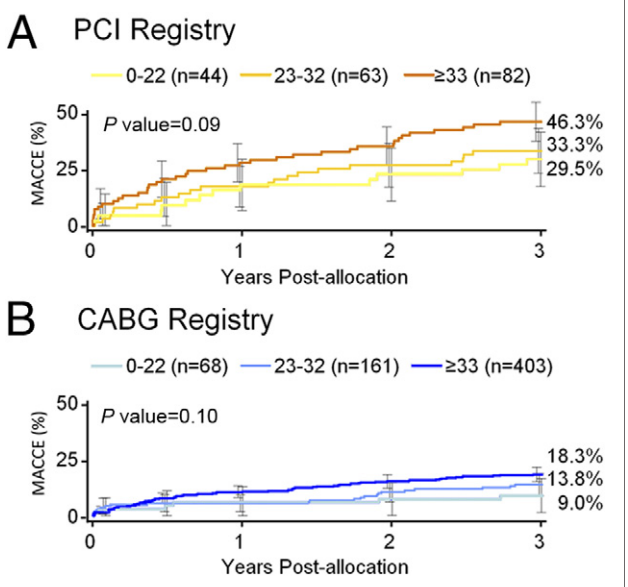

Figure 3. MACCE After PCI or CABG Stratified by SYNTAX Score

Kaplan-Meier incidence of MACCE in the PCI registry **(A)** and CABG registry **(B)**. Abbreviations as in Figures 1 and 2.

CABG outcomes. Procedural outcomes after CABG showed low rates of MACCE (3.4%), for the composite safety endpoint of death/stroke/MI (3.3%), and the individual components of MACCE: stroke (1.2%), MI (1.6%), and repeat revascularization (0.3%) (Table 2). After 3 years, the MACCE rate was 16.4% (Fig. 2, Table 3).

Patients were divided into low lesion complexity (n = 68, SYNTAX score 16.8 ± 4.1), intermediate complexity (n = 161, SYNTAX score 28.2 ± 2.7), and high complexity (n = 403, SYNTAX score 45.2 ± 10.1). Subgroup analysis demonstrates a stepwise increase in MACCE with higher SYNTAX score; 9.0% in the low-, 13.8% in the intermediate-, and 18.3% in the high-score cohorts (overall p = 0.10) (Fig. 3B). Pairwise testing demonstrated no statistically significant differences (low vs. intermediate, p = 0.32; intermediate vs. high, p = 0.19; low vs. high, p = 0.07). Individual MACCE components were not statistically significant between groups, except for the endpoint of death where there was a difference between the intermediate and high score groups (p = 0.03) (Fig. 4B).

Discussion

The SYNTAX nested registries presented in this study are important to complete the knowledge of the current use of PCI and CABG for 3-vessel or LM coronary artery disease in the real world. The SYNTAX randomized trial, among other trials, included only selective patients in whom both PCI and CABG could be performed with satisfactory results. Those patients not suitable for randomization are crucial to fully understand the indications, strengths, and limitations of PCI and CABG, with the corresponding outcomes. In this study we showed that the Heart Team decided that 35.0% of patients were not suitable for PCI and therefore underwent CABG. Patients were deemed inoperable and received PCI treatment in 6.4% of the cases.

Other studies. Patients in these registries were selected on the basis of clinical judgment of a multidisciplinary team of physicians (7). Results from other studies cannot be compared with the SYNTAX registry results, because this study presents patients in whom only 1 treatment option was considered appropriate. Therefore these patients represent not the total PCI or CABG cohort but only a selected group with different baseline risk and lesion complexity. Many patients receiving either PCI or CABG in other studies would probably have been randomized in the SYNTAX trial (2).

PCI registry. Patients in the SYNTAX PCI registry present a completely different patient population as the patients described in other registries or trials (1,2,11–13). First, the mean age was 71.2 ± 10.4, and nearly 75% of patients were ≥65 years of age; thus patients were significantly older. Second, patients more often presented with an eventful cardiac and noncardiac history. The mean Logistic EuroSCORE was higher in the registry (7.7 ± 9.0) than in the randomized arm (3.8 ± 4.5) as well as the Parsonnet score (14.4 ± 9.5 compared with 8.5 ± 7.0, respectively).

Indeed, the 3-year 38.0% MACCE rate in the PCI registry was much higher than the 28.0% in the randomized trial. However, this is not unexpected, due to the advanced age and severe comorbidities. Both the EuroSCORE and Parsonnet score have been associated with increased rates of adverse events during follow-up (13–15). In addition, some of the patients were included in the PCI registry because they had cancer or other severe diseases. This could be one of the reasons that the death rate is very high.

The high-risk profile of these PCI patients was influential in choosing the treatment strategy. Fewer lesions were stented and the number of stents that were used was much lower. It might be the case that only the culprit lesion was stented, whereas other lesions remained untreated, resulting in a 63.5% rate of incomplete revascularization in the registry. Also, 24% of patients received a bare-metal stent; this might have had an influence on the results as well (16).

CABG registry. Patients included in the CABG registry represent a population completely different from the patients in the PCI registry. Where in the PCI registry patients were high-risk but had similar lesion complexity, in the CABG registry it was the exact opposite. Patients had a similar mean EuroSCORE (4.0 ± 4.4 vs. 3.9 ± 4.4) and Parsonnet score (9.0 ± 7.1 vs. 8.4 ± 6.8) as the randomized patients. However, they were most often denied PCI because of too complex coronary anatomy, demonstrated in a higher SYNTAX score (37.8 ± 13.3 vs. 29.1 ± 11.4),

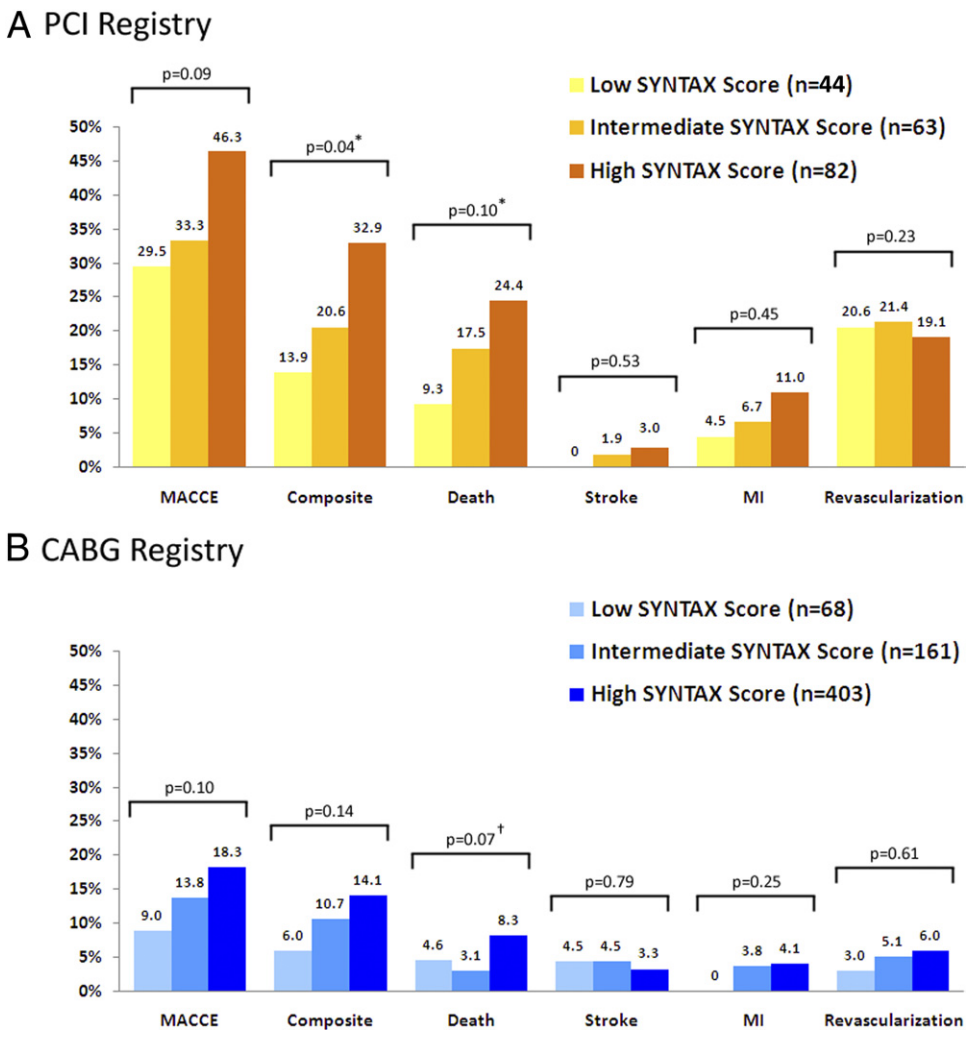

Figure 4. Outcomes Within the PCI and CABG Registries Stratified by SYNTAX Score

Event rates in the PCI registry **(A)** and CABG registry **(B)**. *p < 0.05 for low versus high SYNTAX score group comparison. †p < 0.05 for intermediate versus high SYNTAX score group comparison. composite = composite of death/stroke/myocardial infarction; MI = myocardial infarction; other abbreviations as in Figures 1 and 2.

more patients with a total occlusion (56.4% vs. 22.2%), and a slightly higher rate of bifurcation (80.8% vs. 73.3%).

The 3-year MACCE rate in the CABG registry (16.4%) is actually lower than in the randomized patients (20.2%), which was caused by lower rates of repeat revascularization (4,17). Interestingly, however, the actual difference in MACCE rates between the registry and trial do not increase over follow-up. At 1 year the difference was 3.2%, and at 3 years this was still only 3.8%. Therefore, it seems that the registry patients did significantly better especially during short-term follow-up. This was confirmed by a trend in lower rates of hospital and 30-day MACCE rates in the registry patients (17). This lower incidence of MACCE cannot be described by a difference in risk profile, because patients had similar risk. A previous study showed that it was likely related to procedural characteristics (17). In the registry, patients had a 74.7% rate of complete revascularization, whereas this was only 63.2% in the randomized trial. Furthermore, the number of grafts and distal anastomoses per patient was higher, which was identified to be independently associated with reduced rates of MACCE (17).

SYNTAX score. Since 2009, a large number of studies have tested the accuracy of the SYNTAX score as a risk algorithm in predicting adverse outcomes. A recent review summarized these data and concluded that, especially in LM patients treated with PCI, the score is a useful prognostic tool (18). Although Birim et al. (19) reported a stepwise increase in MACCE rates with higher SYNTAX scores, in patients treated with CABG generally less discriminative power could be attributed to the SYNTAX score. Remarkably, this study shows that in both PCI and CABG

patients a stepwise increase of MACCE rates can be seen with higher SYNTAX scores, although this was not statistically significant in the CABG registry.

There was, however, a significant difference in death between the intermediate- and high-score groups. A hypothesis behind this finding is that in the high SYNTAX score group more patients with extreme high scores were present. Although the predictive power of the SYNTAX score is limited in CABG patients, with extreme scores it is likely that ultimately the score will identify those patients at higher risk. The fact that death did not increase stepwise from low- to high-score groups demonstrates that the increased death in cohort with scores ≥33 might be caused by these extreme cases. Furthermore, these intragroup comparisons are post hoc subgroup analyses with relatively low statistical power, thus a change finding cannot be ruled out.

Study limitations. It is important to recognize that an emphasis should lay on long-term results after PCI and CABG. From this study, follow-up is only available up to 3 years. Ongoing prospective data collection will provide 5-year results.

The PCI registry contains a relatively small number of patients. Therefore some of the results should be interpreted with caution. Furthermore, explorative subgroup analyses by lesion subsets could not performed, due to the low patient number in separate groups.

Conclusions

In the SYNTAX trial the Heart Team concluded that, for 6.4% and 35.0% of patients, the only treatment option was PCI or CABG, respectively. Patients with complex coronary anatomy often underwent CABG, whereas inoperable high-risk patients were included in the PCI registry. Patients deemed inoperable for CABG had a high-risk profile, resulting in a suboptimal outcome after PCI. In patients who are not candidates for PCI, bypass surgery produces excellent results. To identify those patients at high risk for MACCE, the SYNTAX score discriminates well.

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Reprint requests and correspondence: Dr. A. Pieter Kappetein, Department of Cardio-Thoracic Surgery, Erasmus University Medical Center, P.O. Box 2040, 3000 CA Rotterdam, the Netherlands. E-mail: a.kappetein@erasmusmc.nl.

REFERENCES

1. Hlatky MA, Boothroyd DB, Bravata DM, et al. Coronary artery bypass surgery compared with percutaneous coronary interventions for multivessel disease: a collaborative analysis of individual patient data from ten randomised trials. Lancet 2009;373:1190–7.
2. Serruys PW, Morice MC, Kappetein AP, et al. Percutaneous coronary intervention versus coronary-artery bypass grafting for severe coronary artery disease. N Engl J Med 2009;360:961–72.
3. Morice MC, Serruys PW, Kappetein AP, et al. Outcomes in patients with de novo left main disease treated with either percutaneous coronary intervention using paclitaxel-eluting stents or coronary artery bypass graft treatment in the Synergy Between Percutaneous Coronary Intervention With TAXUS and Cardiac Surgery (SYNTAX) trial. Circulation 2010;121:2645–53.
4. Kappetein AP, Feldman TE, Mack MJ, et al. Comparison of coronary bypass surgery with drug-eluting stenting for the treatment of left main and/or three-vessel disease: 3-year follow-up of the SYNTAX trial. Eur Heart J 2011;32:2125–34.
5. Boudriot E, Thiele H, Walther T, et al. Randomized comparison of percutaneous coronary intervention with sirolimus-eluting stents versus coronary artery bypass grafting in unprotected left main stem stenosis. J Am Coll Cardiol 2011;57:538–45.
6. Kapur A, Hall RJ, Malik IS, et al. Randomized comparison of percutaneous coronary intervention with coronary artery bypass grafting in diabetic patients. 1-year results of the CARDia (Coronary Artery Revascularization in Diabetes) trial. J Am Coll Cardiol 2010;55:432–40.
7. Head SJ, Bogers AJ, Serruys PW, Takkenberg JJ, Kappetein AP. A crucial factor in shared decision making: the team approach. Lancet 2011;377:1836.
8. Hannan EL. Drug-eluting stents vs. coronary-artery bypass grafting. N Engl J Med 2008;358:2643–4.
9. Ong AT, Serruys PW, Mohr FW, et al. The SYNergy Between Percutaneous Coronary Intervention With TAXus and Cardiac Surgery (SYNTAX) study: design, rationale, and run-in phase. Am Heart J 2006;151:1194–204.
10. Sianos G, Morel MA, Kappetein AP, et al. The SYNTAX score: an angiographic tool grading the complexity of coronary artery disease. EuroIntervention 2005;1:219–27.
11. Capodanno D, Stone GW, Morice MC, Bass TA, Tamburino C. Percutaneous coronary intervention versus coronary artery bypass graft surgery in left main coronary artery disease: a meta-analysis of randomized clinical data. J Am Coll Cardiol 2011;58:1426–32.
12. Zheng S, Zheng Z, Hou J, Hu S. Comparison between drug-eluting stents and coronary artery bypass grafting for unprotected left main coronary artery disease: a meta-analysis of two randomized trials and thirteen observational studies. Cardiology 2011;118:22–32.
13. Park DW, Kim YH, Song HG, et al. Long-term comparison of drug-eluting stents and coronary artery bypass grafting for multivessel coronary revascularization: 5-year outcomes from the Asan Medical Center-Multivessel Revascularization registry. J Am Coll Cardiol 2011;57:128–37.
14. Lee MS, Kapoor N, Jamal F, et al. Comparison of coronary artery bypass surgery with percutaneous coronary intervention with drug-eluting stents for unprotected left main coronary artery disease. J Am Coll Cardiol 2006;47:864–70.
15. Rodés-Cabau J, Deblois J, Bertrand OF, et al. Nonrandomized comparison of coronary artery bypass surgery and percutaneous coronary intervention for the treatment of unprotected left main coronary artery disease in octogenarians. Circulation 2008;118:2374–81.
16. Stettler C, Wandel S, Allemann S, et al. Outcomes associated with drug-eluting and bare-metal stents: a collaborative network meta-analysis. Lancet 2007;370:937–48.
17. Mohr FW, Rastan AJ, Serruys PW, et al. Complex coronary anatomy in coronary artery bypass graft surgery: impact of complex coronary anatomy in modern bypass surgery? Lessons learned from the SYNTAX trial after two years. J Thorac Cardiovasc Surg 2011;141:130–40.
18. Capodanno D, Tamburino C. Integrating the synergy between percutaneous coronary intervention with Taxus and cardiac surgery (SYNTAX) score into practice: use, pitfalls, and new directions. Am Heart J 2011;161:462–70.
19. Birim O, van Gameren M, Bogers AJ, Serruys PW, Mohr FW, Kappetein AP. Complexity of coronary vasculature predicts outcome of surgery for left main disease. Ann Thorac Surg 2009;87:1097–104, discussion 1104–5.

Key Words: coronary artery bypass grafting (CABG) ■ heart team ■ left main ■ multivessel coronary disease ■ percutaneous coronary intervention (PCI) ■ randomized trial ■ real world ■ registry ■ SYNTAX.