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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

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Aims Long-term randomized comparisons of percutaneous coronary intervention (PCI) to coronary artery bypass grafting (CABG) in left main coronary (LM) disease and/or three-vessel disease (3VD) patients have been limited. This analysis compares 3-year outcomes in LM and/or 3VD patients treated with CABG or PCI with TAXUS Express stents.

Methods and results SYNTAX is an 85-centre randomized clinical trial ($n = 1800$). Prospectively screened, consecutive LM and/or 3VD patients were randomized if amenable to equivalent revascularization using either technique; if not, they were entered into a registry. Patients in the randomized cohort will continue to be followed for 5 years. At 3 years, major adverse cardiac and cerebrovascular events [MACCE: death, stroke, myocardial infarction (MI), and repeat revascularization; CABG 20.2% vs. PCI 28.0%, $P < 0.001$], repeat revascularization (10.7 vs. 19.7%, $P < 0.001$), and MI (3.6 vs. 7.1%, $P = 0.002$) were elevated in the PCI arm. Rates of the composite safety endpoint (death/stroke/MI 12.0 vs. 14.1%, $P = 0.21$) and stroke alone (3.4 vs. 2.0%, $P = 0.07$) were not significantly different between treatment groups. Major adverse cardiac and cerebrovascular event rates were not significantly different between arms in the LM subgroup (22.3 vs. 26.8%, $P = 0.20$) but were higher with PCI in the 3VD subgroup (18.8 vs. 28.8%, $P < 0.001$).

Conclusions At 3 years, MACCE was significantly higher in PCI- compared with CABG-treated patients. In patients with less complex disease (low SYNTAX scores for 3VD or low/intermediate terciles for LM patients), PCI is an acceptable revascularization, although longer follow-up is needed to evaluate these two revascularization strategies.

Keywords SYNTAX • Left main • Multivessel disease • PCI • CABG • Stent thrombosis

Introduction

Coronary artery bypass graft surgery (CABG) has been considered the optimum revascularization treatment for patients with *de novo* left main (LM) disease and/or three-vessel disease (3VD). In the past two decades, percutaneous coronary intervention (PCI) has emerged as a possible alternative in patients with complex coronary disease as stent design, procedural technique, and adjunctive medical therapy have improved.[1,2] Recent revisions to revascularization guidelines have reflected these improvements in PCI outcomes for patients with complex coronary disease.[3,4] In general, during the first year after the index procedure, PCI has been found to be as safe as CABG in patients with severe coronary artery disease; however, the rates of retreatment are significantly

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higher and PCI failed to show non-inferiority compared with CABG due to increased repeat revascularization.[5,6] Additionally, the occurrence of very late stent thrombosis (ST), although rare, is a concern for patients treated with PCI,[7] whereas the risk of stroke is increased following CABG.[6,8–10]

The overall goal of the SYNTAX trial is to assess the most appropriate revascularization strategy by randomizing patients to either PCI with TAXUS Express stents or CABG. The innovative angiographic SYNTAX score was also developed to help prospectively determine the complexity of the coronary anatomy before embarking on intervention.[11,12] The average number of stents and total stented length implanted in SYNTAX is higher than any other contemporary drug-eluting stent vs. CABG study. The primary endpoint at 1 year was not met; the non-inferiority of PCI compared with CABG was not demonstrated and CABG proved to be superior. After 1 year, no differences were observed in safety outcomes (death, stroke, and MI) between CABG and PCI patients, although the rate of revascularization and overall major adverse cardiac and cerebrovascular events (MACCE) was significantly increased in PCI patients and stroke was significantly increased in CABG patients. The current study reports the 3-year outcomes from the SYNTAX trial.

Methods

Study design, subject selection, and follow-up

The SYNergy between PCI with TAXUS and Cardiac Surgery (SYNTAX) trial is a multinational, randomized (1:1) study comparing clinical outcomes after drug-eluting PCI using the TAXUS Express stent (Boston Scientific, Natick, MA, USA) or CABG in patients with 3VD and/or LM disease. Patients in whom equivalent and comparable revascularization could be achieved by either CABG or PCI (as determined by the cardiothoracic surgeon and interventional cardiologist of the 'Heart Team') were randomized ($n = 1800$; CABG $n = 897$ and PCI $n = 903$). In the LM group, patients could have isolated LM disease or LM plus 1, 2, or 3VD. Patients considered unsuitable for one of the treatment options were enrolled in parallel, nested registries (the PCI registry for CABG-ineligible patients, $n = 198$; CABG registry for PCI-ineligible patients, $n = 1077$). Three-year post-allocation follow-up was assessed by clinic visit; further follow-up will be conducted at 4 (telephone call or clinic visit) and 5 years (clinic visit) post-treatment allocation.

The study protocol was reviewed and approved by an Institutional Review Board/Ethics Committee at each participating site. Before enrolment in the study, each patient provided written informed consent. SYNTAX is registered on the National Institute of Health website (www.clinicaltrials.gov) as NCT00114972. The study design, including details on sample size determination, randomization scheme, and primary endpoint results have previously been described in detail.[6,13]

Definitions

The primary clinical endpoint of SYNTAX was the composite of MACCE [all-cause death, cerebrovascular accident (CVA/stroke), MI, and repeat revascularization] through 12-month post-allocation. Patients were treated with the intention of complete revascularization of all vessels/lesions (reference diameter >1.5 mm, stenosis $\geq 50\%$) identified at the Heart Team conference. Completeness of revascularization was assessed post-procedure by the investigator. All deaths were considered cardiac unless an unequivocal, non-cardiac cause could be established. Cerebrovascular events, or stroke, were defined as focal neurological deficits of central origin lasting >72 h resulting in permanent brain damage or body impairment. The definition of MI was based on previous studies.[14–16] Briefly, MI was defined in relation to intervention status as follows: (i) after allocation but before treatment: Q-wave [new pathological Q-waves in ≥ 2 leads lasting ≥ 0.04 s with creatine kinase-MB (CK-MB) levels elevated above normal] and non-Q-wave MI [elevation of CK levels $>2\times$ the upper limit of normal (ULN) with positive CK-MB or elevation of CK levels to $>2\times$ ULN without new Q-waves if no baseline CK-MB was available]; (ii) <7 days after intervention: new Q-waves and either peak CK-MB/total CK $>10\%$ or plasma level of CK-MB $5\times$ ULN; and (iii) ≥ 7 days after intervention: new Q-waves or peak CK-MB/total CK $>10\%$ or plasma level of CK-MB $5\times$ ULN or plasma level of CK $5\times$ ULN. The CK/CK-MB enzyme levels were obtained and measured by a core laboratory for all randomized patients. Per protocol (symptomatic) graft occlusion (GO) and ST were defined as an acute coronary syndrome with confirmed occlusion within or adjacent to a previously treated graft (GO) or lesion (ST) and/or Q-wave MI in the treated vessel territory within 30 days of the index procedure. Additionally, ST was adjudicated according to the Academic Research Consortium (ARC) definitions as definite or probable and by timing of the event: acute (≤ 1 day post-procedure), subacute (2 to ≤ 30 days), late (>30 to ≤ 365 days), and very late (>365 days).[17] All MACCE, GO, and ST events were adjudicated by an independent, Clinical Events Committee which included a neurologist.

SYNTAX score

Angiograms were scored according to the SYNTAX score algorithm (www.syntaxscore.com)[12] by the Angiographic Core Laboratory (Cardialysis BV, Rotterdam, The Netherlands).

Statistical methods

Analyses were conducted using SAS System Software, Version 8.0 or higher (SAS Institute, Cary, NC, USA). Analyses of the randomized cohort were based on the intent-to-treat principle and in the registries were performed in an as-treated manner. Time-to-event rates are presented for overall 3-year data. Discrete variables are presented as counts and percentages. Differences in the time-to-event curves between the treatment groups were evaluated by a two-sided log-rank test. All tests of interaction were from a χ^2 test from a logistic regression model including the factors of interest and the interaction term. A χ^2 or Fisher's exact test was used, as appropriate, for discrete variables.

Results

The baseline clinical characteristics of the randomized treatment groups were well balanced and have previously been published with clinical outcomes up to 1 year of follow-up.[6] Over 3 years of follow-up, 45 CABG patients withdrew their consent, 12 patients were lost to follow-up and 13 patients had no 3-year clinical visit leading to complete data sets in 92.2% ($n = 827$) of patients in the CABG group. Nine PCI patients withdrew their consent, an additional three PCI patients were lost to follow-up and six patients had no 3-year clinical visit resulting in complete clinical follow-up in 98.0% ($n = 885$) of the PCI group at 3 years (*Figure 1*).

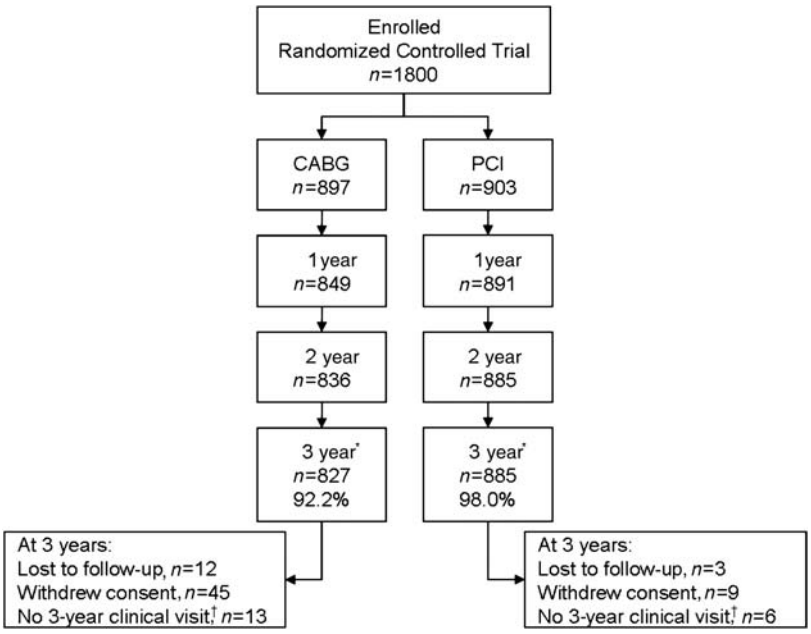

Figure 1 Patient disposition. *Patients evaluable for 3-year major adverse cardiac and cerebrovascular events. †Patients with no 3-year clinical follow-up also includes those patients whose follow-up occurred too early to meet the requirement for adequate follow-up for 3-year major adverse cardiac and cerebrovascular event determination (percutaneous coronary intervention arm $n = 2$). Patients with no 3-year clinical visit have not discontinued their participation in the trial.

Major adverse cardiac and cerebrovascular events at 3-year follow-up in the overall randomized cohort

The rates of MACCE and MACCE components through 3 years, analysed in a time-to-event manner, are presented in *Figures 2* and *3*. Total MACCE through 3 years was significantly higher in the PCI arm compared with the CABG arm (CABG 20.2% vs. PCI 28.0%; $P < 0.001$; *Figure 2A* and *3*). Increased repeat revascularization in the PCI arm was one of the drivers of the difference in MACCE rates between groups at 3 years (CABG 10.7% vs. PCI 19.7%; $P < 0.001$; *Figures 2B* and *3*). The composite safety endpoint of death/stroke/MI was not significantly different between treatment groups 3-year post-randomization (CABG 12.0% vs. PCI 14.1%; $P = 0.21$; *Figures 2C* and *3*). Death from all causes was not different between the treatment groups at 3 years (CABG 6.7% vs. PCI 8.6%; $P = 0.13$, *Figures 2D* and *3*). The cumulative rate of cardiac death was significantly higher at 3 years in the PCI arm (CABG 3.6% vs. PCI 6.0%; $P = 0.02$; *Figure 3*). At 3 years, the incidence of stroke was not significantly different between CABG- (3.4%) and PCI-treated patients (2.0%, $P = 0.07$; *Figures 2E* and *3*). The MI rate at 3 years was 3.6% in the CABG and 7.1% in the PCI cohort ($P = 0.002$; *Figures 2F* and *3*). The rate of post-procedure per protocol GO was 3.2% per patient ($n = 26$) and 1.2% per graft (25/2026) at 3 years, with six patients experiencing a documented GO between the second and third year. The 3-year post-procedure per protocol ST rate was 4.1% per patient ($n = 36$) and 1.2% per stent (45/3715) with four STs occurring more than 2 years after the index procedure. Binary rates of ARC definite/probable ST were 7.4% per patient and 1.6% per stent at 3 years with 23 patients experiencing an ST after the first year of follow-up.

At 3 years, significantly more PCI-randomized patients were receiving dual antiplatelet therapy (DAPT), aspirin therapy, or single antiplatelet therapy compared with patients in the CABG arm (*Table 1*).

Myocardial infarction

A total of 31 CABG-treated ($n = 33$ MI) and 62 PCI-treated ($n = 65$ MI) patients experienced an MI within 3 years of follow-up ($P = 0.002$). The majority of MI occurred periprocedurally in the CABG arm; 4 MIs occurred after randomization but before treatment and an additional 22 occurred within 7 days of the index procedure (see Supplementary material online, *Figure S1*). Fifteen MIs were Q-wave and 11 MIs were non-Q-wave MI (see Supplementary material online, *Figure S1*). In the PCI arm, 2 MIs occurred in patients before and 30 MIs within 7 days following the index treatment (see Supplementary material online, *Figure S1*). The MIs $\geq$7 days after the index procedure in the PCI arm were distributed evenly through the 3 years of follow-up; 13 MIs occurred in the first year of follow-up and 10 MIs occurred in both the second and third year of follow-up. Approximately half of the MIs in the PCI arm were non-Q-wave MI (33/65; see Supplementary material online, *Figure S1*).

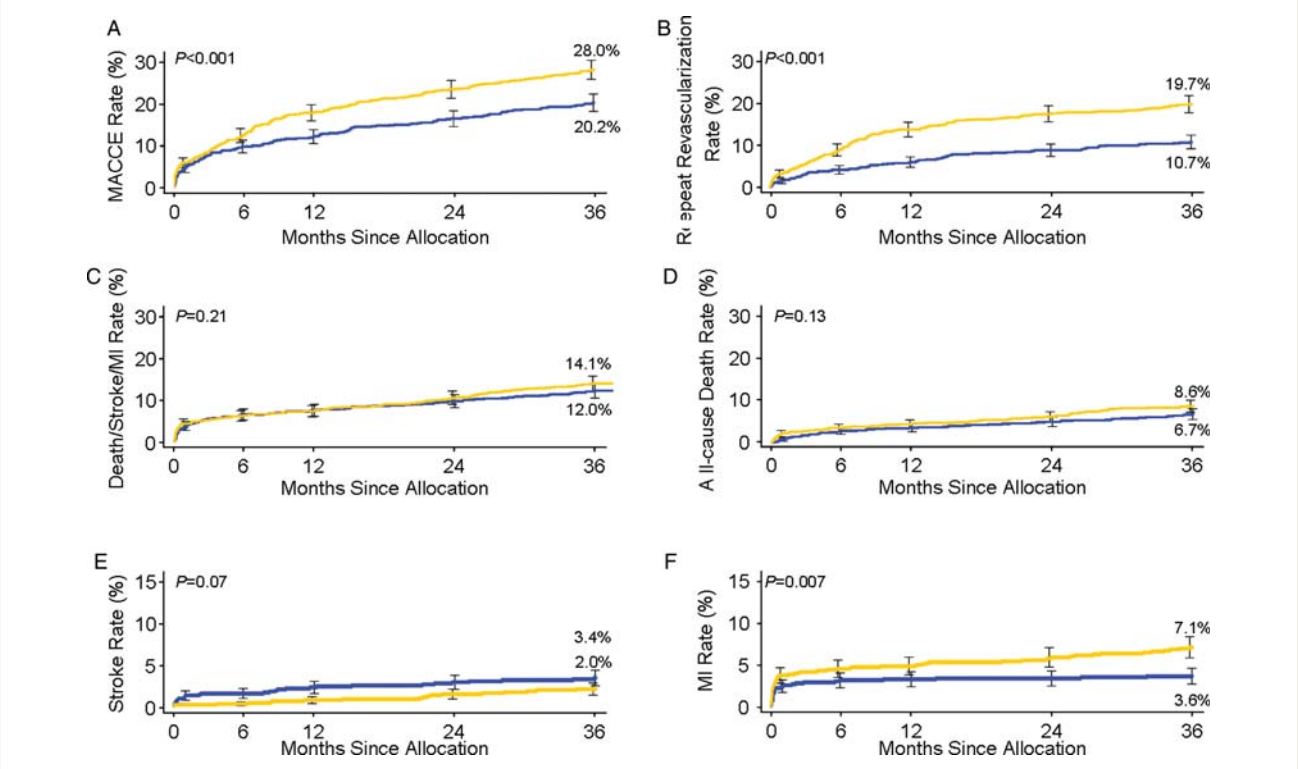

Figure 2 Rates of clinical outcomes among randomized treatment groups. Time-to-event curves in patients treated with coronary artery bypass grafting (blue line) or percutaneous coronary intervention (yellow line) for the composite of major adverse cardiac and cerebrovascular events (*A*), repeat revascularization (*B*), death/stroke/myocardial infarction (*C*), all-cause death (*D*), stroke (*E*), and myocardial infarction (*F*) to 3 years. *P*-values from log-rank test.

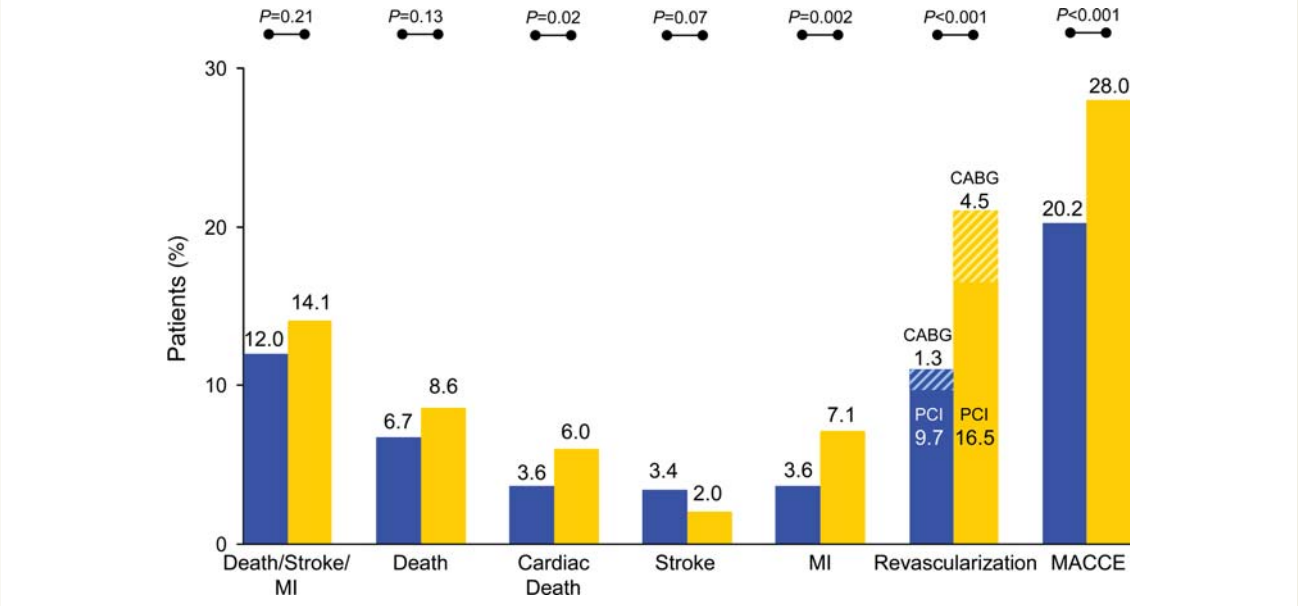

Figure 3 Rates of clinical outcomes among randomized treatment groups. Three-year clinical outcomes in coronary artery bypass grafting (blue bars) or percutaneous coronary intervention (yellow bars). Repeat revascularization is broken down into repeat percutaneous coronary intervention (yellow or blue bars) and repeat coronary artery bypass grafting (striped yellow or blue bars). The Kaplan–Meier event rates, *P*-value from log-rank test.

Table 1 Cardiac-related medications at 3-year follow-up

Medication type	CABG[a]	PCI[a]	*P*-value[b]
Any cardiac-related medication (%)	99.3 (745/750)	99.6 (795/798)	0.49
Dual antiplatelet therapy (aspirin and antiplatelet) (%)	8.5 (64/750)	32.8 (262/798)	<0.001
Aspirin alone	83.3 (625/750)	87.5 (698/798)	0.02
Antiplatelet alone, any	16.3 (122/750)	41.7 (333/798)	<0.001
Thienopyridine antiplatelet alone	12.4 (93/750)	36.6 (292/798)	<0.001
Other antiplatelet medications (%)	4.0 (30/750)	5.6 (45/798)	0.13
Coumadin derivatives (%)	6.8 (51/750)	3.6 (29/798)	0.005
Statin therapy (%)	85.5 (641/750)	86.6 (691/798)	0.52
β-Blockers (%)	77.2 (579/750)	77.2 (616/798)	0.99
ACE-inhibitors (%)	52.5 (394/750)	52.4 (418/798)	0.95
Calcium channel blockers (%)	22.7 (170/750)	25.7 (205/798)	0.17
Angiotensin II receptor antagonists (%)	19.2 (144/750)	21.1 (168/798)	0.36
Anti-arrhythmics (amiodarone) (%)	2.5 (19/750)	0.8 (6/798)	0.006
H2 receptor blockers (%)	12.3 (92/750)	13.4 (107/798)	0.50

[a]Values based on an intent-to-treat analysis.
[b]Binary rates *P*-value from χ^2 test.

Graft occlusion and stent thrombosis

In the CABG arm, MI was a consequence of GO in 6 of 26 CABG-randomized GO patients; each was successfully revascularized. The majority of GO patients in the CABG arm did not experience an MI but did require repeat revascularization (17/26). No events occurred after the GO in three patients. In the PCI arm, 10 of 36 ST patients experienced a fatal MI and 1 patient died after an emergency re-CABG. Eleven patients experienced an MI related to the ST and were successfully revascularized. Fourteen patients (of 36) received revascularization after the ST in the PCI arm. Of the nine patients who experienced a very late ST (>1 year) in the PCI arm, five were receiving DAPT while four were taking aspirin alone. In patients receiving aspirin therapy alone, clopidogrel had been discontinued in two patients 2–4 weeks prior to the ST.

Subgroup analyses

The a priori statistical method was a closed hierarchical testing procedure comparing the overall randomized patient population (including patients with either LM and/or 3VD) first with the 3VD and LM subgroups being compared subsequently only if non-inferiority was concluded for the overall comparison. As non-inferiority was not shown in the overall cohort, specific information for each subgroup should be considered observational and hypothesis-generating only. The 3-year death/stroke/MI, repeat revascularization, and MACCE rates are shown separately for the pre-specified 3VD, LM, and diabetic subgroups of the randomized cohort (*Figure 4*).

There were no significant interactions between LM/3VD status and treatment group for 3-year MACCE or any of the components; the treatment effect of PCI compared with CABG was not significantly different between patients with LM or 3VD. Patients with 3VD treated with PCI experienced significantly more MACCE events, including increased repeat revascularization and combined death/stroke/MI, than those in the CABG arm (*Figure 4A*). Overall mortality (9.5 vs. 5.7%, $P = 0.02$) and cardiac death were significantly increased in 3VD patients treated with PCI (6.2 vs. 2.9%, $P = 0.01$). In the LM cohort, the rates of MACCE and death/stroke/MI were not significantly different in PCI- and CABG-treated patients. The 3-year rate of repeat revascularization was increased in PCI-treated LM patients (*Figure 4B*). There was no difference in all-cause or cardiac death rates in CABG- or PCI-treated patients with LM disease (all-cause: CABG 8.4% vs. PCI 7.3%, $P = 0.64$; cardiac death 4.6 vs. 5.7%, $P = 0.48$). There were no significant interactions observed for the diabetic status and treatment group for 3-year MACCE or any of the components; the treatment effect of PCI compared with CABG was not different based on the diabetic status. The presence of diabetes was associated with increased rates of repeat revascularization and, consequently, MACCE in the PCI arm without increasing the rates of death/stroke/MI over 3 years of follow-up (*Figure 4*). Cardiac death was not significantly different between treatment groups in the subset of diabetic patients (4.8 vs. 8.8%, $P = 0.10$).

Impact of lesion complexity on clinical outcomes

The impact of lesion complexity on clinical outcomes was assessed by examining 3-year patient outcomes relative to their SYNTAX score (*Figure 5*). There was a significant interaction between the SYNTAX score tercile and treatment group for the 3-year outcomes of MACCE, death/stroke/MI, and death ($P = 0.025$, 0.088, and 0.084, respectively). The rates of MACCE and the individual MACCE components were not significantly different in patients with low SYNTAX scores (≤22) treated with either PCI or CABG (*Figure 5A*). In patients with intermediate SYNTAX scores

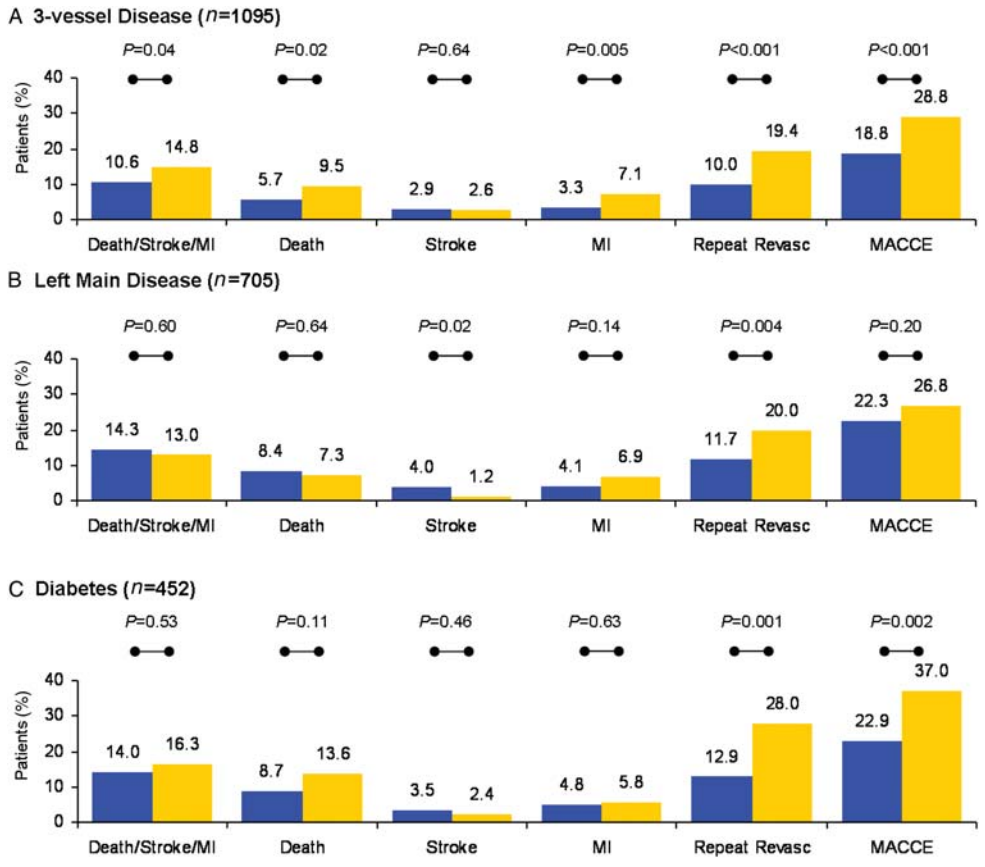

Figure 4 Three-year clinical outcomes according to the treatment group in patients with three-vessel disease, left main disease, or diabetes—death/stroke/myocardial infarction, all-cause death, stroke, myocardial infarction, repeat revascularization (repeat revasc), and major adverse cardiac and cerebrovascular event rates at 3 years in coronary artery bypass grafting (blue bars) or percutaneous coronary intervention-treated (yellow bars) patients with three-vessel (*A*) or left main (*B*) disease or diabetes (*C*). *P*-value from log-rank test.

(23–32), repeat revascularization rates were significantly higher in PCI-treated patients (CABG 10.1% vs. PCI 17.4%, $P = 0.01$), as were MI and MACCE rates (MI: CABG 3.2% vs. PCI 7.6%, $P = 0.02$; MACCE: 18.9 vs. 27.4%, $P = 0.02$; *Figure 5B*). In patients with the most complex anatomical disease (those with SYNTAX scores ≥33), MACCE and its components, apart from stroke, were significantly higher in patients treated with PCI (MACCE: CABG 19.5% vs. PCI 34.1%, $P < 0.001$, *Figure 5C*).

The three-way interaction between the treatment group, LM/3VD status, and SYNTAX score tercile was assessed for 3-year MACCE and components; there were no significant three-way interactions observed.

Patients with 3VD with SYNTAX scores in the lowest tercile exhibited similar MACCE rates between treatment arms (CABG 22.2% vs. PCI 25.8%, $P = 0.45$, *Figure 5D*). In those 3VD patients with intermediate or high SYNTAX scores, the rate of MACCE was significantly increased in favour of CABG (23–32: CABG 16.8% vs. PCI 29.4%, $P = 0.003$; ≥33: CABG 17.9% vs. PCI 31.4%, $P = 0.004$; *Figure 5E* and *F*). Myocardial infarction was significantly higher in the PCI arm of the 3VD intermediate SYNTAX score tercile (3.1 vs. 8.9%, $P = 0.01$). In 3VD patients with SYNTAX score ≥33, mortality (CABG 4.5% vs. PCI 11.1%, $P = 0.03$) and MI (1.9 vs. 7.2%, $P = 0.02$) were significantly higher in the PCI arm.

Major adverse cardiac and cerebrovascular event rates were not significantly different in patients with LM disease who had low or intermediate SYNTAX scores (0–22: CABG 23.0% vs. PCI 18.0%, $P = 0.33$; 23–32: CABG 23.4% vs. PCI 23.4%, $P = 0.90$; *Figure 5G* and *H*). In LM patients with the most complex anatomy (SYNTAX score ≥33), MACCE was significantly increased in PCI-treated patients (CABG 21.2% vs. PCI 37.3%, $P = 0.003$, *Figure 5I*) as was repeat revascularization (9.2 vs. 27.7%, $P < 0.001$). It is of note that the distribution of LM patients with concurrent 3VD was greatest in the 'high' SYNTAX score group in the overall patient population. Additionally, an increased proportion of distal LM lesions were found in the patients with 'high' SYNTAX scores compared with patients in the low and intermediate terciles.

Discussion

Similar to 1-year outcomes in SYNTAX, 3-year MACCE rates were significantly higher in the PCI arm compared with CABG-treated patients. At 3 years, the rate of MI in the PCI arm was significantly

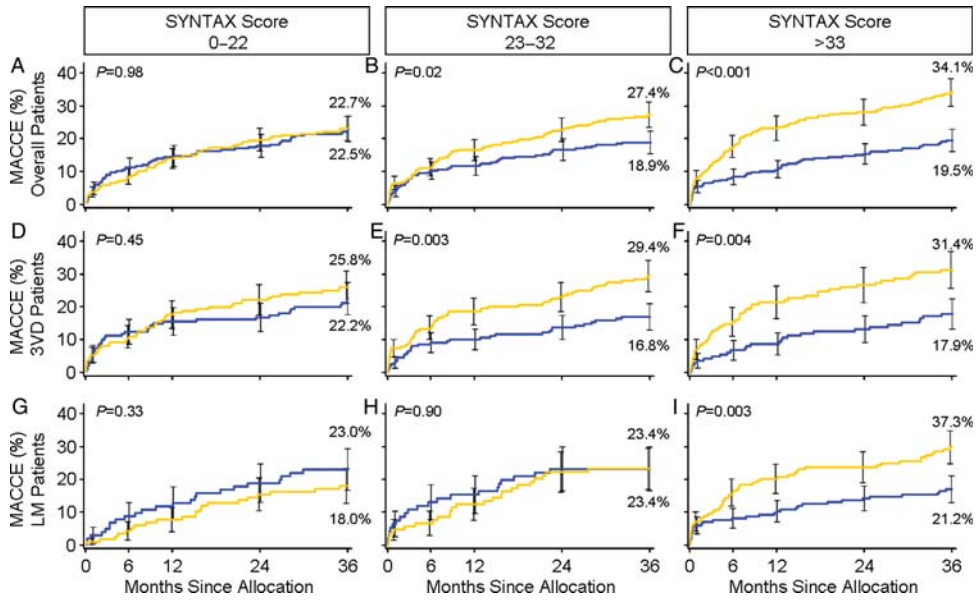

Figure 5 Major adverse cardiac and cerebrovascular event rates according to the subset, treatment group, and SYNTAX score category. Time-to-event curves in the coronary artery bypass grafting (blue line) or percutaneous coronary intervention (yellow line) overall cohorts to 3 years according to the low (0–22, *A*), intermediate (23–32, *B*), or high (≥33, *C*) SYNTAX scores. (*D*–*F*) Major adverse cardiac and cerebrovascular events in three-vessel disease patients with low, intermediate, or high SYNTAX scores, respectively. (*G*–*I*) Major adverse cardiac and cerebrovascular events in patients with left main disease with low, intermediate, or high SYNTAX scores. *P*-value from log-rank test.

increased compared with CABG patients and the difference in stroke rate between treatment arms was not significantly different unlike the outcomes after 1 year of follow-up. SYNTAX patients in the randomized cohort will continue to be followed for 5 years.

The trends in MACCE, death/stroke/MI, all-cause death, and repeat revascularization rates in the overall patient population seen in the first year of follow-up continued through the second and third year, although fewer total events occurred during each additional year of follow-up. Compared with outcomes after 1 year of follow-up, cardiac death was found to be significantly increased in the overall PCI-treated patient population, chiefly in those patients with higher SYNTAX scores at 3 years. The majority of cardiac deaths occurred within the first year of follow-up in both arms; ~40% occurred during the second and third year of follow-up. This difference was cumulative as the interval rates of cardiac death were not significant. Although stroke was significantly increased at 1 year of follow-up for CABG, no difference in stroke was seen during the interval of 1- and 3-year follow-up.

A difference in the MI rate between the two treatment groups was also noted after the report of the first year of follow-up. Two-thirds and one-half of all MIs were periprocedural (occurring within 7 days of the index procedure) in the surgical and PCI cohorts, respectively. The likely cause of the increased MIs in the PCI arm was due to restenosis/further revascularization in these patients with advanced diffuse disease or ST. When compared with CABG patients, MI rates were higher in the 3VD PCI group and not significantly different in the LM PCI cohort.

The clinical consequences of ST were more serious than for patients whose graft occluded. This may be due to the redundancy of patent native arteries available, the presence of collateral vessels in patients undergoing CABG which can be recruited during the process of progressive GO, and to GO being more likely to occur in patients with small target-vessel diameter.[18] The very late ST rate in SYNTAX was higher than in previous studies.[15,19] However, the lesion complexity and, consequently, the average number of stents implanted (4.6 stents per patient) and the average total stented length (86.1 mm) were higher than any other contemporary DES vs. CABG study.[6]

Overall MACCE rates were not significantly different in the pre-specified LM subgroup at 3 years. More PCI patients required reintervention compared with CABG-treated patients between these groups. The current US and European revascularization guidelines assign CABG a IA indication in most patients with 1, 2, or 3VD with low, intermediate, or high SYNTAX scores.[4,20] However, due to positive outcomes from other recent studies of LM patients, these guidelines have upgraded the indication for PCI in the LM artery from a Class III to a Class IIb (ACC/AHA)[4,20] and a Class IIb C to IIa B (ESC-EACTS)[3] indication in patients with isolated LM (ostial or trunk) and with associated 1VD. Additionally, the ESC-EACTS guidelines have also included the treatment of patients with 3VD and low SYNTAX scores as a Class IIa B indication.[3]

Both the presence of multivessel disease and diabetes are known to increase the risks associated with cardiovascular disease. In both of these subgroups, similar to the outcomes

after 1 year of follow-up, the increase in MACCE and revascularization rates was maintained in PCI-treated patients.[6,8,21] Results from the FREEDOM (Future Revascularization Evaluation in Patients with Diabetes Mellitus: Optimal Management of Multivessel Disease)[22] and EXCEL (Evaluation of Xience Prime vs. Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization) trials may provide further insight into the optimal treatment for multivessel, diabetic, and LM patients. Particularly, the impact of newer generation stents or stent platforms and the continued improvements in stenting technique will be seen in these trials.

Stratification of the randomized patient population into terciles derived from the baseline anatomical SYNTAX score confirmed the trends in MACCE rates that were found after 1 year of follow-up. Specifically, an intermediate (23–32) or high SYNTAX score (>33) was correlated with an increase in 3-year MACCE rates after percutaneous revascularization compared with surgery. Repeat revascularization, MI, and mortality were significantly higher in 3VD patients with the highest SYNTAX score. Thus, CABG remains the standard for more complex anatomy, whereas PCI in this trial demonstrated similar outcomes to CABG in patients with less complex disease, measured by lower SYNTAX score for 3VD and lower and intermediate scores for LM disease. The SYNTAX score has been successfully applied to other patient groups retrospectively and has shown value in predicting or correlating high anatomical complexity with increased adverse cardiac events making it an effective risk assessment tool.[23–27]

In the SYNTAX trial at 1 year, a significant difference in secondary prevention medical therapy was observed; patients in the surgical cohort were less likely to receive aspirin, thienopyridines, or statins compared with PCI patients. At 3 years, antiplatelet treatment was significantly different between the two treatment arms; patients in the CABG arm were significantly undertreated with single or DAPT than patients in the PCI arm.

Revascularization of all lesions identified at the heart team conference was required to meet the definition of complete revascularization. An anatomic definition of revascularization was used (treatment of lesions with reference diameter >1.5 mm, stenosis ≥50%) when compared with a functional classification (by fractional flow reserve testing). The rates of complete revascularization were 63 and 57% ($P = 0.005$) in the CABG and PCI arms, respectively.[6,13] The rate of complete revascularization in surgically treated patients was low compared with other studies in the literature, in part, due to differing definitions.[16,28,29] In the SYNTAX study, the investigators had to indicate which vessels they intended to graft or stent before actual treatment took place. Comparison with the treatment report revealed whether complete or incomplete revascularization was performed; this is in contrast to other studies where the operators indicated themselves whether they had performed a complete revascularization after the treatment had taken place.

The period of enrolment and index revascularization in SYNTAX occurred during a time of evolving strategies regarding complete revascularization in PCI. The results of FAME and other studies have shown that only those haemodynamically relevant stenoses should be treated unless symptoms of residual myocardial ischaemia arise requiring intervention upon non-culprit vessels.[30,31] Clinical outcomes may differ according to the completeness of revascularization.[32]

Study limitations

The SYNTAX trial was designed to overcome many limitations of previous comparisons of PCI and CABG. In spite of this, there is inadequate statistical power to detect differences in low-frequency events (e.g. stroke, MI) between arms. Additionally, analyses of the LM and 3VD subgroups, although sufficiently powered, can only be considered hypothesis-generating as SYNTAX did not meet its primary endpoint. The analyses of LM or 3VD patients by SYNTAX score were not pre-specified and should be considered exploratory and hypothesis-generating only. A larger number of patients withdrew from the CABG arm post-allocation ($n = 45$) than the PCI arm ($n = 9$), suggesting greater concern on the part of some patients to submit to the more invasive procedure. Sensitivity analyses suggest that the outcomes could have been influenced by non-evaluable patients if they all died. This is unlikely as a total of 57/827 CABG and 77/885 PCI patients who were evaluable died within 3 years of follow-up. The effect of this imbalance was minimized by including all data available up to the point of withdrawal (or lost to follow-up) were included in the analysis set and outcomes were analysed in an intent-to-treat manner. Details related to medical therapy were collected only at 1 and 3 years. Data regarding medical therapy at other intervals is lacking. Finally, the intermediate short (3-year) follow-up time may not provide an accurate estimate of long-term differences in outcomes between the two revascularization methods.

Conclusions

At 3 years, MACCE was increased in PCI patients compared with CABG; no difference was observed in the combined safety endpoint of death, MI, and stroke. Analysis of pre-specified subgroups suggests that for 3VD patients, MACCE, mortality, and the combined safety endpoint of death, MI, and stroke were increased with PCI, whereas for patients with LM disease, there were no significant differences in these outcomes with PCI. In relation to anatomical complexity, patients with less complex coronary anatomy (low SYNTAX scores in 3VD patients or low/intermediate SYNTAX scores in LM patients), PCI can be an acceptable alternative treatment option to CABG. Patients with more complex disease (3VD patients with intermediate/high SYNTAX scores and LM patients with high scores) have an increased risk of an MACCE event with PCI and CABG is the preferred treatment option.

Supplementary material

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

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CARDIOVASCULAR FLASHLIGHT

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Right heart complications of ventriculoatrial shunt

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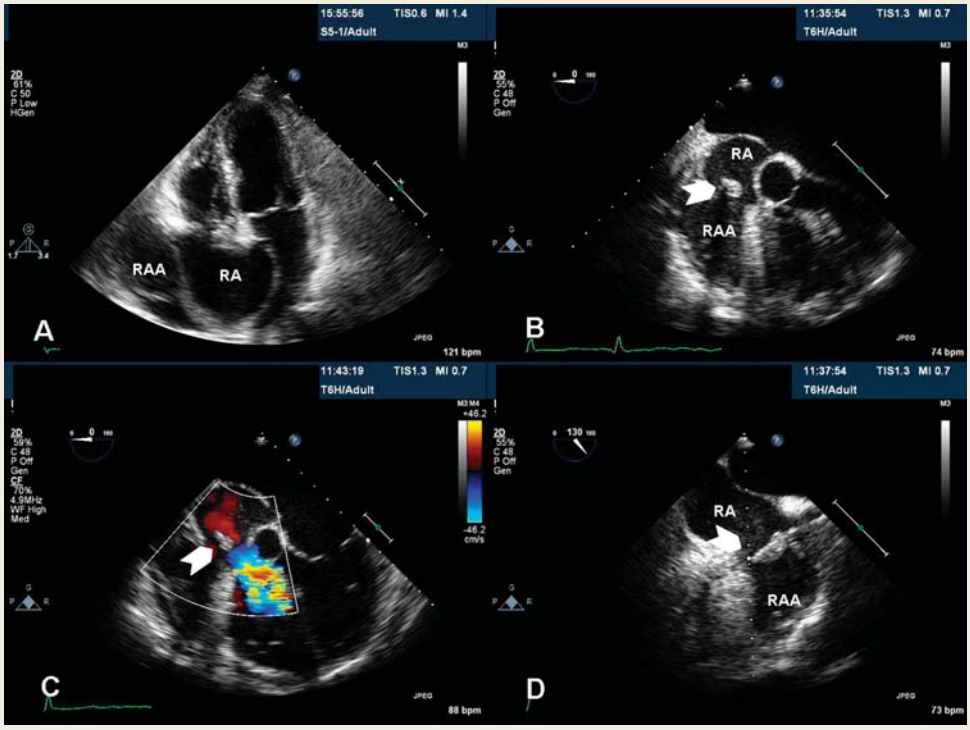

A 57-year-old male patient was treated in the intensive therapy unit for pneumonia and new-onset atrial fibrillation. He had a ventriculoatrial (VA) shunt since childhood which was placed for hydrocephalus. He had no other medical problems and had been lost to follow-up. Transthoracic echocardiography (*Panel A*) revealed significant calcific tricuspid stenosis, a dilated right atrium (RA), an unusually large right atrial appendage (RAA), and an aneurysmal interatrial septum. Subsequent transoesophageal echocardiography (*Panels B–D*) confirmed severe tricuspid stenosis with a mean gradient of 5 mmHg and turbulent transvalvular Doppler flow (*Panel C*). Furthermore, a mobile mass was noted at the tip of the VA shunt (*Panels B–D*, arrow) that was best visualized on the bicaval view (*Panel D*, arrow). This was most likely the result of an inflammatory response and thrombus. There was minimal tricuspid regurgitation and no pulmonary hypertension. Blood and urine cultures proved negative and empirical antibiotic therapy was given for 2 weeks. The patient made a good recovery and was discharged with anticoagulation and beta-blockers. At 6-monthly follow-up, he was found to be asymptomatic. Right heart complications can occur years after VA shunt placement. If symptomatic tricuspid stenosis develops, percutaneous valvuloplasty or surgical valve replacement should be considered. Surveillance of patients with VA shunts is currently poorly defined. There is also a paucity of published literature regarding the same. Our case illustrates the need for long-term clinical and echocardiographic follow-up in patients with VA shunts.