

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



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Summary

Background We report the 5-year results of the SYNTAX trial, which compared coronary artery bypass graft surgery (CABG) with percutaneous coronary intervention (PCI) for the treatment of patients with left main coronary disease or three-vessel disease, to confirm findings at 1 and 3 years.

Methods The randomised, clinical SYNTAX trial with nested registries took place in 85 centres in the USA and Europe. A cardiac surgeon and interventional cardiologist at each centre assessed consecutive patients with de-novo three-vessel disease or left main coronary disease to determine suitability for study treatments. Eligible patients suitable for either treatment were randomly assigned (1:1) by an interactive voice response system to either PCI with a first-generation paclitaxel-eluting stent or to CABG. Patients suitable for only one treatment option were entered into either the PCI-only or CABG-only registries. We analysed a composite rate of major adverse cardiac and cerebrovascular events (MACCE) at 5-year follow-up by Kaplan-Meier analysis on an intention-to-treat basis. This study is registered with ClinicalTrials.gov, number NCT00114972.

Findings 1800 patients were randomly assigned to CABG (n=897) or PCI (n=903). More patients who were assigned to CABG withdrew consent than did those assigned to PCI (50 vs 11). After 5 years' follow-up, Kaplan-Meier estimates of MACCE were 26.9% in the CABG group and 37.3% in the PCI group ($p<0.0001$). Estimates of myocardial infarction (3.8% in the CABG group vs 9.7% in the PCI group; $p<0.0001$) and repeat revascularisation (13.7% vs 25.9%; $p<0.0001$) were significantly increased with PCI versus CABG. All-cause death (11.4% in the CABG group vs 13.9% in the PCI group; $p=0.10$) and stroke (3.7% vs 2.4%; $p=0.09$) were not significantly different between groups. 28.6% of patients in the CABG group with low SYNTAX scores had MACCE versus 32.1% of patients in the PCI group ($p=0.43$) and 31.0% in the CABG group with left main coronary disease had MACCE versus 36.9% in the PCI group ($p=0.12$); however, in patients with intermediate or high SYNTAX scores, MACCE was significantly increased with PCI (intermediate score, 25.8% of the CABG group vs 36.0% of the PCI group; $p=0.008$; high score, 26.8% vs 44.0%; $p<0.0001$).

Interpretation CABG should remain the standard of care for patients with complex lesions (high or intermediate SYNTAX scores). For patients with less complex disease (low SYNTAX scores) or left main coronary disease (low or intermediate SYNTAX scores), PCI is an acceptable alternative. All patients with complex multivessel coronary artery disease should be reviewed and discussed by both a cardiac surgeon and interventional cardiologist to reach consensus on optimum treatment.

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Introduction

Coronary artery bypass graft surgery (CABG) has been the standard of care for revascularisation of patients with complex coronary artery disease since its introduction in 1968.¹ When percutaneous coronary intervention (PCI) was introduced in 1977,² it was thought to be appropriate only for patients with single-vessel disease, but as operator ability and device technologies have advanced, the use of PCI has expanded to treat patients with increasingly complex disease, such as multivessel and left main coronary disease.

The optimum method for revascularisation of these patients has been a matter of debate, with many published trials comparing outcomes of CABG and PCI with drug-eluting stents (DES).³⁻¹³ Most of these trials have been limited by non-randomised patient selection, inclusion of less complex disease, or insufficient statistical power. The SYNERGY between percutaneous coronary intervention with TAXUS and cardiac surgery (SYNTAX) trial¹⁴ assessed the optimum revascularisation treatment for patients with de-novo left main coronary disease or three-vessel disease (or both), by randomly assigning patients to either PCI with a first-generation

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paclitaxel-eluting stent or CABG. For the primary endpoint of major adverse cardiac and cerebrovascular events (MACCE) at 1 year, PCI did not meet the goal of non-inferiority compared with CABG, because the PCI group had a significantly higher rate of repeat revascularisation than did the CABG group.¹⁵ Rates of death and myocardial infarction were similar between the two groups, and stroke was significantly increased in the CABG group compared with the PCI group. At 3 years, rates of MACCE, myocardial infarction, and repeat revascularisation were significantly higher in the PCI group than in the CABG group, whereas rates of the composite safety endpoint of death or stroke or myocardial infarction, and stroke alone, were not significantly different between treatment groups.¹⁶

Here we present the final results of the SYNTAX trial after 5 years of follow-up, with the aim to confirm the 1-year and 3-year findings.

Methods

Study design and patients

The design and methods for this trial have been previously described^{14–16} and are briefly summarised here. SYNTAX was a randomised clinical trial with nested registries that took place in 85 centres in the USA and Europe. A heart team, consisting of a cardiac surgeon and interventional cardiologist, at each centre screened consecutive patients with de-novo three-vessel disease or left main coronary disease or both. If regarded as equally suitable for revascularisation with either treatment, patients were randomly assigned to a treatment group. Patients suitable only for PCI were entered into the PCI registry and those suitable only for CABG were entered into the CABG registry. Patients who had previously undergone PCI or CABG, had persisting acute myocardial infarction, or needed concomitant cardiac surgery were excluded. This study was done in accordance with the principles of the Declaration of Helsinki, and all site-specific institutional review boards and applicable regulatory agencies approved the study protocol before study initiation. All patients provided written informed consent before enrolment.

Randomisation

Eligible patients were randomly assigned (1:1) to either PCI with a first-generation paclitaxel-eluting stent (TAXUS Express, Boston Scientific, Natick, MA, USA) or to CABG. Details of who generated the allocation sequence have been published previously.¹⁴ Randomisation occurred via a central interactive voice response system in random block sizes per site on the basis of the presence or absence of left main coronary disease and medically treated diabetes mellitus. Patients and physicians were aware of treatment assignment.

Procedures

Procedures were done according to routine local clinical practice with the intention of achieving complete

revascularisation irrespective of treatment allocation. The paclitaxel-eluting stent was inserted via the femoral, brachial, or radial approach, and staged procedures were permitted if done within 72 h of the initial procedure and during the same hospital stay. All patients who underwent PCI were given a thienopyridine after the procedure for a minimum of 6 months, with aspirin recommended indefinitely. CABG procedures could be done with or without extracorporeal circulation, and use of arterial conduits was encouraged. Minimally invasive direct CABG was not permitted in the randomised cohort. Optimum medical treatment according to American College of Cardiology and American Heart Association treatment guidelines¹⁷ was strongly recommended for all patients.

The primary endpoint of the SYNTAX trial was the composite rate of MACCE at 1 year, defined as all-cause mortality, stroke, myocardial infarction, and repeat revascularisation. Secondary endpoints included MACCE rates at 1 month, 6 months, 3 years, and 5 years, rates of the individual MACCE components, and rates of stent thrombosis or graft occlusion. An independent clinical events committee adjudicated all primary clinical events, and patient safety was assessed at prespecified intervals by an independent data monitoring committee. Patients were scored for anatomic complexity using the SYNTAX score (introduced by the SYNTAX trial as a means to assess and standardise lesion complexity and predict outcomes following revascularisation) by the heart team before randomisation.

Statistical analysis

We defined 5-year outcomes as events occurring within 1825 days for time-to-event analyses and 1855 days after the procedure (1825 days plus protocol-defined 30-day window) for binary analyses. We calculated cumulative event rates using Kaplan-Meier estimates with a log-rank *p* value. Hazard ratios and 95% CIs are from Cox's partial likelihood method. To identify the effect of patient withdrawal on the results at 5 years, we did a sensitivity analysis. We have expressed binary variables as number (%) and continuous variables as mean (SD). We made statistical comparisons for binary analyses using the χ^2 or Fisher's exact test, as appropriate. We did all statistical analyses with SAS (version 9 or higher). We did all analyses in the randomised cohort on an intention-to-treat basis. We analysed the PCI-only and CABG-only registries per protocol.

We predefined three analytic subsets: patients with left main coronary disease (with or without additional vessel involvement), those with three-vessel disease in the absence of left main coronary disease, and those with diabetes. The statistical design of the SYNTAX trial specified a hierarchical approach that allowed comparison of the predefined subgroups only if the overall primary endpoint of non-inferiority was met. Since non-inferiority was not met at the primary endpoint, results from

For more on the SYNTAX score see www.syntaxscore.com

subsets in this analysis should be regarded as observational and hypothesis-generating only.

This study is registered with ClinicalTrials.gov, number NCT00114972.

Role of the funding source

The SYNTAX trial design and conduct was overseen by the SYNTAX steering committee, on which representatives of the sponsor served. The study sponsor was responsible for data collection and verification, with oversight from independent clinical event and data monitoring committees. All members of the steering committee had full access to all the study data, participated in the analysis and interpretation of the data, and reviewed and approved the final version of the manuscript. The corresponding author had final responsibility for the decision to submit for publication.

Results

Of 1800 patients enrolled in the randomised cohort, 897 were assigned to CABG and 903 to PCI. 805 (89.7%) patients in the CABG group and 871 (96.5%) in the PCI group completed 5 years' follow-up (figure 1). After randomisation, more patients who were assigned CABG withdrew consent than did those assigned to PCI (50 patients in the CABG group vs 11 in the PCI group); of those who withdrew consent, 21 patients assigned to CABG and two assigned to PCI did so before receiving treatment.

Patient baseline and lesion characteristics have been previously described;¹⁵ in brief, the mean age of patients in the randomised cohort was 65.0 years (SD 9.8) in the CABG group and 65.2 years (9.7) in the PCI group, 708 (78.9%) patients in the CABG group and 690 (76.4%) in the PCI group were male, and 221 (24.6%) in the CABG group versus 231 (25.6%) in the PCI group had medically treated diabetes, of whom 93 (10.4%) and 89 (9.9%), respectively, needed insulin. The mean average baseline SYNTAX score was 29.1 (SD 11.4) in the CABG group and 28.4 (11.5) in the PCI group, with a mean of more than four clinically significant coronary lesions treated per patient (4.4 [SD 1.8] lesions in the CABG group vs 4.3 [1.8] lesions in the PCI group).

Antiplatelet drug use was significantly higher in patients in the PCI group compared with those in the CABG group throughout the first year of follow-up (appendix). At 5 years, however, the proportion of patients who received acetylsalicylic acid (out of those for whom we had data) did not differ significantly between groups (588 [85.0%] of 692 patients in the CABG group vs 642 [87.1%] of 737 patients in the PCI group; $p=0.24$), although significantly more patients in the PCI group were receiving dual antiplatelet therapy than those in the CABG group (63 [9.1%] of 692 vs 202 [27.4%] of 737; $p<0.0001$), mainly because of a higher rate of thienopyridine use in patients assigned to PCI (84 [12.1%] of 692 vs 236 [32.0%] of 737; $p<0.0001$; appendix).

At 5 years' follow-up, Kaplan-Meier estimates of MACCE rates were 26.9% for the CABG group versus 37.3% in the PCI group ($p<0.0001$). The rates of myocardial infarction, the combination of death or stroke or myocardial infarction, and repeat revascularisation were significantly higher in patients who were assigned PCI than in those who were assigned CABG (figure 2). The rates of all-cause mortality and stroke, however, were not significantly different between groups (figure 2). The Kaplan-Meier estimate of cardiac death was significantly higher in the PCI group compared with the CABG group at 5 years (5.3% in the CABG group vs 9.0% in the PCI group; $p=0.003$). At 5 years, 4.0% of the CABG group had stent thrombosis or graft occlusion compared with 5.5% of the PCI group. Clinical events after stent thrombosis or graft occlusion are presented in the appendix. Of 32 patients in the CABG group with stent thrombosis or graft occlusion, 21 (66%) had subsequent repeat revascularisation, and seven (22%) had myocardial infarction. Of 47 patients in the PCI group with stent thrombosis or graft occlusion, the proportions of patients with subsequent repeat revascularisation and myocardial infarction were nearly identical (16 [34%] and 17 [36%], respectively), with 14 (30%) having cardiac-related death. Our sensitivity analysis of the different rates of patient withdrawal on results at 5 years showed that MACCE rates were significantly higher in the PCI group than in the CABG group, irrespective of whether all non-assessable patients were thought to be dead, or alive and event-free (appendix).

At 5 years, Kaplan-Meier estimates of the proportion of patients in the left main coronary disease subgroup with

See Online for appendix

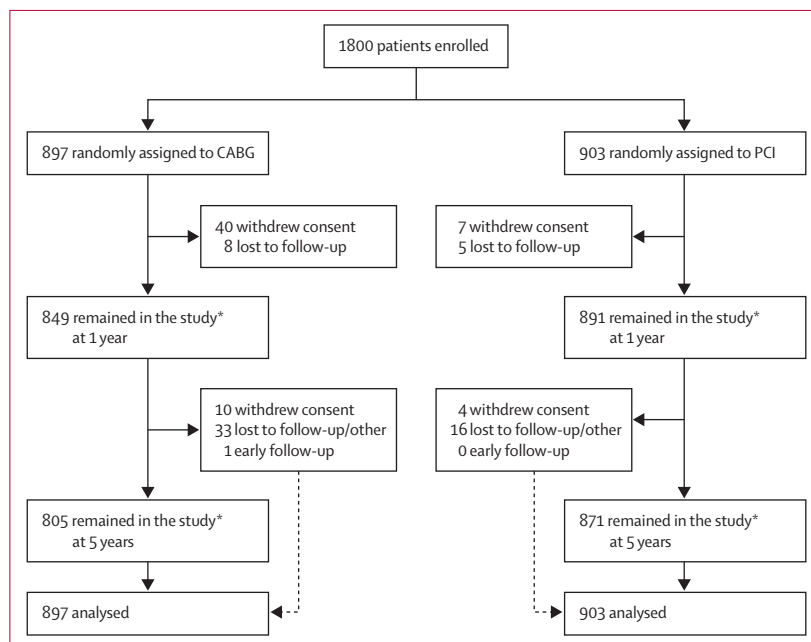


Figure 1: Patient distribution through the SYNTAX trial at 5 years' follow-up

*Enrolled patients who had not withdrawn from the trial who had either completed follow-up within the protocol-specified timeframe or were confirmed dead.

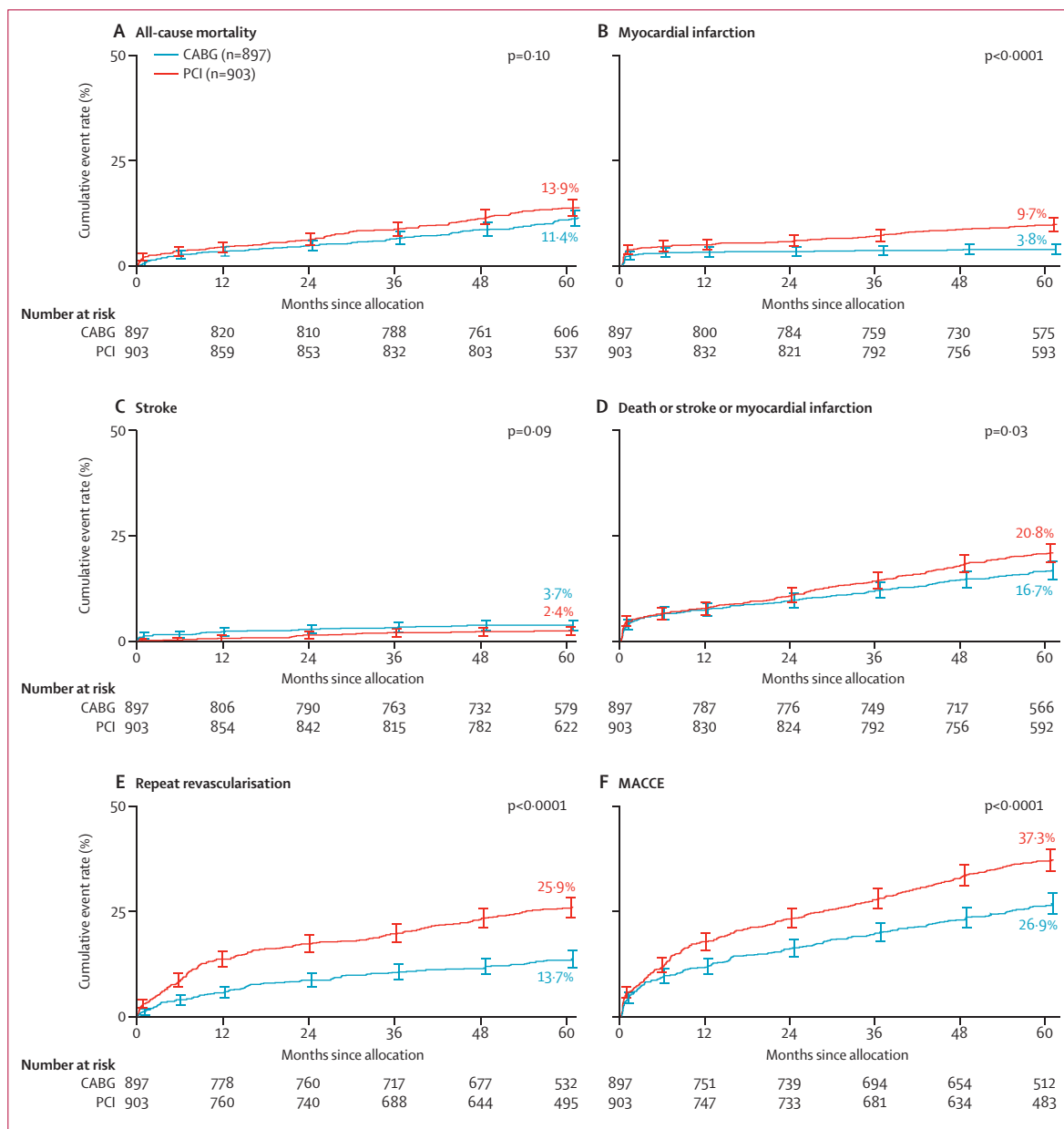


Figure 2: Kaplan-Meier cumulative event curves at 5 years' follow-up
 CABG=coronary artery bypass graft surgery. PCI=percutaneous coronary intervention. MACCE=major adverse cardiac and cerebrovascular events.

MACCE did not significantly differ between treatment groups (31.0% in the CABG group vs 36.9% in the PCI group; p=0.12). By contrast, in the three-vessel disease subgroup, Kaplan-Meier estimates of MACCE rates were more than 50% higher at 5 years in patients assigned to PCI than in those assigned to CABG (24.2% in the CABG group vs 37.5% in the PCI group; p<0.0001). The interaction test for treatment group (CABG or PCI) by left main or three-vessel disease status yielded a p value of 0.10 for MACCE at 5 years. In patients with medically treated diabetes, MACCE rates at 5 years were

significantly higher in those in the PCI group than in those in the CABG group (29.0% in the CABG group vs 46.5% in the PCI group; p=0.0002), with numbers increased in both groups compared with the overall population. The p value for interaction of treatment group by diabetes status was 0.17 for MACCE at 5 years. MACCE rates at 5 years in patients with low SYNTAX scores at baseline did not differ significantly between treatment groups (figure 3A); however, in patients with intermediate or high SYNTAX scores, patients assigned to CABG had significantly lower MACCE rates at 5 years

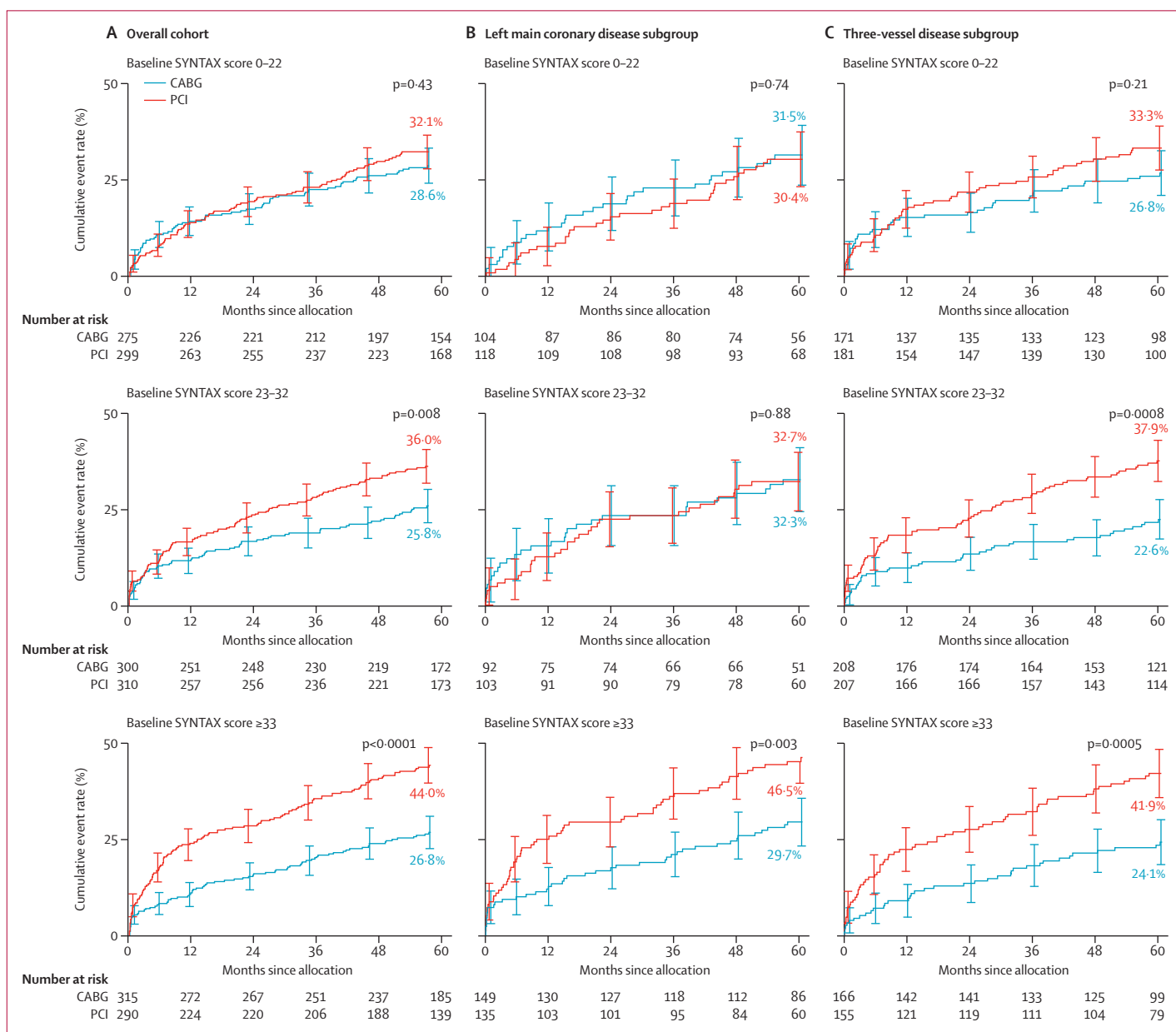


Figure 3: Kaplan-Meier cumulative event curves for MACCE by baseline SYNTAX score tercile (A) overall cohort; (B) left main coronary disease subgroup; and (C) three-vessel disease subgroup.

(figure 3A), driven by better survival, lower myocardial infarction rates, and less repeat revascularisation than in patients assigned to PCI (table 1). In patients with left main coronary disease, MACCE rates did not significantly differ between groups in patients with low or intermediate SYNTAX scores (figure 3B), but significantly more patients in the PCI group with high SYNTAX scores had MACCE than those in the CABG group (figure 3B). By contrast, in the three-vessel disease subgroup, MACCE rates did not significantly differ between groups in patients with low SYNTAX scores, but were significantly

increased in patients in the PCI group with intermediate or high SYNTAX scores (figure 3C). The p value for the interaction of treatment group by SYNTAX score tercile was 0.07 for MACCE at 5 years.

Of the 192 patients analysed per protocol in the PCI registry, 57 (30.0%) had died at 5 years, and 184 (95.8%) completed 5 years' follow-up. In the CABG registry, 1077 patients were enrolled and, per protocol, 644 were randomly selected for clinical follow-up post procedure. Of the 644 patients selected for clinical follow-up, 79 (12.3%) had died at 5 years, and 607 (94.3%)

	CABG	PCI	Hazard ratio (95% CI)	p value
SYNTAX score 0–22, n	275	299		
MACCE	74 (28.6%)	94 (32.1%)	1.13 (0.83–1.53)	0.43
Death or stroke or MI	39 (14.9%)	47 (16.1%)	1.05 (0.69–1.61)	0.81
Death, all-cause	26 (10.1%)	26 (8.9%)	0.88 (0.51–1.51)	0.64
Cardiac death	10 (3.8%)	14 (4.8%)	1.24 (0.55–2.80)	0.60
Stroke	10 (4.0%)	5 (1.8%)	0.43 (0.15–1.26)	0.11
MI	11 (4.2%)	22 (7.8%)	1.79 (0.87–3.70)	0.11
Repeat revascularisation	41 (16.9%)	66 (23.0%)	1.46 (0.99–2.16)	0.056
SYNTAX score 23–32, n	300	310		
MACCE	72 (25.8%)	110 (36.0%)	1.50 (1.11–2.01)	0.008
Death or stroke or MI	50 (18.0%)	63 (20.7%)	1.17 (0.80–1.69)	0.42
Death, all-cause	35 (12.7%)	42 (13.8%)	1.10 (0.70–1.72)	0.68
Cardiac death	19 (7.1%)	26 (8.8%)	1.25 (0.69–2.26)	0.45
Stroke	10 (3.6%)	6 (2.0%)	0.55 (0.20–1.53)	0.25
MI	10 (3.6%)	33 (11.2%)	3.11 (1.53–6.31)	0.0009
Repeat revascularisation	34 (12.7%)	70 (24.1%)	2.03 (1.35–3.06)	0.0005
SYNTAX score ≥33, n	315	290		
MACCE	80 (26.8%)	126 (44.0%)	1.89 (1.43–2.50)	<0.0001
Death or stroke or MI	51 (17.1%)	75 (26.1%)	1.63 (1.14–2.32)	0.007
Death, all-cause	33 (11.4%)	55 (19.2%)	1.84 (1.19–2.83)	0.005
Cardiac death	14 (4.9%)	38 (13.6%)	2.99 (1.62–5.52)	0.0002
Stroke	11 (3.7%)	9 (3.5%)	0.89 (0.37–2.16)	0.80
MI	12 (3.9%)	28 (10.1%)	2.57 (1.31–5.06)	0.004
Repeat revascularisation	35 (12.1%)	83 (30.9%)	2.86 (1.93–4.25)	<0.0001

Data are Kaplan-Meier estimates of event rates, expressed as percent of patients. Some patients had missing data for baseline SYNTAX score and were excluded from the analysis. Some patients had more than one event. CABG=coronary artery bypass graft surgery. PCI=percutaneous coronary revascularisation. MACCE=major adverse cardiac and cerebrovascular events. MI=myocardial infarction.

Table 1: Study outcomes at 5 years' follow-up, by baseline SYNTAX score tercile

completed 5 years' follow-up. 5-year outcomes in the nested registries are shown in table 2.

Discussion

Results of this final 5-year analysis of the SYNTAX trial show that CABG remains the standard of care for patients with complex coronary lesions, driven by favourable rates of MACCE, cardiac death, myocardial infarction, and repeat revascularisation in the CABG group compared with the PCI group. Results from SYNTAX have been previously reported at the primary endpoint of 1 years' and at 3 years' follow-up.^{15,16} The new, 5-year findings show the continuing separation in event rates between the two treatment groups, particularly for repeat revascularisation and myocardial infarction. After 5 years, patients with the highest complexity of PCI (high SYNTAX score) in the CABG group had lower mortality than did those in the PCI group. In patients with low SYNTAX scores, MACCE rates did not significantly differ between treatment groups. In patients with an intermediate SYNTAX score, mortality rates were similar between treatment groups, but significantly more patients in the PCI group had MACCE than did those in the CABG group, driven by significantly increased rates of myocardial infarction and repeat revascularisation in the PCI group. By contrast, at the 1-year and 3-year follow-up, patients in the intermediate tercile had equivalent outcomes between CABG and PCI; therefore, with continued follow-up, the eligibility of patients for either treatment has tightened. Based on the overall results of the trial at 5 years, outcomes suggest roughly two-thirds of all patients with complex coronary disease are still best treated with CABG; however, for the remaining patients, PCI is an excellent alternative to surgery (appendix).

The SYNTAX trial was the first randomised trial to compare CABG and PCI in patients with very complex coronary disease. Methods used in the SYNTAX trial and findings at 1-year follow-up led to changes to revascularisation guidelines in both Europe and the USA, introduced the SYNTAX score for standardised determination of lesion complexity (subsequently adopted by the US Food and Drug Administration [FDA] as an inclusion criterion for trials), and formalised the basis of the heart team concept (now adopted in many centres for the assessment of treatment decisions in complex coronary or valvular heart disease and used by the FDA for assessment of patient eligibility for transcatheter aortic valve implantation). Results of this 5-year analysis support the primary endpoint findings at 1 year and provide long-term outcome data from the largest prespecified randomised cohort of patients with left main coronary disease available.

When the SYNTAX trial was designed, revascularisation with PCI had evolved from use in uncomplicated, focal lesions to use in increasingly complex disease previously considered the domain of CABG. Part of the

	CABG registry (n=644)	PCI registry (n=192)
MACCE	146 (23.2%)	94 (42.9%)
Death or stroke or MI	117 (18.6%)	67 (35.3%)
Death, all-cause	79 (12.6%)	57 (30.0%)
Cardiac death	22 (3.6%)	17 (9.5%)
Stroke	31 (5.1%)	5 (3.1%)
MI	24 (3.8%)	17 (9.8%)
Repeat revascularisation	41 (6.7%)	41 (23.6%)
PCI	40 (6.6%)	36 (20.6%)
CABG	1 (0.2%)	8 (4.6%)
Stent thrombosis or graft occlusion	26 (4.2%)	4 (2.2%)

Data are Kaplan-Meier estimates of event rates, expressed as percent of patients. Due to large differences in baseline characteristics, we have not made any statistical comparisons between the two registries. Some patients had more than one event. CABG=coronary artery bypass graft surgery. PCI=percutaneous coronary intervention. MACCE=major adverse cardiac and cerebrovascular events. MI=myocardial infarction.

Table 2: Study outcomes at 5 years' follow-up in patients in the PCI-only and CABG-only registries

SYNTAX objective was to identify the so-called upper limits of suitability for revascularisation with PCI. Patients in SYNTAX had more advanced and complex disease than had ever been enrolled in previous clinical trials—eg, in the randomised PCI cohort, patients received a mean average of 4.6 stents (86.1 mm of stented vessel), and non-randomised patients with multivessel^{18–20} or left main coronary disease^{10,11,19,21} had higher overall mortality at 5 years than has been reported for other clinical trials (panel).

The application of the SYNTAX score has created a new era in the objective assessment of coronary artery disease complexity, making interpretation of previous trials with more crude assessment of coronary severity difficult.^{22,23} The recent ASCERT (American College of Cardiology Foundation [ACCF] and Society of Thoracic Surgeons [STS] collaboration on the Comparative Effectiveness of Revascularization sTrategies) registry linking the ACCF National Cardiovascular Data Registry and the STS Adult Cardiac Surgery Database with Medicare data provides evidence for significantly better long-term survival with CABG compared with PCI,²³ providing survival information after revascularisation for nearly 200 000 patients. However, this analysis is limited by a lack of prospective randomisation and the unanswered question of whether selection bias can be adequately compensated for via propensity-adjusted statistical analyses.³³ Additionally, the ASCERT study did not use a measure of coronary disease severity, such as the SYNTAX score, and is thus limited in its ability to provide comparative information for the optimum revascularisation method for a given level of coronary anatomic complexity. In the SYNTAX trial, we noted a significant difference in outcomes depending on baseline severity of coronary artery disease. In patients with low SYNTAX scores (0–22), we reported no significant difference between groups in any clinical endpoint at 5 years (table 1). By contrast, in patients with intermediate SYNTAX scores (23–32), 5-year rates of myocardial infarction and repeat revascularisation (and therefore, MACCE) were significantly increased in the PCI group compared with the CABG group, although this did not translate to a difference in mortality (either overall or cardiac related). However, in patients with the highest baseline SYNTAX scores (≥ 33), all clinical endpoints apart from stroke were significantly increased in the PCI group at 5 years compared with the CABG group. These results suggest that patients with intermediate or high SYNTAX scores are best treated with CABG, but that patients with less complex disease (ie, SYNTAX score ≤ 22) can be treated with first-generation DES with equivalent outcomes. Our results parallel those of the recently published FREEDOM (Future REvascularization Evaluation in patients with Diabetes mellitus: Optimal management of Multivessel disease) trial,²⁴ which assessed CABG versus PCI in 1900 patients with multivessel disease

Panel: Research in context

Systematic review

We searched PubMed with the terms “drug-eluting stents” and “coronary artery bypass graft surgery”. We completed the last search in July, 2012. Search results were manually filtered and restricted to those of patients with stable angina treated in native coronary vessels. Although many trials have reported long-term outcomes of percutaneous coronary intervention (PCI) versus coronary artery bypass graft surgery (CABG), most of those trials predate the drug-eluting stents (DES) era and assessed simple balloon angioplasty, with or without bare-metal stents, compared with CABG. Few studies of DES versus CABG in patients with left main coronary disease or three-vessel disease have reached 5 years’ follow-up, and of these none was a prospective randomised trial that simultaneously assessed cohorts of DES versus CABG. Randomised controlled trials and observational studies with at least 5 years’ follow-up have consistently shown significantly increased need for repeat revascularisation with PCI versus CABG in patients with left main coronary disease, but no difference in mortality or combined rates of death and myocardial infarction.^{7–11} By contrast, although patients with multivessel disease also have increased rates of repeat revascularisation versus CABG, the findings for mortality, myocardial infarction, and stroke are more mixed. Many retrospective reviews with at least 5 years’ follow-up and large analyses of Medicare claims have reported a mortality benefit for CABG over PCI,^{13,22–26} but this effect is not consistent across studies^{4,19,20,27} and might perhaps relate to baseline severity of disease.²⁸ In randomised controlled trials of patients with multivessel disease and stable angina, findings of most showed no significant difference in mortality across at least 5 years’ follow-up^{3,29–31} with the exception of the Stent or Surgery study,³² which reported a mortality benefit for CABG at 6 years. The SYNTAX trial has previously reported outcomes at the primary endpoint of 1 year¹⁵ and at 3 years.¹⁶ At 1 year, the rate of major adverse cardiac and cerebrovascular events (MACCE) was significantly higher with PCI versus CABG, driven mainly by significantly increased repeat revascularisation rates in the PCI group. By contrast, stroke was significantly increased in the CABG group, with no significant differences reported between groups for death or myocardial infarction.¹⁵ At 3 years, rates of MACCE, myocardial infarction, and repeat revascularisation were higher in the PCI group than in the CABG group, whereas rates of the composite safety endpoint of death or stroke or myocardial infarction, and stroke alone, were not significantly different between treatment groups.¹⁶

Interpretation

The optimum revascularisation strategy for an individual patient will depend on a careful consideration of the risks and benefits of each procedure in conjunction with the baseline risk profile and patient preferences.

and diabetes. In the overall population of that study, patients in the CABG group had significantly lower rates of the composite endpoint of all-cause death, cerebrovascular accident, or myocardial infarction compared with patients in the first-generation DES group (18.7% in the CABG group vs 26.6% in the PCI group; $p=0.005$). However, as in the SYNTAX study, the FREEDOM trial reported no difference between treatment groups for the composite endpoint of all-cause death, cerebrovascular accident, or myocardial infarction for patients with SYNTAX scores of lower than 22, and a mortality benefit associated with CABG in patients with SYNTAX scores of 23–32. However, for patients with SYNTAX scores of 33 or higher in the FREEDOM trial, no significant difference between treatment groups for this endpoint was reported. The reason for this difference in outcomes is unclear, but might be related to statistical power, since less than 20% of patients in the FREEDOM trial had a SYNTAX score of 33 or higher.²⁴

At 1-year follow-up in the SYNTAX trial, stroke rates were significantly higher in patients in the CABG group than in those in the PCI group, although this significance was attenuated by 5 years of follow-up, as noted in previous trials.^{20,29}

Despite having even more complex anatomy (mean SYNTAX score 37.8) than the randomised surgical cohort, the outcomes of the CABG registry (23.2% had MACCE at 5 years) support the results of the randomised patients. These findings emphasise that results after surgery are much less affected by anatomic complexity than are results after PCI, as shown by the SYNTAX score. In this respect, several proposals to refine the SYNTAX score by adding in clinical variables have been put forward, including measures of frailty, that might improve stratification of clinical risk in patients with complex coronary disease.³⁴ In particular, the recent development of a global risk score—a combination of the SYNTAX score and additive EuroSCORE that uses a simple treatment algorithm—might provide enhanced identification of low-risk patients who could safely and efficaciously be treated with CABG or PCI.³⁵

Despite the joint assessment of patients by the heart team, more than four times as many CABG patients withdrew consent to participate in the study compared with PCI patients (50 vs 11, respectively). Of these, close to half of the patients in the CABG group declined to participate after being randomly assigned but before receiving treatment (21 of 50), as opposed to 2 of 11 patients in the PCI group, probably because patients were concerned about the greater invasiveness of CABG. A sensitivity analysis showed that the primary endpoint results were not significantly affected by this imbalance, but this difference in withdrawal rates should be noted and taken into consideration in the design of future trials.

As mentioned, this study is not powered to make comparisons between subgroups or between individual MACCE components; therefore, these results should be regarded as observational and hypothesis-generating only and need to be confirmed in subsequent adequately powered clinical trials. Additionally, the unexpected finding of an imbalance in withdrawal rates between groups after randomisation might affect the reliability of the conclusions drawn from the study, although the sensitivity analysis that showed no difference in MACCE results even if all missing patients had died provides some reassurance. Limitations inherent in the use of an unweighted composite endpoint such as MACCE should also be noted. In this trial, the primary endpoint components of death, myocardial infarction, stroke, and repeat revascularisation were weighted equally without regard to clinical effect. This limitation is perhaps less relevant in patients with higher SYNTAX scores, in whom a clear mortality benefit with CABG is noted, but for patients with lower SYNTAX scores, the potential clinical effect should be balanced against the expected frequency of the event when discussing risk with the patient. Additionally, since the purpose of the SYNTAX trial was to assess the optimum method of revascularisation for patients with complex coronary artery disease, we were not able to assess whether some patients might have benefited from optimum medical therapy rather than a procedural intervention.

Generalising the results of a trial to real-world populations has inherent limitations, even when inclusion and exclusion criteria and standardisation of treatment, equipment, and facilities are strictly controlled for. In the SYNTAX trial, the screening process showed that nearly a third (1262 [29.1%] of 4337) of screened patients were not eligible for the trial, mainly because these patients chose not to take part or did not meet one or more inclusion criteria.¹⁵ Finally, it is unclear how the study results would differ with the use of fractional flow reserve³⁶ or newer-generation DES (with lower repeat revascularisation and associated stent thrombosis rates³⁷) or improvements in antiplatelet therapy and CABG techniques (eg, more arterial revascularisation, improved perioperative care). The EXCEL trial is investigating use of newer-generation DES versus CABG in 2600 patients with low-risk or intermediate-risk left main lesions, and results are expected to provide additional insight into the optimum revascularisation technique in this subgroup of patients.

The final 5-year results of the SYNTAX trial show that surgery remains the standard for patients with complex multivessel disease. However, in patients with less complex disease (ie, left main coronary disease with low or intermediate SYNTAX scores, or three-vessel disease with low SYNTAX scores), PCI is a reasonable alternative treatment to CABG. Treatment advice for an individual patient should take into account patient preferences, as well as the risks and benefits of the respective treatment options.

Contributors

FWM, M-CM, APK, TEF, ES, AC, MJM, DRH, KDD, and PWS designed the study, enrolled patients, and collected, analysed, and interpreted the data. M-aM participated in the study design and data analysis as part of the core laboratory. NVD participated in the study design and oversaw data collection and verification. FWM, VMH, and KDD drafted the report, which was critically reviewed by all authors. All authors approved the final version of the manuscript for submission.

Conflicts of interest

TEF has received consulting and lecture fees and research support from Boston Scientific and Abbott. NVD, VMH, and KDD own stock in and are full-time employees of Boston Scientific. All other authors declare that they have no conflicts of interest.

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