Coronary artery bypass grafting vs. percutaneous coronary intervention for patients with three-vessel disease: final five-year follow-up of the SYNTAX trial

Stuart J. Head[1][†], Piroze M. Davierwala[2][†], Patrick W. Serruys[1], Simon R. Redwood[3], Antonio Colombo[4], Michael J. Mack[5], Marie-Claude Morice[6], David R. Holmes Jr[7], Ted E. Feldman[8], Elisabeth Ståhle[9], Paul Underwood[10], Keith D. Dawkins[10], A. Pieter Kappetein[1], and Friedrich W. Mohr[2]*

[1]Erasmus University Medical Center, Rotterdam, The Netherlands; [2]Herzzentrum Universität Leipzig, Strumpelstrasse 39, Leipzig 4289, Germany; [3]Guy's and St. Thomas' Hospital, London, UK; [4]San Raffaele Scientific Institute, Milan, Italy; [5]Medical City Hospital, Dallas, TX, USA; [6]Institut Hospitalier Jacques Cartier, Générale de santé, Massy, France; [7]May Clinic Rochester, Rochester, MN, USA; [8]Evanston Hospital, Evanston, IL, USA; [9]University Hospital Uppsala, Uppsala, Sweden; and [10]Boston Scientific Corporation, Natick, MA, USA

Aims	Coronary artery bypass grafting (CABG) has been considered the standard of care for patients with three-vessel disease (3VD), but long-term comparative results from randomized trials of CABG vs. percutaneous coronary intervention (PCI) using drug-eluting stents (DES) remain limited.
Methods and results	Patients with *de novo* 3VD or left main disease were randomly assigned to PCI with the paclitaxel-eluting first-generation stent or CABG in the SYNTAX trial. This pre-specified analysis presents the 5-year outcomes of patients with 3VD ($n = 1095$). The rate of major adverse cardiac and cerebrovascular events (MACCE) was significantly higher in patients with PCI compared with CABG (37.5 vs. 24.2%, respectively; $P < 0.001$). Percutaneous coronary intervention as opposed to CABG resulted in significantly higher rates of the composite of death/stroke/myocardial infarction (MI) (22.0 vs. 14.0%, respectively; $P < 0.001$), all-cause death (14.6 vs. 9.2%, respectively; $P = 0.006$), MI (9.2 vs. 4.0%, respectively; $P = 0.001$), and repeat revascularization (25.4 vs. 12.6%, respectively; $P < 0.001$); however, stroke was similar between groups at 5 years (3.0 vs. 3.5%, respectively; $P = 0.66$). Results were dependent on lesion complexity (P for interaction = 0.12); in patients with a low (0–22) SYNTAX score, PCI vs. CABG resulted in similar rates of MACCE (33.3 vs. 26.8%, respectively; $P = 0.21$) but significantly more repeat revascularization (25.4% vs. 12.6%, respectively; $P = 0.038$), while in intermediate (23–32) or high ($\geq$33) SYNTAX score terciles, CABG demonstrated clear superiority in terms of MACCE, death, MI, and repeat revascularization. Differences in MACCE between PCI and CABG were larger in diabetics [hazard ratio (HR) = 2.30] than non-diabetics (HR = 1.51), although the P for interaction failed to reach significance for MACCE (P for interaction = 0.095) or any of the other endpoints.
Conclusion	Five-year results of patients with 3VD treated with CABG or PCI using the first-generation paclitaxel-eluting DES suggest that CABG should remain the standard of care as it resulted in significantly lower rates of death, MI, and repeat revascularization, while stroke rates were similar. For patients with low SYNTAX scores, PCI is an acceptable revascularization strategy, although at a price of significantly higher rates of repeat revascularization.
Clinical trial registration	NCT00114972.
Keywords	Percutaneous coronary intervention • Coronary artery bypass grafting • Three-vessel disease • Randomized trial • SYNTAX • Incomplete revascularization • Diabetes

* Corresponding author. Tel: +49 341 865 1421, Fax: +49 341 865 1452, Email: mohrf@medizin.uni-leipzig.de

† These authors contributed equally to the manuscript.

Introduction

Because of the rapid progress in percutaneous coronary intervention (PCI) technology from balloon angioplasty to bare-metal stents (BMS) and subsequently drug-eluting stents (DES), several randomized clinical trials have been conducted over the last two decades to compare the outcomes of PCI with coronary artery bypass grafting (CABG), which has been considered the 'gold standard' for treatment of multivessel stable coronary artery disease (CAD).[1,2] Consistent improvements in outcomes of PCI led to a wider spectrum of patients being treated with PCI, including those with more complex CAD.

The SYNTAX trial, which is one of the most recent and largest randomized controlled trials comparing PCI using the paclitaxel-eluting first-generation stent with CABG, aimed at providing the best possible evidence to determine the most appropriate treatment option for patients encountered by surgeons and interventional cardiologists in their 'real-world' daily practice. The trial failed to establish non-inferiority of PCI to CABG for the treatment of left main (LM) and/or three-vessel disease (3VD) at 1 year, because of significantly higher rates of major adverse cardiac and cerebrovascular events (MACCE) after PCI.[3] However, the data demonstrated considerable variation in the treatment effect of PCI, especially with reference to the pre-specified subgroups of LM or 3VD, and complexity of CAD as determined by the SYNTAX score.[3] Based on these 1 year results, both European and North-American guidelines recommend PCI as a valuable treatment option for patients with LM disease and an alternative to CABG in patients with less complex 3VD (SYNTAX score < 23).[4,5]

For judicious decision-making, it is essential to consider the risk/benefit ratios of PCI and CABG for 3VD; weighing procedural invasiveness and the associated short-term complications against long-term event rates of death, myocardial infarction (MI), repeat revascularization, and improvements in health-related quality of life.[6] The present report therefore presents a comprehensive analysis of the 5-year outcomes of the predefined 3VD subgroup of patients receiving PCI or CABG in the SYNTAX trial.

Methods

Study design

The study design, methods as well as mid-term outcomes of the SYNTAX trial have been published previously.[3,7,8] Briefly, SYNTAX was a prospective, multinational, randomized, clinical study in which 1800 patients with *de novo* LM and/or 3VD, in whom clinical equipoise was deemed with revascularization by either treatment, were randomly assigned to undergo PCI with TAXUS Express paclitaxel-eluting stents (Boston Scientific, Natick, MA, USA) or CABG. Patients in whom PCI or CABG was considered the treatment of choice by a multidisciplinary Heart Team were enrolled in a CABG-ineligible PCI registry (*n* = 198) or PCI-ineligible CABG registry (*n* = 1077), respectively.[9] A yearly follow-up of all patients was performed by clinic visits or telephone contact up to 5 years.

Randomization was stratified by clinical site, the presence of LM disease, and medically treated diabetes mellitus. A separate analysis of patients with 3VD was pre-specified in the trial protocol, provided non-inferiority was met for the primary endpoint. However, since non-inferiority was not met, the current analysis should be interpreted as 'hypothesis generating'. The trial is registered at ClinicalTrials.gov with number NCT00114972.

Definitions

The primary endpoint of the SYNTAX trial was the rate of MACCE at 12 months after allocation and is a composite of all-cause death, stroke, MI, and repeat revascularization. Secondary endpoints consisted of (i) a composite safety endpoint of death/stroke/MI, (ii) individual endpoints of all-cause death, cardiac death, stroke, MI, and repeat revascularization, and (iii) symptomatic graft occlusion and stent thrombosis (ST). These events were considered at 1 month post-procedure and yearly post-allocation. Definitions of these events have been reported previously.[7] An independent clinical events committee adjudicated all primary clinical events.

The vessels (diameter ≥1.5 mm and significant stenosis >50%) deemed important to revascularize were determined by the Heart Team prior to randomization. The group of 3VD consists of patients with significant stenosis in vessels supplying all three major epicardial territories in the absence of LM disease, as determined by the site investigators. Incomplete revascularization (IR) was assessed by correlating this pre-operative documentation to the actual revascularization performed during the procedure and was recorded by the investigator.

Statistical methods

Continuous variables are expressed as mean ± SD and compared using the Student *t*-test. Discrete data are presented as frequencies and compared with a χ^2 or Fisher's exact tests, where appropriate. Analyses were performed according to intention to treat. Short-term outcomes were considered to be within 30 days post-procedure and were calculated as binary rates. Long-term event rates were estimated using Kaplan–Meier curves with a statistical comparison made by log-rank test. Patients lost to follow-up or who withdrew consent were non-assessable and were censored at the last available follow-up time, assumed to be event free. A sensitivity analysis was performed in which non-assessable patients were assumed to have had an event.

Subgroup analyses were performed according to SYNTAX score tercile, diabetic status, and IR, with *P*-values for interaction calculated using χ^2 testing. Multivariable proportional hazard models with a *P*-value of 0.10 as entry and exit criteria were constructed to identify whether PCI treatment vs. CABG was an independent predictor of MACCE, the composite safety endpoint, and all-cause death during follow-up. Variables included in the model were believed to be clinically relevant, and PCI vs. CABG was forced in each model (see Supplementary material online, *Appendix*). A two-sided *P*-value of <0.05 was considered to indicate statistical significance. All statistical analyses were performed using the SPSS software, version 20 (IBM Corporation, Armonk, NY, USA).

Results

Baseline characteristics

Of the 1800 patients randomized in the SYNTAX trial, 1095 patients had 3VD. Of these, 549 were randomly assigned to CABG and 546 to PCI. There were no differences between treatment groups in terms of age, gender, presence of cardiac risk factors and associated co-morbidities, or expected surgical mortality as assessed by the logistic EuroSCORE (*Table 1*). The extent and complexity of CAD were also evenly distributed between the two groups. The majority of patients underwent elective revascularization with no differences between groups.

Table I Baseline characteristics of patients with three-vessel disease

	CABG (n = 549)	PCI (n = 546)	P-value
Age	64.5 ± 9.6 (549)	65.1 ± 9.6 (546)	0.32
Male	81.1% (445/549)	79.3% (433/546)	0.47
Body mass index	28.0 ± 4.2 (549)	28.1 ± 4.7 (545)	0.88
Current smoker	20.8% (114/548)	18.9% (103/546)	0.42
Diabetes	30.4% (167/549)	31.1% (170/546)	0.80
Medically treated diabetes	26.0% (143/549)	28.0% (153/546)	0.46
Insulin-requiring diabetes	10.7% (59/549)	11.4% (62/546)	0.75
Hyperlipidaemia	78.3% (426/544)	77.2% (416/539)	0.66
Blood pressure ≥130/85 mmHg	65.0% (357/549)	70.1% (383/546)	0.07
Previous MI	39.1% (213/545)	34.2% (184/538)	0.10
Congestive heart failure	5.7% (31/540)	4.2% (23/543)	0.26
Carotid artery disease	7.5% (41/549)	7.7% (42/546)	0.89
Previous stroke	5.3% (29/546)	3.9% (21/544)	0.25
Previous transient ischaemic attack	5.7% (31/545)	4.2% (23/544)	0.27
Peripheral vascular disease	10.0% (55/549)	8.2% (45/546)	0.31
Creatinine >200 μmol/L	1.5% (8/549)	0.9% (5/546)	0.41
Chronic obstructive pulmonary disease	9.5% (52/549)	7.7% (42/546)	0.29
Unstable angina	27.3% (150/549)	27.8% (152/546)	0.85
Ejection fraction <30%[a]	3.1% (17/549)	1.3% (7/546)	0.040
Elective revascularization	94.1% (497/528)	95.2% (518/544)	0.43
Logistic EuroSCORE	3.7 ± 3.7 (549)	3.5 ± 3.5 (546)	0.56
Parsonnet score	8.0 ± 6.5 (549)	8.3 ± 6.3 (546)	0.50
Coronary complexity[b]			
Number of lesions	4.9 ± 1.6 (545)	4.9 ± 1.5 (543)	0.39
Any total occlusion	6.2% (167/2686)	6.5% (171/2632)	0.68
Any bifurcation	25.9% (697/2686)	25.3% (667/2632)	0.61
Diffuse disease or small vessels	11.6% (63/545)	13.4% (73/543)	0.35
SYNTAX score	28.4 ± 10.4 (545)	27.6 ± 9.8 (543)	0.17

CABG, coronary artery bypass grafting; MI, myocardial infarction; PCI, percutaneous coronary intervention.
Values are shown as mean ± SD (n) or % (n/N).
[a]Or indicated by clinical site as 'poor' if exact value was not available.
[b]Core laboratory reported.

Procedural characteristics

Patients randomized to CABG had significantly longer waiting times for the procedure as opposed to PCI (Table 2). Procedure times and post-procedural hospital stay for patients who underwent CABG were significantly longer than those who underwent PCI.

Amongst patients randomized to CABG, off-pump surgery was performed in only 13.9% of patients. Bilateral internal mammary arteries were used in 30.6% of patients, with total arterial revascularization being performed in 17.0% of patients. The mean number of grafts and distal anastomoses per patient were 2.9 ± 0.7 and 3.4 ± 0.8, respectively. Patients undergoing PCI received a mean of 5.3 ± 2.1 stents with a mean stent length of 99.4 ± 45.5 mm per patient. A total stent length of >100 mm was implanted in >40% of patients. Patients who underwent CABG less commonly had IR; however, it did not reach statistical significance.

Patients who underwent PCI generally received more secondary preventive medication during follow-up than those who underwent CABG. Antiplatelet therapy was given more frequently in the PCI group at all time points, and at 5 years was still significantly higher following PCI than CABG for administration of a thienopyridine (36.7 vs. 11.0%, respectively; P < 0.001) and dual antiplatelet therapy (20.8 vs. 6.4%, respectively; P < 0.001). The use of other medications was exclusively higher after PCI during the first year of follow-up, but at 5 years rates were comparable between PCI and CABG: beta-blockers (75.7 vs. 76.1%, respectively; P = 0.90), ACE-inhibitors (55.2 vs. 52.9%, respectively; P = 0.49), calcium-channel blockers (25.4 vs. 22.3%, respectively; P = 0.28), angiotensin II-receptor antagonists (20.3 vs. 20.9%, respectively; P = 0.82), and statins (83.2 vs. 85.3%, respectively; P = 0.40) (Supplementary material online, Table S1).

Pre-procedural MACCE was 0.7% (n = 4) in the CABG group and 0.2% (n = 1) in the PCI group (P = 0.38). A total of 19 patients died within 30 days after revascularization: 12 after PCI and 7 after CABG (P = 0.28) (Table 2). Although the stroke rate was non-significantly

Table 2 Procedural characteristics of patients with three-vessel disease

	CABG (*n*=549)	PCI (*n* = 546)	*P*-value
Allocation to procedure (days)	19.2 ± 28.1 (528)	7.6 ± 14.1 (544)	<0.001
Procedure time (h)	3.5 ± 1.0 (522)	1.8 ± 1.0 (544)	<0.001
Bypass time (min)	89.2 ± 33.6 (436)	–	
Cross clamp time (min)	57.3 ± 23.6 (402)	–	
Off-pump surgery	13.9% (72/517)	–	
Complete arterial	17.0% (88/517)	–	
Bilateral internal mammary artery use	30.6% (158/517)	–	
Number of grafts, *n*	2.9 ± 0.7 (517)	–	
Arterial grafts, *n*	1.5 ± 0.7 (517)	–	
Venous grafts, *n*	1.4 ± 0.9 (517)	–	
Number of distal anastomoses, *n*	3.4 ± 0.8 (517)	–	
Number of stents implanted, *n*	–	5.3 ± 2.1 (530)	
Total stent length implanted (mm)	–	99.4 ± 45.5 (530)	
Long stenting (>100 mm)	–	41.5% (220/530)	
Incomplete revascularization	42.8% (226/528)	48.3% (263/544)	0.069
Post-procedural hospital stay (days)	9.5 ± 8.1 (528)	3.6 ± 5.1 (544)	<0.001
30-day post-procedural outcomes			
MACCE	4.8% (25/524)	7.0% (38/543)	0.12
Death/stroke/MI	4.0% (21/524)	5.5% (30/543)	0.25
All-cause death	1.3% (7/524)	2.2% (12/543)	0.28
Stroke	1.3% (7/524)	0.4% (2/543)	0.10
MI	1.7% (9/524)	4.2% (23/543)	0.016
Repeat revascularization	1.1% (6/524)	3.9% (21/543)	0.005
PCI	0.4% (2/424)	2.6% (14/543)	0.003
CABG	0.8% (4/524)	1.3% (7/543)	0.40

CABG, coronary artery bypass grafting; MACCE, major adverse cardiac and cerebrovascular events; MI, myocardial infarction; PCI, percutaneous coronary intervention.
Values are shown as mean ± SD (*n*) or % (*n*/*N*).

higher after CABG (*P* = 0.10), MI and repeat revascularization occurred significantly more frequently after PCI. The rate of MACCE at 30 days was comparable between PCI and CABG (7.0 vs. 4.8%, respectively; *P* = 0.064).

Five-year outcomes

At 5 years follow-up, 88% of CABG-randomized and 96% of PCI-randomized 3VD patients were available for analysis (see Supplementary material online, *Figure S1*). Overall, the occurrence of MACCE at 5 years was significantly higher in patients who underwent PCI when compared with those who underwent CABG [37.5 (*n* = 123) vs. 24.2% (*n* = 201), respectively; *P* < 0.001] (*Figure 1A*). Similarly, the composite safety endpoint of death/stroke/MI was more commonly observed after PCI than after CABG [22.0 (*n* = 118) vs. 14.0% (*n* = 71), respectively; *P* < 0.001] (*Figure 1B*), with the difference driven by significantly higher rates of all-cause death [14.6 (*n* = 78) vs. 9.2% (*n* = 46), respectively; *P* = 0.006] and MI [10.6 (*n* = 55) vs. 3.3% (*n* = 17), respectively; *P* < 0.001] (*Figures 1C* and *E*). Furthermore, patients had significantly higher rates of cardiac death after PCI vs. CABG [9.2 (*n* = 48) vs. 4.0% (*n* = 20), respectively; hazard ratio (HR) 2.34, 95% CI 1.39–3.95; *P* < 0.001]. Patients required repeat revascularization more frequently after PCI than after

CABG [25.4 (*n* = 130) vs. 12.6% (*n* = 61), respectively; *P* < 0.001] (*Figure 1F*), driven by significant differences in both repeat PCI [21.5 (*n* = 110) vs. 12.3% (*n* = 59), respectively; HR 1.96, 95% CI 1.41–2.65; *P* < 0.001] and repeat CABG [5.6 (*n* = 28) vs. 1.0% (*n* = 5), respectively; HR 5.56, 95% CI 2.15–14.41; *P* < 0.001]. Graft occlusion after surgery occurred in 18 patients (3.7%), resulting in an MI in 3 patients, repeat revascularization in 12 patients, and 3 patients required no treatment; there were no deaths. Thirty PCI patients (5.8%) experienced ST; of these, 9 patients died, 11 experienced an MI, and 10 underwent repeat revascularization. Occurrence of angina was also significantly higher at all time points after PCI than after CABG (*Figure 2*).

In the sensitivity analysis, assuming all patients who were lost to follow-up or withdrew consent had an event, MACCE remained significantly higher after PCI than after CABG (40.7 vs. 34.6%, respectively; HR 1.23, 95% CI 1.01–1.49; *P* = 0.040), although there was no longer a difference in the composite of all-cause death/stroke/MI (26.0 vs. 26.6%, respectively; HR 0.96, 95% CI 0.76–1.21; *P* = 0.72).

Predictors of 5-year outcomes

The multivariable proportional hazard model revealed treatment with PCI to be an independent predictor of MACCE over 5-year
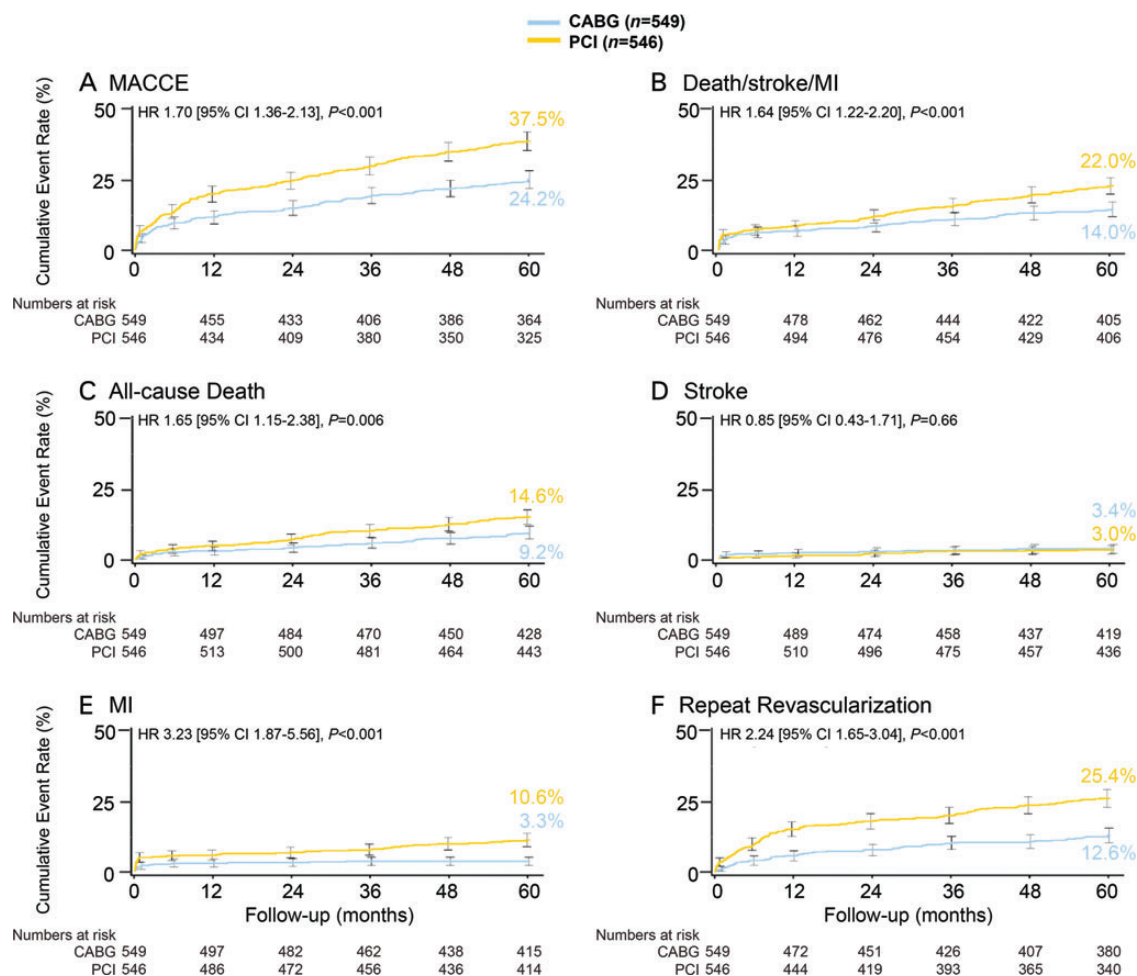
Figure 1 Five-year estimates of adverse events. Kaplan−Meier curves for (A) MACCE, (B) all-cause death/stroke/MI, (C) all-cause death, (D) stroke, (E) MI, and (F) repeat revascularization. Bars represent ± 1.5 standard error. P-values from log-rank test. CABG, coronary artery bypass grafting; CI, confidence interval; HR, hazard ratio; PCI, percutaneous coronary intervention; MACCE, major adverse cardiac and cerebrovascular events; MI, myocardial infarction.
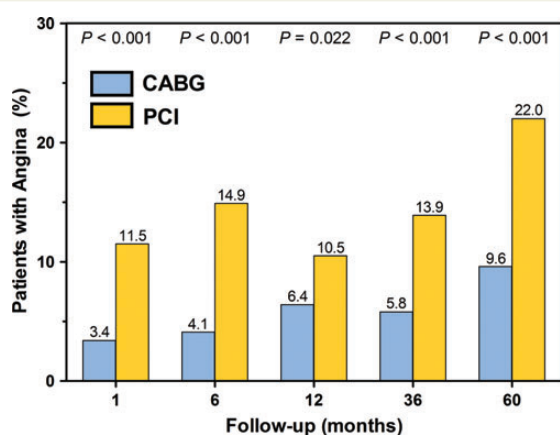
Figure 2 Presence of angina during follow-up. CABG, coronary artery bypass grafting; PCI, percutaneous coronary intervention.

follow-up (HR 1.66, 95% CI 1.32−2.09; $P < 0.001$), in addition to several pre-operative patient characteristics and IR (*Table 3*). Furthermore, treatment with PCI not only remained a significant independent predictor of the composite safety endpoint (HR 1.81, 95% CI 1.33−2.46; $P < 0.001$) but also of all-cause death (HR 1.81, 95% CI 1.24−2.67; $P = 0.002$).

Subgroup analyses of 5-year outcomes

Medically treated diabetes

Overall, 296 patients (CABG, $n = 143$ and PCI, $n = 153$) with 3VD had medically treated diabetes (*Figure 3A*). The MACCE rates in diabetic patients with 3VD were significantly higher in the PCI group than the CABG group (HR 2.30, 95% CI 1.50−3.55; $P < 0.001$). Significantly higher event rates were also seen after PCI vs. CABG in the composite safety endpoint of death/stroke/MI, all-cause death, MI, and repeat revascularization. Stroke rates were comparable. Although the differences in event rates among non-diabetic patients (CABG, $n = 406$ and PCI, $n = 393$) were smaller between groups,

Table 3 Multivariable predictors of adverse events

	HR (95% CI)	P-value
MACCE		
PCI treatment vs. CABG	1.66 (1.32−2.09)	<0.001
Age	1.01 (1.00−1.03)	0.024
Poor LV function	2.08 (1.03−4.21)	0.042
Hypertension	1.31 (0.98−1.75)	0.067
Peripheral vascular disease	1.76 (1.27−2.43)	0.001
Incomplete revascularization	1.37 (1.10−1.72)	0.006
Enrolment in the United States	1.47 (1.06−2.06)	0.023
Composite safety endpoint of death/stroke/MI		
PCI treatment vs. CABG	1.81 (1.33−2.46)	<0.001
Age	1.04 (1.02−1.06)	<0.001
Poor LV function	3.23 (1.50−6.96)	0.003
Moderate LV function	1.43 (1.02−2.02)	0.040
Hypertension	1.47 (0.98−2.20)	0.061
Peripheral vascular disease	1.90 (1.28−2.83)	0.002
History of TIA or stroke	1.50 (0.97−2.30)	0.066
Chronic obstructive pulmonary disease	1.87 (1.23−2.84)	0.003
All-cause death		
PCI treatment vs. CABG	1.81 (1.24−2.67)	0.002
Age	1.07 (1.05−1.10)	<0.001
Previous MI	1.38 (0.94−2.03)	0.098
Poor LV function	3.17 (1.25−8.08)	0.015
Moderate LV function	1.58 (1.03−2.41)	0.035
Peripheral vascular disease	3.13 (2.00−4.89)	<0.001
Chronic obstructive pulmonary disease	2.25 (1.38−3.68)	0.001
Creatinine ≥200 μmol/L	2.46 (0.87−6.94)	0.090

CABG, coronary artery bypass grafting; HR, hazard ratio; LV, left ventricular; MACCE, major adverse cardiac and cerebrovascular events; MI, myocardial infarction; PCI, percutaneous coronary intervention; TIA, transient ischaemic attack.

PCI in comparison with CABG still had significantly higher rates of MACCE (HR 1.51, 95% CI 1.15−1.96; *P* = 0.002), the composite safety endpoint, MI, and repeat revascularization, but with similar rates of all-cause death and stroke (*Figure 3B*). There were no significant treatment-by-diabetes interactions.

SYNTAX terciles
Differences in event rates between PCI and CABG showed a step-wise increase with increasing SYNTAX scores for all events, except stroke, for which no differences were observed through all SYNTAX score terciles (*Figure 4*). For patients with a low SYNTAX score (0−22), no significant differences were noted between PCI and CABG treatment groups in rates of MACCE, the composite safety endpoint of death/stroke/MI, all-cause death, and MI. Patients who underwent PCI did have a significantly higher rate of repeat revascularization than those who underwent CABG. Patients with intermediate (23−33) or high SYNTAX scores (≥33), patients who underwent CABG had significantly lower rates of MACCE, the composite safety endpoint of death/stroke/MI, as well as

individual components all-cause death, MI and repeat revascularization (*Figure 4*). There was no evidence of significant treatment-by-SYNTAX score tercile interaction.

Incomplete revascularization
In the CABG cohort, outcomes were similar in patients with complete and IR (*Table 4*). Conversely, in the PCI cohort, patients who underwent incomplete as opposed to complete revascularization had significantly higher rates of MACCE (42.6 vs. 32.7%, respectively; *P* = 0.010) and repeat revascularization (30.6 vs. 20.4%, respectively; *P* = 0.003). However, occurrence of the composite of death/stroke/MI and its individual endpoints were similar (*Table 4*). There were no significant interactions between completeness of revascularization and treatment.

Discussion

The 5-year analysis of patients with 3VD randomized in the SYNTAX trial demonstrated that treatment with PCI resulted in significantly higher rates of MACCE, which were driven not only by increased rates of repeat revascularization but also by significantly higher all-cause death and MI. Stroke rates were, however, comparable between CABG and PCI. The 5-year outcomes show a persistent divergence in all event rates except stroke. These results were further validated by the fact that treatment with PCI was found to be an independent predictor, not only of 5-year MACCE but also of all-cause death and composite safety endpoint of death/stroke/MI.

The SYNTAX trial has been crucial for establishing the optimal revascularization strategies for patients with LM disease and 3VD. Remarkably, the treatment effect of PCI vs. CABG differed significantly between patients with LM disease and 3VD. Left main PCI has become more common since the results from the SYNTAX trial established similar safety and efficacy in comparison with CABG.[10] However, for multivessel disease, unlike previous trials using simple balloon angioplasty or BMS,[1,2] this study for the first time provides robust evidence that CABG is superior to PCI using first-generation DES in reducing long-term hard clinical endpoints of death and MI. The present study included more complex patients than previous trials, in which inclusion of patients with two-vessel disease probably mitigated the advantages of better survival and freedom from MI after CABG. Until this analysis, only large registries have demonstrated a long-term survival benefit in patients with 3VD disease treated with CABG. Registries always encompass a selection bias for which no degree of adjustment can be applied, thus potentially having unknown cofounders. Nevertheless, Hannan and coauthors reported significantly better adjusted HRs for death after CABG vs. PCI with BMS, and subsequently found similar results when PCI was performed with first-generation DES.[11,12] The ASCERT study, which is the largest propensity-adjusted analysis of registry data involving nearly 200,000 patients, also reported a significantly lower 4-year mortality after CABG than after PCI (16.4 vs. 20.8%, respectively; risk ratio 0.79, 95% CI 0.76−0.82).[13]

Although occurrence of MI was significantly higher even at 30 days after PCI than after CABG, 30-day mortality and the composite of death/stroke/MI were comparable between the two treatment groups. The 30-day stroke rate, though higher, was not significantly increased after CABG (*Table 2*). This non-significant difference in
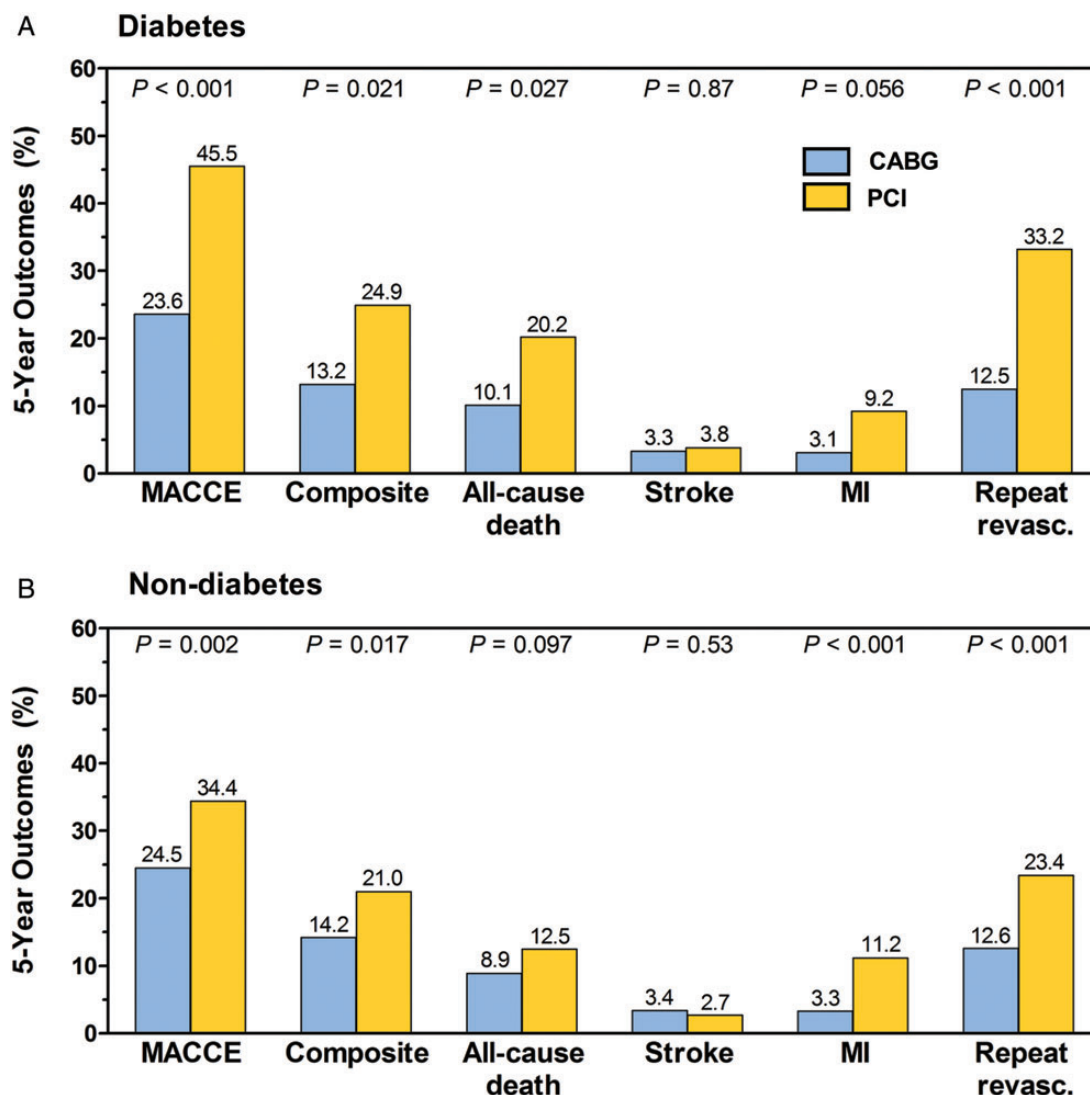
Figure 3 Five-year estimates of adverse events in patients with diabetes (A) and without diabetes (B). Treatment-by-diabetes interactions failed to reach statistical significance for MACCE (P = 0.095), the composite safety endpoint (P = 0.44), all-cause death (P = 0.37), stroke (P = 0.63), MI (P = 0.88), and repeat revascularization (P = 0.15). Values are Kaplan–Meier event rates with P-values from log-rank test. CABG, coronary artery bypass grafting; composite, composite safety endpoint of all-cause death/stroke/MI; PCI, percutaneous coronary intervention; MACCE, major adverse cardiac and cerebrovascular events; MI, myocardial infarction.

stroke rate was evident during the first year (1.9 vs. 0.8%, P = 0.09), but declined over extended follow-up.[14] The early occurrence of stroke after CABG could potentially have been reduced by use of off-pump surgery with minimal or no aortic manipulation and the use of epiaortic scanning, especially in patients with aortic calcification.[15] A reduction in post-operative MI and long-term improvement in graft patency may have been achieved by use of intraoperative graft flow measurements.[16] Although not standard of care, greater use of multiple arterial grafts, particularly bilateral internal mammary arteries (30.6%) and total arterial grafting (17.0%) may have also further improved the long-term results of CABG. Numerous such technical advancements in CABG continue to enhance post-operative short- and long-term outcomes of CABG.[15,17] A recent analysis of ~1 500 000 patients in the Society of Thoracic Surgeons database who

underwent isolated CABG between 2000 and 2009 demonstrated a significant reduction in in-hospital mortality and morbidity, despite an increasing operative risk.[18] Furthermore, in concordance with previous studies, secondary preventive medication remains suboptimal following CABG in comparison to PCI, in particular within the first year of follow-up. Why this continuous to be an issue remains unclear, but it appears that country-wide intensive education and quality improvement programs required to significantly increase compliance following revascularization could potentially further enhance long-term results following surgical revascularization.

Likewise, several newer-generation DES have been developed since the use of the paclitaxel-eluting stent in the SYNTAX trial and have replaced the latter in current clinical practice due to significant reductions in MI, ST, and repeat revascularization.[19] Recent
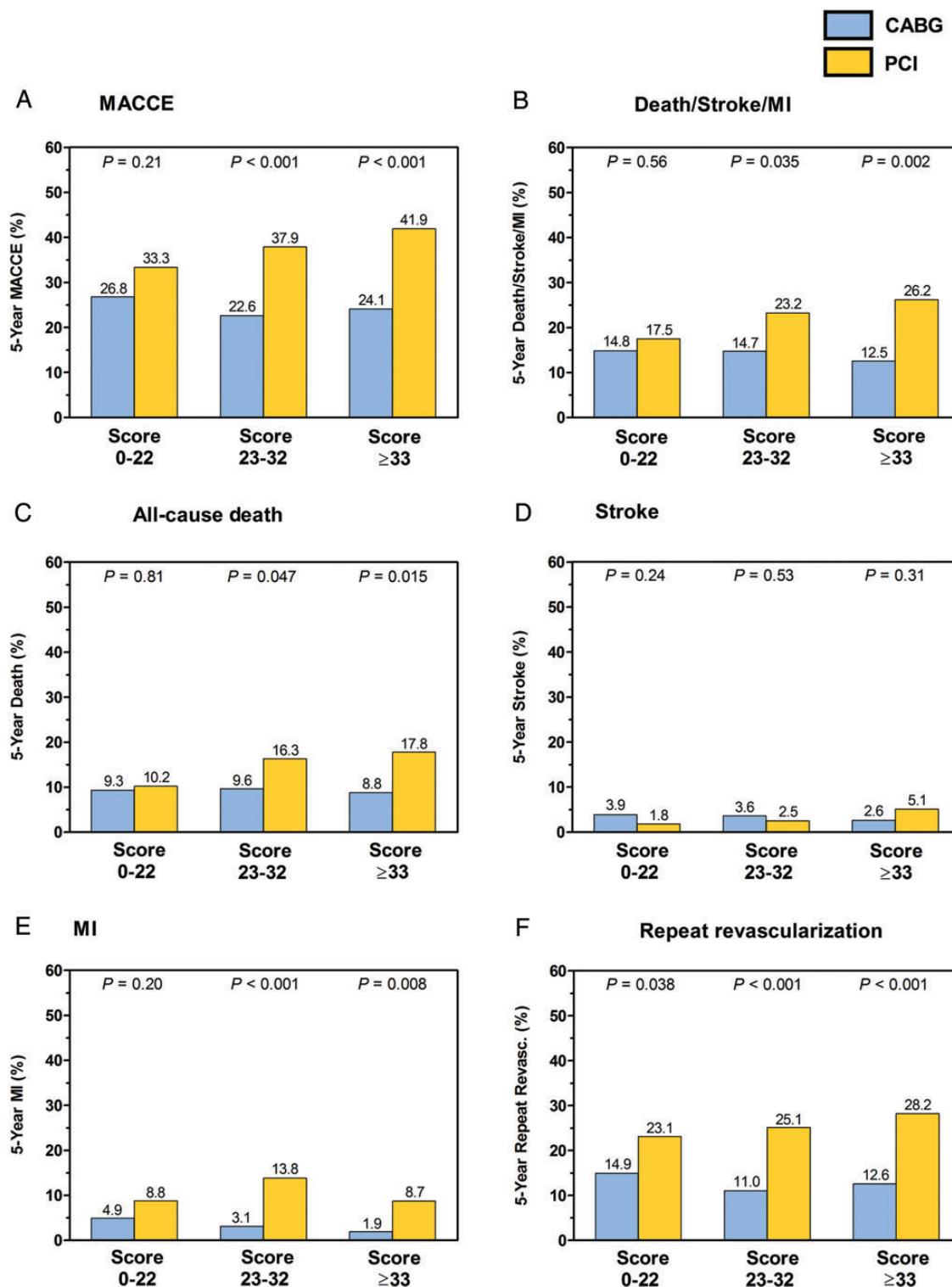
Figure 4 Five-year estimates of adverse events according to the SYNTAX score. (*A*) MACCE, (*B*) the composite safety endpoint of all-cause death/stroke/MI, (*C*) all-cause death, (*D*) stroke, (*E*) MI, and (*F*) repeat revascularization. Treatment-by-SYNTAX score tercile interactions failed to reach statistical significance for MACCE ($P = 0.12$), the composite safety endpoint ($P = 0.085$), all-cause death ($P = 0.15$), stroke ($P = 0.12$), MI ($P = 0.16$), and repeat revascularization ($P = 0.32$). Values are Kaplan–Meier event rates with *P*-values from log-rank test. CABG, coronary artery bypass grafting; PCI, percutaneous coronary intervention; MACCE, major adverse cardiac and cerebrovascular events; MI, myocardial infarction.

Table 4 Five-year outcomes according to completeness of revascularization

Clinical outcome	CABG (n = 528)			PCI (n = 544)			Interaction P-value
	Incomplete (n = 226)	Complete (n = 302)	P-value	Incomplete (n = 263)	Complete (n = 281)	P-value	
MACCE	26.9% (59)	22.2% (63)	0.17	42.6% (111)	32.7% (90)	0.010	0.62
Death/stroke/MI	14.6% (32)	13.3% (38)	0.64	24.2% (63)	20.0% (55)	0.23	0.72
All-cause death	10.1% (22)	8.3% (23)	0.41	16.2% (42)	13.1% (36)	0.31	0.97
Stroke	4.7% (10)	2.4% (7)	0.18	3.8% (9)	2.3% (6)	0.36	0.81
MI	3.2% (7)	3.4% (10)	0.90	10.0% (25)	11.3% (30)	0.69	0.95
Repeat revascularization	15.3% (32)	10.6% (29)	0.091	30.6% (77)	20.4% (53)	0.003	0.75
PCI	14.9% (31)	10.3% (28)	0.088	25.3% (63)	18.0% (63)	0.026	
CABG	0.9% (2)	1.0% (3)	0.91	8.1% (20)	3.2% (20)	0.012	

CABG, coronary artery bypass grafting; MACCE, major adverse cardiac and cerebrovascular events; MI, myocardial infarction; PCI, percutaneous coronary intervention.
Values are Kaplan–Meier event rates with P-values from log-rank test.

analyses even revealed lower rates of all-cause death with newer stents/scaffolds.[20,21] Biodegradable polymer scaffolds may further improve outcomes following PCI.[22] Despite these technological improvements in stents, the basic method of implantation within the diseased segment of the coronary artery offers no safeguard against the advancement of the pre-existing or evolution of new disease, as the native coronary artery continues to remain the source of inflow. Contrarily, bypass conduits, which are the new sources of inflow after CABG, are most often anastomosed to coronary arteries beyond the diseased segments, thus rendering the type, length, degree, and complexity of stenoses irrelevant. While newer-generation DES might diminish the difference between PCI and CABG, especially in repeat revascularization and MI due to ST, the principle difference in the method of revascularization is the major contributing factor to the long-term benefit seen with CABG.

Additionally, IR may be another factor responsible for differences in 5-year outcomes between PCI and CABG in the current study, as it negatively impacted only PCI and not CABG results. This could be explained by either a small sample size, because IR with CABG was associated with increased adverse events in an analysis of the combined SYNTAX trial and registry,[23,24] or it was caused by dissimilarities in the type and, hence, consequences of IR between the two therapies. IR occurs more frequently in patients with highly complex CAD, in particular chronic total occlusions, undergoing PCI;[24,25] resulting in higher post-operative residual SYNTAX scores with large areas of non-revascularized/ischaemic myocardium that could potentially increase the risk of death during follow-up.[26,27] Conversely, IR in CABG usually encompasses either small vessels with less ischaemic myocardium at risk or diffusely diseased vessels which are often well collateralized. It must also be considered that lesions of 50% angiographic severity are counted in the SYNTAX score and are not routinely bypassed, but contribute to IR by definition. For these reasons, IR with CABG is often considered to be more acceptable than with PCI.[28] The increased incidence of IR especially with higher SYNTAX scores correlated well with the differing treatment effect of PCI vs. CABG according to SYNTAX score terciles; although no significant IR-by-treatment interaction ($P = 0.23$) was observed.

CABG was superior to PCI in patients with intermediate or high SYNTAX scores. Although PCI and CABG had equivalent safety profiles in patients with low-SYNTAX scores, PCI resulted in significantly higher rates of repeat revascularization.

However, accumulating data suggest that complete anatomical revascularization is not always necessary but decisions depend on the functional assessment of a lesion. Revascularization of non-significant stenosis, as measured by fractional flow reserve (FFR), increases the risk of death and MI during follow-up.[29] The FAME trial demonstrated that exclusive functional and not pure anatomical complete revascularization by FFR- instead of angiography-guided PCI resulted in a significant reduction in use of stents and consequently reduced the 1-year rate of a composite of death, MI, and repeat revascularization.[30] This has been confirmed recently in a 'real-world' scenario.[31] Similarly, a recent study revealed that FFR- vs. angiography-guided CABG was associated with a lower number of bypass grafts, but comparable rates of major adverse cardiac events at 3-year follow-up (12 vs. 11%, respectively; $P = 0.91$). However, rates of recurrent angina significantly declined (31 vs. 47%, respectively; $P < 0.001$).[32] The impact of FFR-guided revascularization on the PCI vs. CABG treatment effect will be determined in the FAME III trial.

In accordance with the data on the SYNTAX score and completeness of revascularization, the current European guidelines provide a IIa B recommendation for PCI in patients with 3VD and SYNTAX scores ≤ 22, provided full functional revascularization is feasible.[4] However, it should be noted that this SYNTAX score cut-off value can always be overruled when important factors other than anatomical complexity of the lesion have to be taken into consideration. Moreover, the current SYNTAX score cut-offs of 23 and 32 were derived from the SYNTAX trial and still require confirmation from other large randomized trials comparing PCI with CABG.[9] The choice of treatment strategy should therefore not solely depend on lesion complexity, but the Heart Team should also consider clinical parameters, comorbidities, treatment preferences, and operator skills, particularly in patients with low SYNTAX scores for whom both PCI and CABG are excellent options.[33] A much considered

factor is diabetes, the presence of which has been shown to be a strong indicator for CABG, since these patients are at an increased risk of adverse events during follow-up and have a higher long-term mortality with PCI than CABG.[34–36] The current analysis also confirmed that PCI was associated with HRs of 2.30 in diabetic and 1.51 in non-diabetic patients. Additionally, the difference in MACCE and composite safety endpoint of death/stroke/MI remained significant in favour of CABG amongst both diabetic and non-diabetic patients. The non-significant interaction term ($P = 0.095$) suggests that the treatment effect of PCI vs. CABG for 3VD remains consistent irrespective of diabetic status.

In order to incorporate clinical parameters into decision-making and to improve patient selection, the SYNTAX II score was developed based on anatomical complexity and six clinical factors found to be independent predictors of 4-year mortality in the randomized SYNTAX trial. Further validation will be forthcoming from the SYNTAX II trial (NCT02015832).[37] Using SYNTAX II scores for patients with 3VD to predict 4-year mortality, CABG was favoured in 84.2% of patients in the SYNTAX trial. In the current analysis of 5-year outcomes, the Kaplan–Meier curves continued to diverge beyond this point with all-cause death rates between 4 and 5 years of 2.4% for CABG and 2.8% for PCI ($P = 0.74$) (Figure 1).

Study limitations

The SYNTAX trial, which involved a hierarchical statistical testing plan, was powered only for the overall 3VD/LM population and subsequently for the 3VD subgroup only if non-inferiority for the primary endpoint for the whole population was met; however, given that the latter pre-requisite was not satisfied, the analyses presented here must be considered observational and 'hypothesis generating' only. In addition, the number of patients in each subgroup according to SYNTAX score terciles was small and not adequately powered. Groups of patients who underwent off-pump and/or total arterial grafting were too small with limited statistical power to evaluate the impact of these techniques on the treatment effect of PCI vs. CABG.

Conclusions

The 5-year outcomes in patients with 3VD in the randomized arm of the SYNTAX trial suggest that treatment with CABG as opposed to PCI with the first-generation paclitaxel-eluting DES resulted in significantly lower rates of death and MI, and should therefore remain the standard of care for 3VD. Patients with complex CAD (intermediate or high SYNTAX scores) particularly benefit from CABG, whereas PCI is an acceptable treatment option in patients with less complex disease (low SYNTAX scores), though at a price of significantly higher rates of repeat revascularization. Randomized trials are needed to reassess revascularization options in the era of newer-generation DES.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

References

1. Hlatky MA, Boothroyd DB, Bravata DM, Boersma E, Booth J, Brooks MM, Carrie D, Clayton TC, Danchin N, Flather M, Hamm CW, Hueb WA, Kahler J, Kelsey SF, King SB, Kosinski AS, Lopes N, McDonald KM, Rodriguez A, Serruys P, Sigwart U, Stables RH, Owens DK, Pocock SJ. 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**: 1190–1197.
2. Daemen J, Boersma E, Flather M, Booth J, Stables R, Rodriguez A, Rodriguez-Granillo G, Hueb WA, Lemos PA, Serruys PW. Long-term safety and efficacy of percutaneous coronary intervention with stenting and coronary artery bypass surgery for multivessel coronary artery disease: a meta-analysis with 5-year patient-level data from the ARTS, ERACI-II, MASS-II, and SoS trials. *Circulation* 2008;**118**:1146–1154.
3. Serruys PW, Morice MC, Kappetein AP, Colombo A, Holmes DR, Mack MJ, Stahle E, Feldman TE, van den Brand M, Bass EJ, Van Dyck N, Leadley K, Dawkins KD, Mohr FW, SYNTAX Investigators. Percutaneous coronary intervention versus coronary-artery bypass grafting for severe coronary artery disease. *N Engl J Med* 2009;**360**:961–972.
4. Wijns W, Kolh P, Danchin N, Di Mario C, Falk V, Folliguet T, Garg S, Huber K, James S, Knuuti J, Lopez-Sendon J, Marco J, Menicanti L, Ostojic M, Piepoli MF, Pirlet C, Pomar JL, Reifart N, Ribichini FL, Schalij MJ, Sergeant P, Serruys PW, Silber S, Sousa Uva M, Taggart D. Guidelines on myocardial revascularization. *Eur Heart J* 2010;**31**:2501–2555.
5. Writing Committee Members, Levine GN, Bates ER, Blankenship JC, Bailey SR, Bittl JA, Cercek B, Chambers CE, Ellis SG, Guyton RA, Hollenberg SM, Khot UN, Lange RA, Mauri L, Mehran R, Moussa ID, Mukherjee D, Nallamothu BK, Ting HH. 2011 ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention: Executive Summary: A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Society for Cardiovascular Angiography and Interventions. *Circulation* 2011;**124**:2574–2609.
6. Federspiel JJ, Stearns SC, van Domburg RT, Sheridan BC, Lund JL, Serruys PW. Risk-benefit trade-offs in revascularisation choices. *EuroIntervention* 2011;**6**:936–941.
7. Kappetein AP, Feldman TE, Mack MJ, Morice MC, Holmes DR, Stahle E, Dawkins KD, Mohr FW, Serruys PW, Colombo A. 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**:2125–2134.
8. Mohr FW, Morice MC, Kappetein AP, Feldman TE, Stahle E, Colombo A, Mack MJ, Holmes DR Jr., Morel MA, Van Dyck N, Houle VM, Dawkins KD, Serruys PW. Coronary artery bypass graft surgery versus percutaneous coronary intervention in patients with three-vessel disease and left main coronary disease: 5-year follow-up of the randomised, clinical SYNTAX trial. *Lancet* 2013;**381**:629–638.
9. Head SJ, Holmes DR Jr., Mack MJ, Serruys PW, Mohr FW, Morice MC, Colombo A, Kappetein AP, SYNTAX Investigators. Risk profile and 3-year outcomes from the SYNTAX percutaneous coronary intervention and coronary artery bypass grafting nested registries. *JACC Cardiovasc Interv* 2012;**5**:618–625.
10. Morice MC, Serruys PW, Kappetein AP, Feldman TE, Ståhle E, Colombo A, Mack MJ, Holmes DR, Choi JW, Ruzyllo W, Religa G, Huang J, Roy K, Dawkins KD, Mohr FW. Five-year outcomes in patients with left main disease treated with either percutaneous coronary intervention or coronary artery bypass grafting in the SYNTAX trial. *Circulation* 2014. [Epub ahead of print].
11. Hannan EL, Racz MJ, Walford G, Jones RH, Ryan TJ, Bennett E, Culliford AT, Isom OW, Gold JP, Rose EA. Long-term outcomes of coronary-artery bypass grafting versus stent implantation. *N Engl J Med* 2005;**352**:2174–2183.

12. Hannan EL, Wu C, Walford G, Culliford AT, Gold JP, Smith CR, Higgins RS, Carlson RE, Jones RH. Drug-eluting stents vs. coronary-artery bypass grafting in multivessel coronary disease. *N Engl J Med* 2008;**358**:331–341.

13. Weintraub WS, Grau-Sepulveda MV, Weiss JM, O'Brien SM, Peterson ED, Kolm P, Zhang Z, Klein LW, Shaw RE, McKay C, Ritzenthaler LL, Popma JJ, Messenger JC, Shahian DM, Grover FL, Mayer JE, Shewan CM, Garratt KN, Moussa ID, Dangas GD, Edwards FH. Comparative effectiveness of revascularization strategies. *N Engl J Med* 2012;**366**:1467–1476.

14. Mack MJ, Head SJ, Holmes DR Jr, Stahle E, Feldman TE, Colombo A, Morice MC, Unger F, Erglis A, Stoler R, Dawkins KD, Serruys PW, Mohr FW, Kappetein AP. 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. *JACC Cardiovasc Interv* 2013;**6**:344–354.

15. Head SJ, Borgermann J, Osnabrugge RL, Kieser TM, Falk V, Taggart DP, Puskas JD, Gummert JF, Kappetein AP. Coronary artery bypass grafting: part 2 – optimizing outcomes and future prospects. *Eur Heart J* 2013;**34**:2873–2886.

16. Jokinen JJ, Werkkala K, Vainikka T, Perakyla T, Simpanen J, Ihlberg L. Clinical value of intra-operative transit-time flow measurement for coronary artery bypass grafting: a prospective angiography-controlled study. *Eur J Cardiothorac Surg* 2011;**39**:918–923.

17. Head SJ, Kieser TM, Falk V, Huysmans HA, Kappetein AP. Coronary artery bypass grafting: part 1 – the evolution over the first 50 years. *Eur Heart J* 2013;**34**: 2862–2872.

18. ElBardissi AW, Aranki SF, Sheng S, O'Brien SM, Greenberg CC, Gammie JS. Trends in isolated coronary artery bypass grafting: an analysis of the Society of Thoracic Surgeons adult cardiac surgery database. *J Thorac Cardiovasc Surg* 2012;**143**:273–281.

19. Stefanini GG, Holmes DR Jr. Drug-eluting coronary-artery stents. *N Engl J Med* 2013; **368**:254–265.

20. Gada H, Kirtane AJ, Newman W, Sanz M, Hermiller JB, Mahaffey KW, Cutlip DE, Sudhir K, Hou L, Koo K, Stone GW. 5-year results of a randomized comparison of XIENCE V everolimus-eluting and TAXUS Paclitaxel-eluting stents: final results from the SPIRIT III trial (clinical evaluation of the XIENCE V everolimus eluting coronary stent system in the treatment of patients with de novo native coronary artery lesions). *JACC Cardiovasc Interv* 2013;**6**:1263–1266.

21. Sarno G, Lagerqvist B, Frobert O, Nilsson J, Olivecrona G, Omerovic E, Saleh N, Venetzanos D, James S. Lower risk of stent thrombosis and restenosis with unrestricted use of 'new-generation' drug-eluting stents: a report from the nationwide Swedish Coronary Angiography and Angioplasty Registry (SCAAR). *Eur Heart J* 2012;**33**:606–613.

22. Stefanini GG, Kalesan B, Serruys PW, Heg D, Buszman P, Linke A, Ischinger T, Klauss V, Eberli F, Wijns W, Morice MC, Di Mario C, Corti R, Antoni D, Sohn HY, Eerdmans P, van Es GA, Meier B, Windecker S, Juni P. Long-term clinical outcomes of biodegradable polymer biolimus-eluting stents versus durable polymer sirolimus-eluting stents in patients with coronary artery disease (LEADERS): 4 year follow-up of a randomised non-inferiority trial. *Lancet* 2011;**378**:1940–1948.

23. Mohr FW, Rastan AJ, Serruys PW, Kappetein AP, Holmes DR, Pomar JL, Westaby S, Leadley K, Dawkins KD, Mack MJ. 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**:130–140.

24. Farooq V, Serruys PW, Garcia-Garcia HM, Zhang Y, Bourantas CV, Holmes DR, Mack M, Feldman T, Morice MC, Stahle E, James S, Colombo A, Diletti R, Papafaklis MI, de Vries T, Morel MA, van Es GA, Mohr FW, Dawkins KD, Kappetein AP, Sianos G, Boersma E. The negative impact of incomplete angiographic revascularization on clinical outcomes and its association with total occlusions: the SYNTAX (Synergy Between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery) trial. *J Am Coll Cardiol* 2013;**61**:282–294.

25. Head SJ, Mack MJ, Holmes DR Jr., Mohr FW, Morice MC, Serruys PW, Kappetein AP. Incidence, predictors and outcomes of incomplete revascularization after percutaneous coronary intervention and coronary artery bypass grafting: a subgroup analysis of 3-year SYNTAX data. *Eur J Cardiothorac Surg* 2012;**41**:535–541.

26. Farooq V, Serruys PW, Bourantas CV, Zhang Y, Muramatsu T, Feldman T, Holmes DR, Mack M, Morice MC, Stahle E, Colombo A, de Vries T, Morel MA, Dawkins KD, Kappetein AP, Mohr FW. Quantification of incomplete revascularization and its association with five-year mortality in the synergy between percutaneous coronary intervention with taxus and cardiac surgery (SYNTAX) trial validation of the residual SYNTAX score. *Circulation* 2013;**128**:141–151.

27. Shaw LJ, Berman DS, Maron DJ, Mancini GB, Hayes SW, Hartigan PM, Weintraub WS, O'Rourke RA, Dada M, Spertus JA, Chaitman BR, Friedman J, Slomka P, Heller GV, Germano G, Gosselin G, Berger P, Kostuk WJ, Schwartz RG, Knudtson M, Veledar E, Bates ER, McCallister B, Teo KK, Boden WE, COURAGE Investigators. Optimal medical therapy with or without percutaneous coronary intervention to reduce ischemic burden: results from the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial nuclear substudy. *Circulation* 2008;**117**:1283–1291.

28. Taggart DP. Incomplete revascularization: appropriate and inappropriate. *Eur J Cardiothorac Surg* 2012;**41**:542–543.

29. Pijls NH, van Schaardenburgh P, Manoharan G, Boersma E, Bech JW, van't Veer M, Bar F, Hoorntje J, Koolen J, Wijns W, de Bruyne B. Percutaneous coronary intervention of functionally nonsignificant stenosis: 5-year follow-up of the DEFER Study. *J Am Coll Cardiol* 2007;**49**:2105–2111.

30. Tonino PA, De Bruyne B, Pijls NH, Siebert U, Ikeno F, van' t Veer M, Klauss V, Manoharan G, Engstrom T, Oldroyd KG, Ver Lee PN, MacCarthy PA, Fearon WF, FAME Study Investigators. Fractional flow reserve versus angiography for guiding percutaneous coronary intervention. *N Engl J Med* 2009;**360**:213–224.

31. Park SJ, Ahn JM, Park GM, Cho YR, Lee JY, Kim WJ, Han S, Kang SJ, Park DW, Lee SW, Kim YH, Lee CW, Mintz GS, Park SW. Trends in the outcomes of percutaneous coronary intervention with the routine incorporation of fractional flow reserve in real practice. *Eur Heart J* 2013;**34**:3353–3361.

32. Toth G, De Bruyne B, Casselman F, De Vroey F, Pyxaras S, Di Serafino L, Van Praet F, Van Mieghem C, Stockman B, Wijns W, Degrieck I, Barbato E. Fractional flow reserve-guided versus angiography-guided coronary artery bypass graft surgery. *Circulation* 2013;**128**:1405–1411.

33. Head SJ, Kaul S, Mack MJ, Serruys PW, Taggart DP, Holmes DR Jr., Leon MB, Marco J, Bogers AJ, Kappetein AP. The rationale for Heart Team decision-making for patients with stable, complex coronary artery disease. *Eur Heart J* 2013;**34**:2510–2518.

34. Farkouh ME, Domanski M, Sleeper LA, Siami FS, Dangas G, Mack M, Yang M, Cohen DJ, Rosenberg Y, Solomon SD, Desai AS, Gersh BJ, Magnuson EA, Lansky A, Boineau R, Weinberger J, Ramanathan K, Sousa JE, Rankin J, Bhargava B, Buse J, Hueb W, Smith CR, Muratov V, Bansilal S, King S 3rd, Bertrand M, Fuster V, FREEDOM Trial Investigators. Strategies for multivessel revascularization in patients with diabetes. *N Engl J Med* 2012;**367**:2375–2384.

35. Kappetein AP, Head SJ, Morice MC, Banning AP, Serruys PW, Mohr FW, Dawkins KD, Mack MJ, SYNTAX Investigators. Treatment of complex coronary artery disease in patients with diabetes: 5-year results comparing outcomes of bypass surgery and percutaneous coronary intervention in the SYNTAX trial. *Eur J Cardiothorac Surg* 2013;**43**:1006–1013.

36. Verma S, Farkouh M, Yanagawa B, Fitchett D, Ahsan M, Ruel M, Sud S, Gupta M, Singh S, Gupta N, Cheema A, Leiter L, Fedak P, Teoh H, LAtter D, Fuster V, Friedrich JO. Comparison of coronary artery bypass surgery and percutaneous coronary intervention in patients with diabetes: a meta-analysis of randomised controlled trials. *Lancet Diab Endocrinol* 2013;**1**:317–328.

37. Farooq V, van Klaveren D, Steyerberg EW, Meliga E, Vergouwe Y, Chieffo A, Kappetein AP, Colombo A, Holmes DR Jr., Mack M, Feldman T, Morice MC, Stahle E, Onuma Y, Morel MA, Garcia-Garcia HM, van Es GA, Dawkins KD, Mohr FW, Serruys PW. Anatomical and clinical characteristics to guide decision making between coronary artery bypass surgery and percutaneous coronary intervention for individual patients: development and validation of SYNTAX score II. *Lancet* 2013;**381**:639–650.