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Causes of Death Following PCI Versus CABG in Complex CAD

5-Year Follow-Up of SYNTAX

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ABSTRACT

BACKGROUND There are no data available on specific causes of death from randomized trials that have compared coronary artery bypass grafting (CABG) with percutaneous coronary intervention (PCI).

OBJECTIVES The purpose of this study was to investigate specific causes of death, and its predictors, after revascularization for complex coronary disease in patients.

METHODS An independent Clinical Events Committee consisting of expert physicians who were blinded to the study treatment subclassified causes of death as cardiovascular (cardiac and vascular), noncardiovascular, or undetermined according to the trial protocol. Cardiac deaths were classified as sudden cardiac, related to myocardial infarction (MI), and other cardiac deaths.

RESULTS In the randomized cohort, there were 97 deaths after CABG and 123 deaths after PCI during a 5-year follow-up. After CABG, 49.4% of deaths were cardiovascular, with the greatest cause being heart failure, arrhythmia, or other causes (24.6%), whereas after PCI, the majority of deaths were cardiovascular (67.5%) and as a result of MI (29.3%). The cumulative incidence rates of all-cause death were not significantly different between CABG and PCI (11.4% vs. 13.9%, respectively; $p = 0.10$), whereas there were significant differences in terms of cardiovascular (5.8% vs. 9.6%, respectively; $p = 0.008$) and cardiac death (5.3% vs. 9.0%, respectively; $p = 0.003$), which were caused primarily by a reduction in MI-related death with CABG compared with PCI (0.4% vs. 4.1%, respectively; $p < 0.0001$). Treatment with PCI versus CABG was an independent predictor of cardiac death (hazard ratio: 1.55; 95% confidence interval: 1.09 to 2.33; $p = 0.045$). The difference in MI-related death was seen largely in patients with diabetes, 3-vessel disease, or high SYNTAX (TAXUS Drug-Eluting Stent Versus Coronary Artery Bypass Surgery for the Treatment of Narrowed Arteries) trial scores.

CONCLUSIONS During a 5-year follow-up, CABG in comparison with PCI was associated with a significantly reduced rate of MI-related death, which was the leading cause of death after PCI. Treatments following PCI should target reducing post-revascularization spontaneous MI. Furthermore, secondary preventive medication remains essential in reducing events post-revascularization. (TAXUS Drug-Eluting Stent Versus Coronary Artery Bypass Surgery for the Treatment of Narrowed Arteries [SYNTAX]; NCT00114972) (J Am Coll Cardiol 2016;67:42-55) © 2016 by the American College of Cardiology Foundation.

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Coronary artery bypass grafting (CABG) and percutaneous coronary intervention (PCI) are both used for myocardial revascularization in patients with complex coronary artery disease (CAD) with an indication for revascularization (1). A large number of studies have reported or compared outcomes of CABG and PCI as optimum treatment strategies (2), but data are limited on the causes, circumstances, and the mechanisms of death after these procedures.

Observational studies have reported causes of death after PCI and CABG (3–5), but these results are difficult to interpret because the cause of death may not always be clear in retrospect. Therefore, data from randomized trials in which a Clinical Events Committee (CEC) adjudicates deaths provide more valuable information. Two randomized clinical trials that compared CABG with medical therapy have shown that CABG was particularly effective in reducing rates of sudden cardiac death (5,6), but no comparisons between PCI and CABG on the specific causes of death are available from randomized trials.

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Assessment of the cause of death in contemporary practice should help to target potential underlying mechanisms of death and further develop effective interventions to improve survival after myocardial revascularization. The goal of the present study was to investigate the specific cause of death, and its predictors, in patients enrolled in the SYNTAX (TAXUS Drug-Eluting Stent Versus Coronary Artery Bypass Surgery for the Treatment of Narrowed Arteries) trial, which represents a contemporary cohort of patients who underwent CABG or received drug-eluting stents (DES).

METHODS

STUDY DESIGN, PATIENTS, AND RANDOMIZATION. The design, methods, and procedural details of the SYNTAX trial have been reported previously (7–9). The SYNTAX study was a prospective, multinational, randomized trial conducted in 85 centers in the United States and Europe. In this study, 1,800 patients with de novo left main (LM) or 3-vessel disease (3VD) were randomly assigned to undergo CABG or PCI with first-generation paclitaxel-eluting stents (Taxus Express, Boston Scientific, Natick, Massachusetts). Based on clinical judgment and consensus of a heart team that consisted of a cardiac surgeon and interventional cardiologist at each center, patients with anticipated clinical equipoise through CABG and PCI were randomized (CABG, n = 897 and PCI, n = 903). Randomization occurred via a central interactive voice response system in random block sizes per site based on the presence or absence of LM disease and medically treated diabetes mellitus. Patients suitable for PCI only entered the PCI registry (CABG ineligible patients, n = 198), whereas those suitable for CABG only entered the CABG registry (PCI ineligible patients, n = 1,077) (10). Within the nested registries, all PCI patients and 649 randomly allocated CABG patients underwent 5-year follow-up. Routine follow-up assessments were performed by clinical visits or telephone interviews at 1, 6, and 12 months, and annually thereafter. All the clinical endpoints were assessed by the event-adjudication CEC. Data collection and quality were monitored systematically by the principal investigators and safety monitoring committee. Complete 5-year follow-up (clinical follow-up or death) after randomization to CABG and PCI was achieved in 805 (89.7%) and 871 (96.5%) patients, respectively. Follow-up was complete for 184 patients (95.8%) in the PCI registry and for 607 patients (94.3%) in the CABG registry.

The post-procedure medication regimens and the use of secondary-prevention therapy according to American College of Cardiology and American Heart Association treatment guidelines (11,12) was strongly recommended for all patients. Medication use for the randomized cohort was collected at baseline, discharge, at 1 and 6 months, and at 1, 3, and 5 years post-allocation. For the nested registries, this was collected at baseline and discharge.

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.

DEFINITIONS. The definitions used for the classifications of adverse events have been previously reported elsewhere (9). Mortality data during the course of follow-up were collected prospectively. Collection started directly after randomization to finalizing the 5-year follow-up; therefore, this included post-randomization pre-procedural deaths, operative deaths, and deaths during follow-up. For each death event, standardized electronic case report forms were used by local principal investigators to categorize a terminal event in detail. The case report form included a structured narrative description of date and location of death, onset of adverse events that preceded the fatal outcome, circumstances of death, and description of treatments, if initiated. For all deaths, all available information was obtained and

ABBREVIATIONS AND ACRONYMS

3VD = 3-vessel disease
CABG = coronary artery bypass grafting
CAD = coronary artery disease
CEC = Clinical Events Committee
CHF = congestive heart failure
CI = confidence interval
DES = drug-eluting stent
HR = hazard ratio
LM = left main
MI = myocardial infarction
PCI = percutaneous coronary intervention

forwarded to the independent CEC, including the death certificates, the coroner's report, and other records (hospital discharge summary, pathology, laboratory, radiology, and other diagnostic data). The CEC was composed of physicians who were experts in cardiology, cardiac surgery, and neurology. Two CEC members reviewed all deaths independently in a blinded manner. Disagreements between reviewers and principal investigators were discussed and resolved by full CEC consensus.

Because the SYNTAX study began before publication of the Academic Research Consortium definition (13), it used specially designed definitions of death. The CEC classified deaths into cardiovascular or noncardiovascular, according to the trial protocol. Cardiovascular deaths were further classified as cardiac (sudden cardiac deaths, myocardial infarction [MI], progressive heart failure, and arrhythmia) and cardiac others (which included other cardiac causes, e.g., cardiac tamponade and cardiac deaths with insufficient information for definitive classification), vascular (stroke, aortic dissection, and pulmonary embolism), and vascular others (major hemorrhage, peripheral embolism, and other). Using these classifications, the following cardiac subgroups were defined and analyzed: 1) sudden cardiac deaths; 2) MI-related deaths; and 3) congestive heart failure (CHF), arrhythmia, and all other cardiac deaths, the latter of which were combined together into a single subgroup because of the low number of cases in each particular subgroup. Noncardiovascular deaths included those resulting from chronic respiratory disease, pneumonia, malignancy, diabetes mellitus, and other conditions (which included infections, accidents, suicides, trauma-related, chronic disease, and others). When a specific cause of death could not be determined from the available evidence, the death was classified as undetermined. Every death was attributed to one of the specific causes exclusively.

Major adverse events were considered nonfatal if no death occurred within 30 days of the event, and when it was not possible to establish any association between the event and death from the narrative description of death.

During the Heart Team meeting, both the interventional cardiologist and surgeon documented which vessels that were ≥1.5 mm diameter and >50% stenosis needed revascularization. In the original trial protocol, incomplete revascularization was defined when the actual revascularization did not correlate with this pre-operative Heart Team statement.

STATISTICAL ANALYSES. All analyses in the randomized cohort were done according to the intention-to-treat principle, whereas in the nested registries, outcomes were presented according to the as-treated principle. As previously described, no statistical comparisons between the PCI and CABG registries were performed (10).

Continuous variables were reported as mean ± SD and compared with the Student *t* test. Binary variables were expressed as counts and/or percentages and compared with the chi-square test or Fisher exact test, as appropriate. Five-year rates of death were estimated using the Kaplan-Meier method, and comparisons between PCI and CABG were done using the log-rank test. For the randomized cohort, subgroup analyses were performed for pre-specified groups of patients with LM or 3VD and diabetic patients or nondiabetic patients, and post-hoc groups according to SYNTAX score tertiles (low 0 to 22, intermediate 23 to 32, and high ≥33) and completeness of revascularization. The p values for interaction were performed using chi-square tests. Cox proportional hazard models for specific causes of death during the 5-year follow-up were constructed to provide hazard ratios (HRs) associated with PCI versus CABG treatment. The proportional hazards assumption of the Cox models was evaluated with Schoenfeld residuals (14). There was no evidence of departure from the assumption of proportionality. Multivariate analyses were performed using Cox proportional hazard models with backward selection of variables to construct a set of independent predictors. Variables considered of clinical importance and with a p value <0.15 in univariate analysis were considered in the multivariate models (Online Appendix). Models were constructed for the overall randomized cohort and CABG and PCI randomized groups separately, as well as for the PCI and CABG registry patients separately. The performance of the models was tested using receiver-operating characteristics curves. A 2-sided p value of <0.05 was considered to be statistically significant for all tests. Analyses were performed using SPSS version 20.0 statistical software (IBM, Armonk, New York).

RESULTS

CAUSES OF DEATH. During the 5-year follow-up, there were 123 deaths after PCI and 97 deaths after CABG in the randomized cohort. Among PCI patients, the majority of deaths were cardiovascular (67.5%, n = 83), of which nearly all deaths were from cardiac causes (**Table 1**). The largest cause of cardiovascular death after PCI was related to MI (**Figure 1A**). In the CABG group, cardiovascular deaths accounted for 49.4% (n = 48), noncardiovascular deaths for 48.5%

TABLE 1 Specific Causes of Death in the SYNTAX Trial

Causes of Death	PCI	CABG	HR (95% CI)	p Value	PCI Registry	CABG Registry
Total	123 (13.9)	97 (11.4)	1.23 (0.94–1.60)	0.10	57 (30.0)	79 (12.6)
Cardiovascular death	83 (9.6)	48 (5.8)	1.62 (1.13–2.31)	0.008	22 (12.1)	29 (4.7)
Cardiac	78 (9.0)	43 (5.3)	1.70 (1.17–2.47)	0.003	17 (9.5)	22 (3.6)
Sudden cardiac death	24 (2.8)	15 (1.9)	1.61 (0.83–3.11)	0.16	5 (2.7)	6 (1.0)
Myocardial infarction	36 (4.1)	4 (0.4)	8.43 (2.99–23.67)	<0.0001	3 (1.8)	2 (0.3)
Heart failure	7 (0.8)	13 (1.6)	0.50 (0.20–1.26)	0.14	5 (2.7)	6 (1.0)
Arrhythmia	1 (0.1)	1 (0.1)	0.95 (0.06–15.14)	0.97	0	1 (0.2)
Other	10 (1.1)	11 (1.4)	0.85 (0.36–2.01)	0.71	4 (2.2)	6 (1.0)
CHF/cardiac other	18 (2.1)	24 (3.0)	0.67 (0.37–1.24)	0.20	9 (4.8)	14 (2.2)
Vascular	5 (0.6)	5 (0.5)	0.93 (0.27–3.23)	0.91	5 (2.7)	7 (1.1)
CVA	3 (0.3)	3 (0.3)	0.94 (0.19–4.64)	0.94	1 (0.5)	3 (0.5)
Aortic dissection	0	0	-	>0.99	0	2 (0.3)
Pulmonary embolism	0	1 (0.1)	0.014 (0–138,818)	0.60	2 (1.1)	0
Other	2 (0.2)	1 (0.1)	1.86 (0.17–20.55)	0.61	2 (1.1)	2 (0.3)
Noncardiovascular death	40 (4.3)	47 (5.6)	0.85 (0.55–1.31)	0.46	29 (14.9)	33 (5.3)
Chronic respiratory disease	0	1 (0.1)	0.015 (0–141,247)	0.61	3 (1.8)	1 (0.2)
Pneumonia	4 (0.4)	3 (0.3)	1.88 (0.34–10.29)	0.46	6 (3.1)	3 (0.5)
Cancer	20 (2.2)	20 (2.4)	1.04 (0.55–1.97)	0.90	8 (4.2)	20 (3.1)
DM	1 (0.1)	0	60.88 (0–595,324)	0.62	0	1 (0.2)
Other	15 (1.6)	23 (2.8)	0.61 (0.32–1.17)	0.14	12 (5.9)	8 (1.3)
Undetermined death	0	2 (0.2)	0.016 (0–1262)	0.47	6 (3.1)	17 (2.6)

Values are number of events (%), unless otherwise indicated.

CABG = coronary artery bypass grafting; CHF = congestive heart failure; CI = confidence interval; CVA = cerebral vascular accident; DM = diabetes mellitus; HR = hazard ratio; PCI = percutaneous coronary intervention; SYNTAX = TAXUS Drug-Eluting Stent Versus Coronary Artery Bypass Surgery for the Treatment of Narrowed Arteries.

(n = 47), and 2.1% (n = 2) of deaths occurred due to undetermined causes (Table 1). Of cardiovascular death, only a few deaths were from vascular causes. The greatest cause of cardiovascular death after CABG was CHF, arrhythmia, or other causes (Figure 1A).

In the PCI registry, 22 (38.6%) patients died of cardiovascular causes, and the majority of deaths (50.9%, n = 33) were due to noncardiovascular causes (Figure 1B). Within the CABG registry, cardiovascular deaths represented 36.7% (n = 29) of deaths, whereas noncardiovascular deaths occurred in 41.8% (n = 33) of cases. Of note, noncardiovascular deaths were most often caused by malignancies.

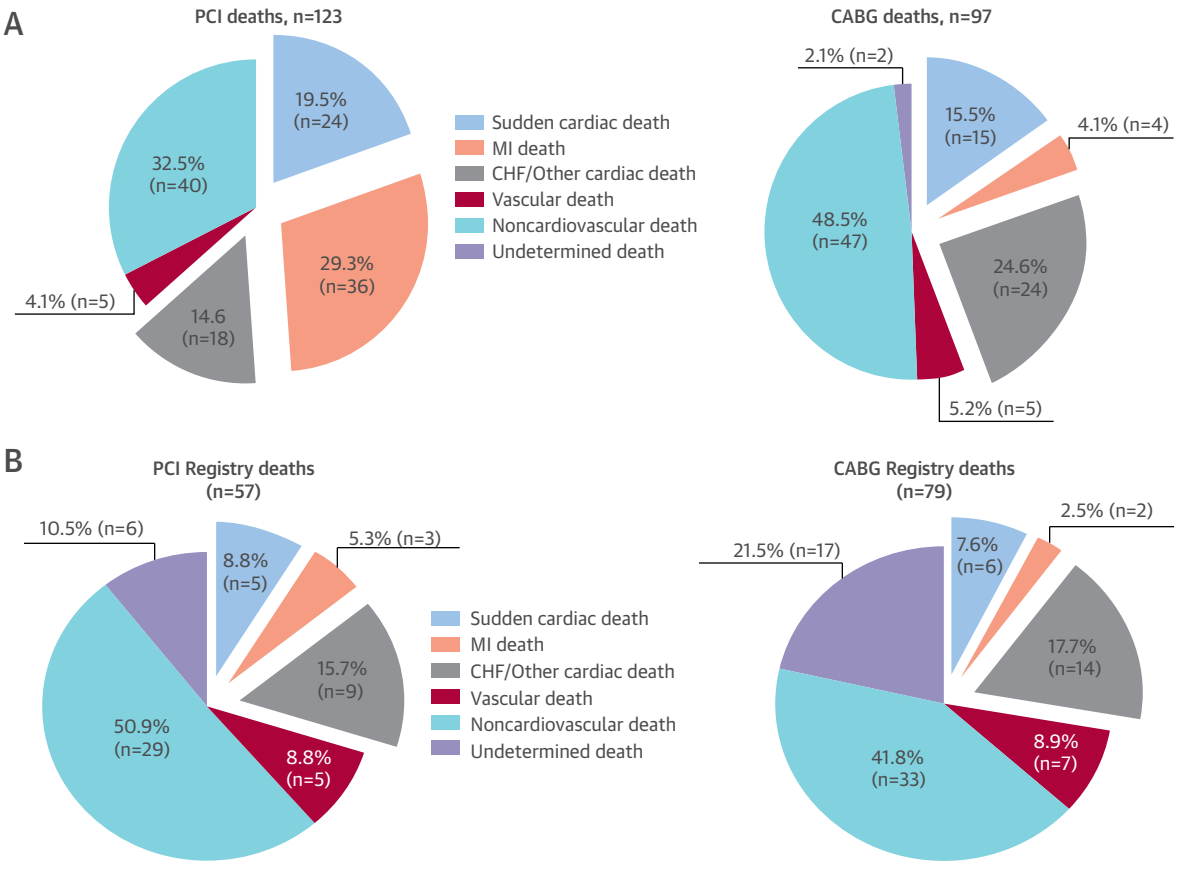
INCIDENCES OF DEATH. At 5-year follow-up, there was a significant difference in favor of CABG in terms of cardiovascular death (p = 0.008), but not of noncardiovascular death (p = 0.46) (Figure 2). The difference in cardiovascular death was the result of a significantly lower rate of death due to MI (CABG 0.4% vs. PCI 4.1%; p < 0.0001), whereas rates of sudden cardiac death or death by CHF or arrhythmia were similar. All-cause death rates were not significantly different (p = 0.10) (Figure 2).

Rates of all-cause death at 5-year follow-up were 30.0% (n = 57) in the PCI registry and 12.6% (n = 79) in the CABG registry (Table 1). Specific causes of death are shown in Figure 3.

SUBGROUP ANALYSES. Subgroup analyses revealed that the reduced rates of cardiac death after CABG in comparison with PCI were particularly evident in patients with diabetes, 3VD, and a high SYNTAX score, although none of the interaction tests were significant (Figure 4A). More in-depth subgroup analyses in rates of sudden cardiac deaths, MI-related deaths, and CHF and/or other cardiac deaths were performed to detect the cause of this difference (Figure 4B). Among all patient subgroups, the rate of sudden cardiac death was numerically higher after PCI than after CABG, although this failed to reach statistical significance. Only patients with a high SYNTAX score had significantly higher rates of sudden cardiac death after PCI versus CABG (HR: 5.09; 95% confidence interval [CI]: 1.46 to 17.71; p = 0.011). Differences in MI-related deaths were consistently in favor of CABG and were particularly prominent in patients with diabetes, 3VD, and higher SYNTAX scores. There were no differences between PCI and CABG in terms of deaths due to CHF or other cardiac causes, although patients with a lower SYNTAX score did appear to have a nonsignificant benefit with PCI (Figure 4B).

Incomplete revascularization with PCI was associated with risk of cardiac deaths (HR: 1.89; 95% CI: 1.20 to 2.98; p = 0.006), which was driven by deaths due

FIGURE 1 **Causes of Death in the SYNTAX Randomized Cohort and Nested Registries**



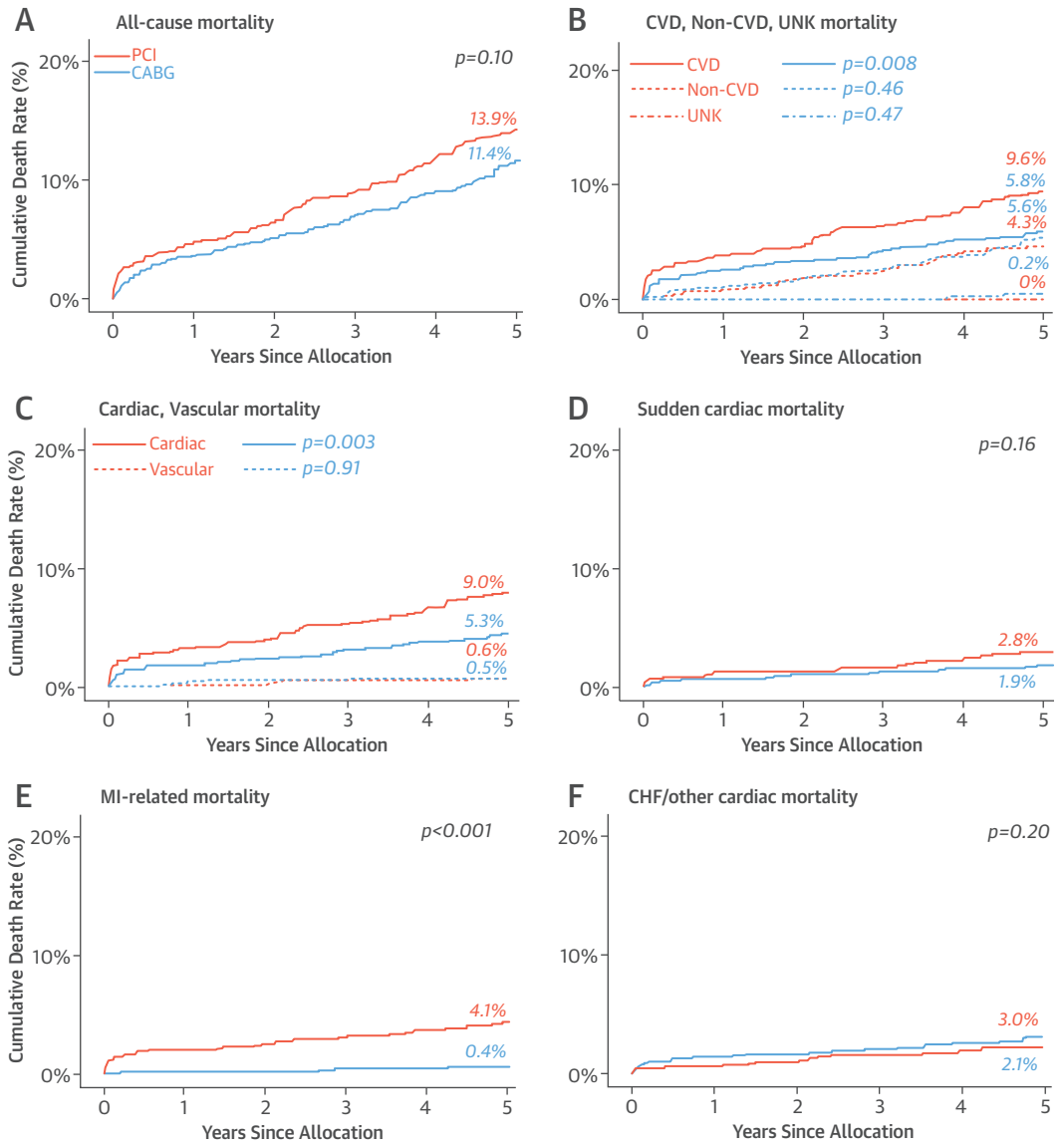
Causes of death in the SYNTAX **(A)** randomized cohort and **(B)** nested registries. CABG = coronary artery bypass grafting; CHF = congestive heart failure; MI = myocardial infarction; Other Cardiac = arrhythmia and all other cardiac deaths; PCI = percutaneous coronary intervention; SYNTAX = TAXUS Drug-Eluting Stent Versus Coronary Artery Bypass Surgery for the Treatment of Narrowed Arteries.

to CHF and/or other cardiac causes (HR: 5.97; 95% CI: 1.72 to 20.78; p = 0.005) (Figure 4C). In CABG patients, there was no increased risk in any specific causes of death associated with incomplete revascularization (Figure 4C).

PATIENT CHARACTERISTICS AND PREDICTORS OF ALL-CAUSE AND CARDIAC DEATH. Randomized trial. Significant baseline and lesion characteristics of patients who were alive or dead at 5 years after revascularization are summarized in Table 2 (complete results are in the Online Table 1). Patients who died after both PCI or CABG had a higher risk profile at baseline than those who were still alive; they were older, had a higher presence of co-morbidities (diabetes, peripheral vascular disease, chronic obstructive pulmonary disease, carotid artery disease, and creatinine >200 μmol/l), which resulted in higher EuroSCORE values. Moreover, rates of medically treated diabetes and the mean SYNTAX score were significantly higher in patients who died after PCI, but these rates were not higher in patients who died after CABG.

In multivariate analysis, PCI versus CABG treatment was not an independent predictor of all-cause death. Although, in the overall model, as well as in the separate PCI and CABG models, numerous baseline variables, such as older age and the presence of co-morbidities, were independent predictors (Table 3). Moreover, procedural events such as incomplete revascularization, post-procedural prescription of medication as secondary prevention, and the occurrence of nonfatal adverse events were predictive of all-cause death. In separate models, results were largely similar, although incomplete revascularization, medically treated diabetes and left ventricular function were only predictors in the PCI model and not in the CABG model (Table 3). In contrast, renal failure and chronic obstructive pulmonary disease were only predictors in the CABG model.

FIGURE 2 Kaplan-Meier Cumulative Event Curves by Specific Causes of Deaths in the SYNTAX Randomized Cohort

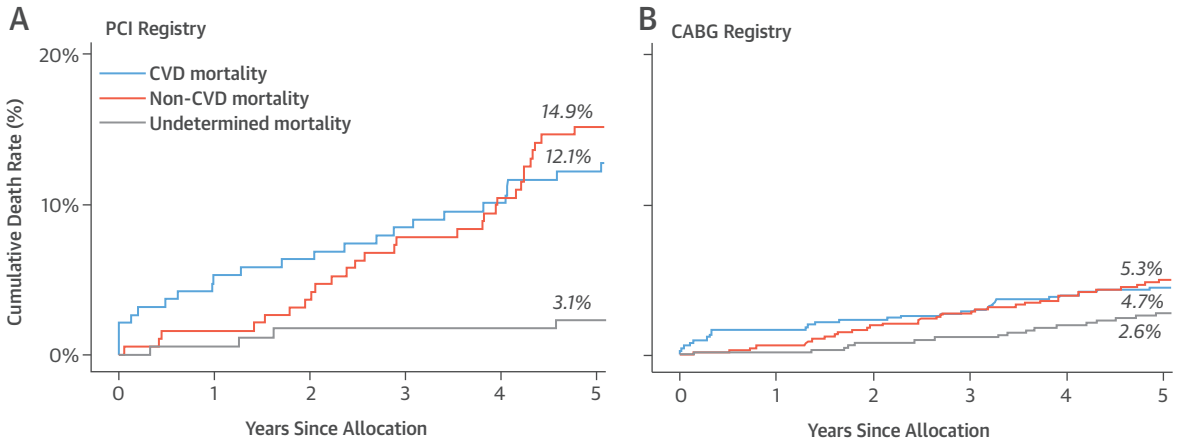


Analyses include Kaplan-Meier estimates of all-cause mortality **(A)**; a subdivision in cardiovascular, non-cardiovascular, and unknown cause of mortality **(B)**; subdividing cardiovascular mortality in cardiac and vascular mortality **(C)**; and cardiac death subdivided into individual components of sudden cardiac mortality **(D)**, MI-related mortality **(E)**, and CHF/other cardiac mortality **(F)**. CVD = cardiovascular; Non-CVD = noncardiovascular; UNK = unknown/undetermined; other abbreviations as in Figure 1.

Treatment with PCI versus CABG was an independent predictor of cardiac death (HR: 1.55; 95% CI: 1.0 to 2.33; p = 0.045) (Table 4). Furthermore, the independent predictors in the overall and PCI models for cardiac death were nearly identical as for all-cause death (Table 4). An additional predictor for cardiac events after PCI was the SYNTAX score. The CABG model included previous MI and bypass time as additional independent predictors, whereas other baseline characteristics no longer were predictors.

Nested registries. Baseline and procedural characteristics of patients alive at the end of follow-up and patients who died during follow-up are reported in the Online Table 2. In the multivariate models that predicted all-cause and cardiac death, results were relatively similar to the randomized cohort, with a number of baseline, procedural, and post-procedural

FIGURE 3 **The Kaplan-Meier Cumulative Event Curves by Specific Causes of Deaths in the SYNTAX Nested Registries**



The Kaplan-Meier cumulative event curves by specific causes of deaths in the SYNTAX PCI **(A)** and CABG **(B)** nested registries. Abbreviations as in Figures 1 and 2.

variables as independent predictors (Table 5). Of note, in the PCI registry, LM disease and the SYNTAX score were predictors.

DISCUSSION

The present study provides crucial perspectives on causes of death within the SYNTAX trial at 5-year follow-up (Central Illustration). Our findings indicate that treatment with CABG significantly reduces cardiac death compared with PCI, which was due exclusively to a lower incidence of MI-related death. Particularly in patient groups with 3VD and/or a SYNTAX score ≥33, cardiac death was significantly higher after PCI than CABG. Numerous patient baseline characteristics were independent predictors of death, although procedural characteristics (e.g., incomplete revascularization), the use of specific medications, and events during follow-up (e.g., nonfatal MI) also contributed in predicting all-cause and cardiac death.

Similarly to previous randomized trials that compared CABG with PCI using bare-metal stents, long-term rates of all-cause mortality were comparable between CABG and PCI (15,16). Despite the inclusion of patients with more complex disease, such as LM and 3VD, rates of all-cause death in the SYNTAX trial were comparable to that of previous trials. For the patients treated with CABG, this might be the result of more refined operative techniques and conduit choices, among others. For patients who underwent PCI, factors that might have contributed to lowering adverse events during follow-up were the first-time implantation of DES and the increased use of dual antiplatelet therapy. In a recent report on trends in long-term, cause-specific death after PCI, Spoon et al. (17) found that rates of deaths were similar from 1991 to 2012, whereas in more recent procedures, deaths occurred less often from cardiac causes.

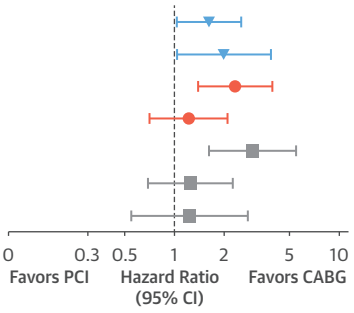
Unfortunately, many previous analyses from randomized trials were limited by few specifics on the causes of cardiac deaths. Anecdotal evidence suggested that the advantage of CABG over medical therapy was particularly driven by reduced rates of sudden cardiac death (5,6,18). A recent analysis of deaths that occurred in the STICH (Surgical Treatment for Ischemic Heart Failure) trial showed that CABG further reduced rates of fatal MI (18). Comparative analyses regarding causes of death between CABG and PCI are restricted to a single observational study of approximately 10,000 patients with 140 sudden cardiac deaths, in which there was no difference in the rate of sudden cardiac death after CABG versus PCI (19).

In the present analysis, there was a significant difference in rates of cardiac death between CABG and PCI. Rates of sudden cardiac death were comparable, but MI-related deaths were significantly lower after CABG. The majority of deaths among patients who underwent PCI were related to MI, which accounted for nearly 50% of the total cardiac deaths. In the BARI 2D (Bypass Angioplasty Revascularization Investigation 2 Diabetes) trial, the reduction in the

FIGURE 4 Hazard Ratios of CABG versus PCI Subgroup Analyses

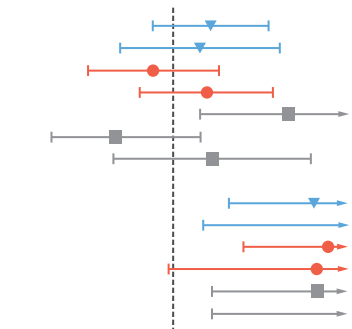
A

Cause of deaths	PCI	CABG	HR (95% CI)	*P*-value	Interaction *P*-value
Cardiac deaths					
Non-diabetic patients	50/672 (7.7%)	30/676 (4.9%)	1.62 (1.03-2.55)	0.035	0.30
Diabetic patients	28/231 (12.7%)	13/221 (6.5%)	2.01 (1.04-3.88)	0.034	
Three-vessel disease	48/546 (9.2%)	20/548 (4.0%)	2.34 (1.39-3.95)	<0.001	0.76
left main disease	30/357 (8.6%)	23/348 (7.2%)	1.23 (0.71-2.11)	0.46	
SYNTAX score≥33	38/290 (13.6%)	14/315 (4.9%)	2.99 (1.62-5.52)	<0.001	0.61
SYNTAX score 23-32	26/310 (8.8%)	19/300 (7.1%)	1.25 (0.69-2.26)	0.45	
SYNTAX score 0-22	14/299 (4.8%)	10/275 (3.8%)	1.24 (0.55-2.80)	0.60	



B

Cause of deaths	PCI	CABG	HR (95% CI)	*P*-value	Interaction *P*-value
Sudden cardiac deaths					
Non-diabetic patients	16/672 (2.5%)	9/676 (1.5%)	1.68 (0.74-3.81)	0.21	0.93
Diabetic patients	8/231 (3.6%)	6/221 (3.0%)	1.45 (0.47-4.43)	0.52	
Three-vessel disease	12/546 (2.3%)	8/548 (1.6%)	1.62 (0.64-4.11)	0.31	0.69
Left main disease	12/357 (3.5%)	7/348 (2.2%)	1.59 (0.62-4.03)	0.33	
SYNTAX score≥33	14/290 (5.0%)	3/315 (1.0%)	5.09 (1.46-17.71)	0.011	0.44
SYNTAX score 23-32	4/310 (1.3%)	8/300 (2.7%)	0.44 (0.13-1.46)	0.18	
SYNTAX score 0-22	6/299 (2.1%)	4/275 (1.4%)	1.72 (0.43-6.86)	0.44	
MI-related deaths					
Non-diabetic patients	23/672 (3.5%)	3/676 (0.5%)	7.26 (2.18-24.18)	0.001	0.096
Diabetic patients	13/231 (5.9%)	1/221 (0.5%)	11.66 (1.52-89.11)	0.018	
Three-vessel disease	28/546 (5.3%)	3/548 (0.6%)	8.78 (2.67-28.87)	<0.001	0.12
Left main disease	8/357 (2.3%)	1/348 (0.3%)	7.42 (0.93-59.36)	0.059	
SYNTAX score≥33	14/290 (5.0%)	2/315 (0.7%)	7.59 (1.72-33.40)	0.007	0.39
SYNTAX score 23-32	15/310 (5.0%)	1/300 (0.4%)	13.19 (1.74-99.87)	0.012	
SYNTAX score 0-22	7/299 (2.4%)	1/275 (0.4%)	6.02 (0.74-48.95)	0.093	
CHF/Other cardiac deaths					
Non-diabetic patients	11/672 (1.7%)	18/676 (2.9%)	0.58 (0.27-1.23)	0.15	0.49
Diabetic patients	7/231 (3.2%)	6/221 (3.1%)	0.90 (0.31-2.56)	0.84	
Three-vessel disease	8/546 (1.5%)	9/548 (1.9%)	0.75 (0.30-1.90)	0.55	0.22
Left main disease	10/357 (2.9%)	15/348 (4.7%)	0.62 (0.28-1.37)	0.24	
SYNTAX score≥33	10/290 (3.5%)	8/315 (2.8%)	1.21 (0.49-2.99)	0.67	0.65
SYNTAX score 23-32	7/310 (2.3%)	10/300 (3.8%)	0.61 (0.23-1.61)	0.32	
SYNTAX score 0-22	1/299 (0.3%)	6/275 (2.4%)	0.28 (0.02-1.20)	0.073	



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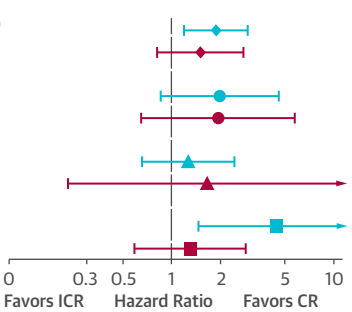
Cause of deaths	CR	ICR	HR (95% CI)	*P*-value	Interaction *P*-value
Cardiac deaths					
PCI group	32/509 (6.7%)	46/388 (11.8%)	1.89 (1.20-2.98)	0.006	0.80
CABG group	23/551 (4.6%)	20/321 (6.6%)	1.51 (0.82-2.77)	0.18	
Sudden cardiac deaths					
PCI group	9/509 (1.9%)	15/388 (3.8%)	1.99 (0.86-4.60)	0.11	0.67
CABG group	7/551 (1.4%)	8/321 (2.5%)	1.94 (0.75-5.76)	0.21	
MI-related deaths					
PCI group	19/509 (4.1%)	17/388 (4.4%)	1.27 (0.66-2.44)	0.47	0.074
CABG group	2/551 (0.4%)	2/321 (0.7%)	1.66 (0.23-11.70)	0.61	
CHF/Other cardiac deaths					
PCI group	4/509 (0.8%)	14/388 (3.6%)	4.46 (1.47-13.56)	0.008	0.14
CABG group	14/551 (2.8%)	10/321 (3.3%)	1.31 (0.59-2.88)	0.51	



(A) Cardiac cause of deaths within subgroups according to diabetes, left main (LM) or 3-vessel disease, and SYNTAX score. **(B)** Specific causes of cardiac deaths within subgroups according to diabetes, LM, or 3-vessel disease, and SYNTAX score. **(C)** Causes of deaths based on revascularization status (incomplete vs. complete) in PCI and CABG groups. CI = confidence interval; CR = complete revascularization; HR = hazard ratio; ICR = incomplete revascularization; other abbreviations as in Figures 1 and 2.

TABLE 2 Baseline Characteristics of the Patients in the SYNTAX Randomized Cohort Who Completed 5-Year Follow-Up

	PCI (n = 871)			CABG (n = 805)		
	Alive (n = 748)	Death (n = 123)	p Value	Alive (n = 708)	Death (n = 97)	p Value
Demographics						
Male	581 (77.7)	82 (66.7)	0.008	563 (79.5)	81 (83.5)	0.36
Age, yrs	64.6 ± 9.6	69.7 ± 8.6	<0.0001	64.1 ± 9.5	70.6 ± 8.1	<0.0001
Medically treated diabetes	177 (23.7)	44 (35.8)	0.004	165 (23.3)	29 (29.9)	0.15
Any	112 (15.0)	24 (19.5)	0.20	96 (13.6)	16 (16.5)	0.43
Requiring insulin	65 (8.7)	20 (16.3)	0.009	69 (9.7)	13 (13.4)	0.26
Hypertension	540 (72.7)	98 (81.0)	0.054	534 (75.9)	80 (84.2)	0.07
Peripheral vascular disease	50 (6.7)	26 (21.1)	<0.0001	59 (8.3)	25 (25.8)	<0.0001
Unstable angina	206 (27.5)	46 (37.4)	0.025	194 (27.4)	26 (26.8)	0.90
Stabile angina	435 (58.2)	61 (49.6)	0.08	430 (60.7)	45 (46.4)	0.007
Creatinine >200 μmol/l	6 (0.8)	4 (3.3)	0.018	8 (1.1)	6 (6.2)	<0.0001
Pulmonary hypertension	7 (0.9)	1 (0.8)	0.90	6 (0.8)	3 (3.1)	0.049
Previous MI	217 (29.4)	54 (44.3)	0.001	227 (32.4)	36 (37.9)	0.28
Carotid artery disease	52 (7.0)	17 (13.8)	0.009	50 (7.1)	17 (17.5)	<0.0001
Chronic obstructive pulmonary disease	52 (7.0)	16 (13.0)	0.02	57 (8.1)	18 (18.6)	0.001
LVEF						
Moderate (30%-49%)	119 (16.3)	34 (28.3)	0.002	119 (17.0)	20 (20.6)	0.37
Poor (<30%)	5 (0.7)	7 (5.8)	<0.0001	12 (1.7)	5 (5.2)	0.028
Baseline anatomical and clinical scores						
SYNTAX score	27.9 ± 11.4	32.4 ± 11.3	<0.0001	29.0 ± 11.3	30.6 ± 12.3	0.19
Additive EuroScore	3.2 ± 2.3	5.3 ± 3.0	<0.0001	3.1 ± 2.3	4.9 ± 2.9	<0.0001
Total Parsonnet score	7.9 ± 6.6	12.3 ± 7.7	<0.0001	7.6 ± 6.3	13.1 ± 7.9	<0.0001
Left main disease	301 (40.2)	45 (36.6)	0.44	273 (38.6)	49 (50.5)	0.024
Procedural characteristics						
Bypass time (min)	–	–	–	84.8 ± 32.6	93.1 ± 48.1	0.046
No. of grafts	–	–	–	2.8 ± 0.7	2.6 ± 0.8	0.036
No. of distal anastomoses	–	–	–	3.2 ± 0.9	3.0 ± 1.0	0.026
No. of stents implanted	4.6 ± 2.3	5.0 ± 2.2	0.053	–	–	–
Staged procedure	97 (13.0)	27 (22.0)	0.008	–	–	–
Incomplete revascularization	317 (42.7)	71 (58.2)	0.001	260 (36.4)	38 (40.9)	0.40
Treatments at baseline						
ARB or ACE inhibitor	432 (57.8)	83 (67.5)	0.042	441 (62.3)	73 (75.3)	0.013
Beta-blocker	555 (74.2)	89 (72.4)	0.67	563 (79.5)	64 (66.0)	0.003
Amiodarone	8 (1.1)	4 (3.3)	0.054	5 (0.7)	1 (1.0)	0.73
Cardiac glycoside	5 (0.7)	3 (2.4)	0.056	4 (0.6)	3 (3.1)	0.012
Diuretics	163 (21.8)	46 (37.4)	<0.0001	149 (21.0)	31 (32.0)	0.016
Treatments at discharge						
Acetylsalicylic acid	641 (86.4)	56 (45.9)	<0.0001	593 (83.9)	32 (34.0)	<0.0001
Thienopyridine antiplatelet	238 (32.1)	34 (27.9)	0.35	94 (13.3)	2 (2.1)	0.002
ARB or ACE inhibitor	547 (73.1)	44 (35.8)	<0.0001	514 (72.6)	35 (36.1)	<0.0001
Beta-blocker	572 (76.4)	52 (42.6)	<0.0001	529 (74.9)	36 (37.1)	<0.0001
Amiodarone	13 (1.7)	7 (5.7)	0.006	15 (2.1)	4 (4.1)	0.22
Statin	631 (85.0)	51 (41.8)	<0.0001	610 (86.3)	28 (29.8)	<0.0001

Values are n (%) or mean ± SD.

ARB = angiotensin receptor blocker; ACE = angiotensin-converting enzyme; LVEF = left ventricular ejection fraction; MI = myocardial infarction; other abbreviations as in Table 1.

composite of death, stroke, and MI with CABG versus medical therapy was driven largely by a reduction in MI, whereas the PCI versus medical therapy analysis showed similar rates of MI among the 2 groups (20). These findings emphasize the importance of MI reduction after PCI. Overall, use of the newer-generation DES (21) and default use of fractional flow reserve (22) are considered to reduce the rate of MI and death by reducing events of stent thrombosis and restenosis in more contemporary trials. The impact of prolonged use and the exact duration of dual antiplatelet therapy on ischemic events remain topics of debate (23,24). Nevertheless, de novo lesions in patients who previously

TABLE 3 Independent Predictors of All-Cause Mortality in the SYNTAX Randomized Cohort

	HR (95% CI)	p Value
SYNTAX randomized cohort		
Age (per 5-yr increase)	1.25 (1.15–1.36)	<0.0001
Medically treated diabetes	1.36 (1.01–1.84)	0.042
Peripheral vascular disease	2.04 (1.46–2.83)	<0.0001
LVEF poor (<30%)	4.47 (2.31–8.66)	<0.0001
Previous MI	1.31 (1.01–1.75)	0.044
Incomplete revascularization	1.37 (1.03–1.81)	0.029
Beta-blocker use at discharge	0.66 (0.47–0.93)	0.019
ARB or ACE inhibitor use at discharge	0.49 (0.35–0.69)	<0.0001
Acetylsalicylic acid use at discharge	0.47 (0.33–0.67)	<0.0001
Statin use at discharge	0.27 (0.19–0.39)	<0.0001
Nonfatal CVA during follow-up	2.07 (1.12–2.95)	0.032
Nonfatal MI during follow-up	3.86 (2.69–5.53)	<0.0001
PCI group		
Age (per 5-yr increase)	1.25 (1.11–1.40)	0.008
Medically treated diabetes	1.66 (1.09–2.53)	0.018
Peripheral vascular disease	2.77 (1.73–4.44)	<0.0001
LVEF poor (<30%)	2.26 (1.67–3.07)	<0.0001
LVEF moderate (30%–49%)	2.37 (1.54–3.63)	<0.0001
Incomplete revascularization	1.73 (1.17–2.58)	0.007
Beta-blocker use at discharge	0.59 (0.37–0.97)	0.036
ARB or ACE inhibitor use at discharge	0.43 (0.27–0.68)	<0.0001
Acetylsalicylic acid use at discharge	0.52 (0.32–0.85)	0.008
Statin use at discharge	0.43 (0.27–0.69)	0.001
Nonfatal MI during follow-up	5.49 (3.68–9.14)	<0.0001
CABG group		
Age (per 5-yr increase)	1.27 (1.09–1.48)	0.002
Peripheral vascular disease	2.01 (1.14–3.54)	0.016
Creatinine blood level >200 μmol/l	4.75 (1.38–16.41)	0.014
Chronic obstructive pulmonary disease	1.92 (1.05–3.48)	0.033
ARB or ACE inhibitor use at discharge	0.52 (0.28–0.94)	0.033
Acetylsalicylic acid use at discharge	0.39 (0.20–0.74)	0.004
Statin use at discharge	0.28 (0.20–0.43)	<0.0001
Nonfatal MI during follow-up	3.88 (1.60–9.39)	0.003

C-statistics for the models were: overall, 0.71 (95% CI: 0.68 to 0.75; $p < 0.0001$); PCI, 0.74 (95% CI: 0.69 to 0.79; $p < 0.0001$); CABG, 0.71 (95% CI: 0.65 to 0.76; $p < 0.0001$).

Abbreviations as in Tables 1 to 3.

TABLE 4 Independent Predictors of Cardiac Mortality in the SYNTAX Randomized Cohort

	HR (95% CI)	p Value
SYNTAX randomized cohort		
PCI treatment vs. CABG	1.55 (1.09–2.33)	0.045
Age (per 5-yr increase)	1.16 (1.04–1.31)	0.009
Peripheral vascular disease	2.55 (1.64–3.98)	<0.0001
LVEF poor (<30%)	5.08 (1.97–13.12)	0.001
LVEF moderate (30%–49%)	1.76 (1.15–2.69)	0.009
Previous MI	1.69 (1.14–2.50)	0.010
Incomplete revascularization	1.67 (1.13–2.45)	0.010
ARB or ACE inhibitor use at discharge	0.58 (0.37–0.92)	0.020
Acetylsalicylic acid use at discharge	0.54 (0.34–0.86)	0.010
Statins use at discharge	0.25 (0.16–0.41)	<0.0001
Nonfatal MI during follow-up	6.16 (3.98–9.53)	<0.0001
PCI group		
Peripheral vascular disease	2.79 (1.54–5.71)	0.001
LVEF poor (<30%)	1.83 (1.26–3.15)	0.006
LVEF moderate (30%–49%)	3.06 (1.84–5.57)	<0.0001
SYNTAX score	1.03 (1.01–1.05)	0.016
Incomplete revascularization	1.83 (1.15–3.24)	0.011
ARB or ACE inhibitor use at discharge	0.48 (0.27–0.81)	0.007
Acetylsalicylic acid use at discharge	0.46 (0.26–0.88)	0.018
Statins use at discharge	0.39 (0.21–0.58)	<0.0001
Nonfatal MI during follow-up	6.79 (4.24–10.72)	<0.0001
CABG group		
Peripheral vascular disease	4.10 (1.88–8.97)	<0.0001
Creatinine blood level >200 μmol/l	5.65 (1.19–26.81)	0.029
Prior MI	2.35 (1.14–4.81)	0.020
Bypass time (min)	1.01 (1.00–1.02)	0.009
Acetylsalicylic acid use at discharge	0.37 (0.16–0.83)	0.016
Statins use at discharge	0.29 (0.18–0.44)	<0.0001
Nonfatal MI during follow-up	7.25 (2.39–22.02)	<0.0001

C-statistics for the models were: overall, 0.72 (95% CI: 0.67 to 0.77; $p < 0.0001$); PCI, 0.70 (95% CI: 0.64 to 0.76; $p < 0.0001$); CABG, 0.75 (95% CI: 0.66 to 0.83; $p < 0.0001$).

Abbreviations as in Tables 1 to 3.

underwent PCI can progress to cause MI and subsequently death, whereas after CABG, the significance of such lesions with an existing patent bypass graft is limited. Even with the use of second-generation DES, the rate of spontaneous MI continues to be higher after PCI than CABG (25). Moreover, the lower rates of MI-related deaths with CABG might result from more complete revascularization and subsequently lower areas of ischemic myocardium (6,26). These concepts were validated in several studies that demonstrated that CABG had more durable protection against MI in patients with extensive CAD (16,27,28).

Because incomplete revascularization with PCI occurs more often in patients with highly complex lesions, and specifically chronic total occlusions (26,29), the present results emphasize these differences between CABG and PCI in the cardiac death subgroup analyses according to SYNTAX score tertiles. In the highest SYNTAX score tertiles, patients who underwent PCI had a higher risk of MI-related death and sudden cardiac deaths. Patients with complex disease undergoing PCI have a continued higher risk of stent thrombosis, which is related to cardiac death (30). In patients with complex disease and incomplete revascularization, lesions without revascularization have a considerable risk of progressing to acute events, a similar finding as in an analysis of the BARI trial that showed that revascularization versus no revascularization reduced the rate of sudden cardiac death (6). Moreover, progression of disease in patients with complex disease and higher SYNTAX scores may be enhanced because

TABLE 5 Independent Predictors of All-Cause and Cardiac Mortality in the SYNTAX Nested Registries

	HR (95% CI)	p Value
PCI registry		
All-cause mortality		
Age (per 5-yr increase)	1.44 (1.23–1.68)	<0.0001
Chronic obstructive pulmonary disease	1.90 (1.01–3.59)	0.047
LVEF poor (<30%)	3.19 (1.33–7.65)	0.009
Left main disease	2.29 (1.25–4.19)	0.007
Previous MI	1.88 (1.04–3.41)	0.037
Beta-blocker use at discharge	0.52 (0.28–0.96)	0.038
Nonfatal MI during follow-up	2.50 (1.07–5.83)	0.033
Cardiac mortality		
Age (per 5-yr increase)	1.53 (1.11–2.09)	0.008
Medically treated diabetes	5.56 (1.40–22.03)	0.015
Creatinine blood level >200 μmol/l	12.18 (1.51–80.44)	0.019
Left main disease	5.66 (1.52–21.10)	0.010
Previous MI	6.65 (1.91–23.15)	0.003
SYNTAX score	1.09 (1.04–1.14)	<0.0001
CABG registry		
All-cause mortality		
Age (per 5-yr increase)	1.21 (1.04–1.41)	0.015
Medically treated diabetes	2.22 (1.34–3.70)	0.002
Chronic obstructive pulmonary disease	3.32 (1.79–6.17)	<0.0001
LVEF moderate (30%–49%)	2.24 (1.33–3.78)	0.002
Procedure time (min)	1.01 (1.00–1.02)	<0.0001
Acetylsalicylic acid use at discharge	0.41 (0.22–0.76)	0.004
Nonfatal MI during follow-up	2.54 (1.08–5.96)	0.033
Cardiac mortality		
LVEF moderate (30%–49%)	4.05 (1.66–9.87)	0.002
Acetylsalicylic acid use at discharge	0.30 (0.18–0.80)	0.009
Nonfatal MI during follow-up	5.29 (1.52–18.41)	0.016

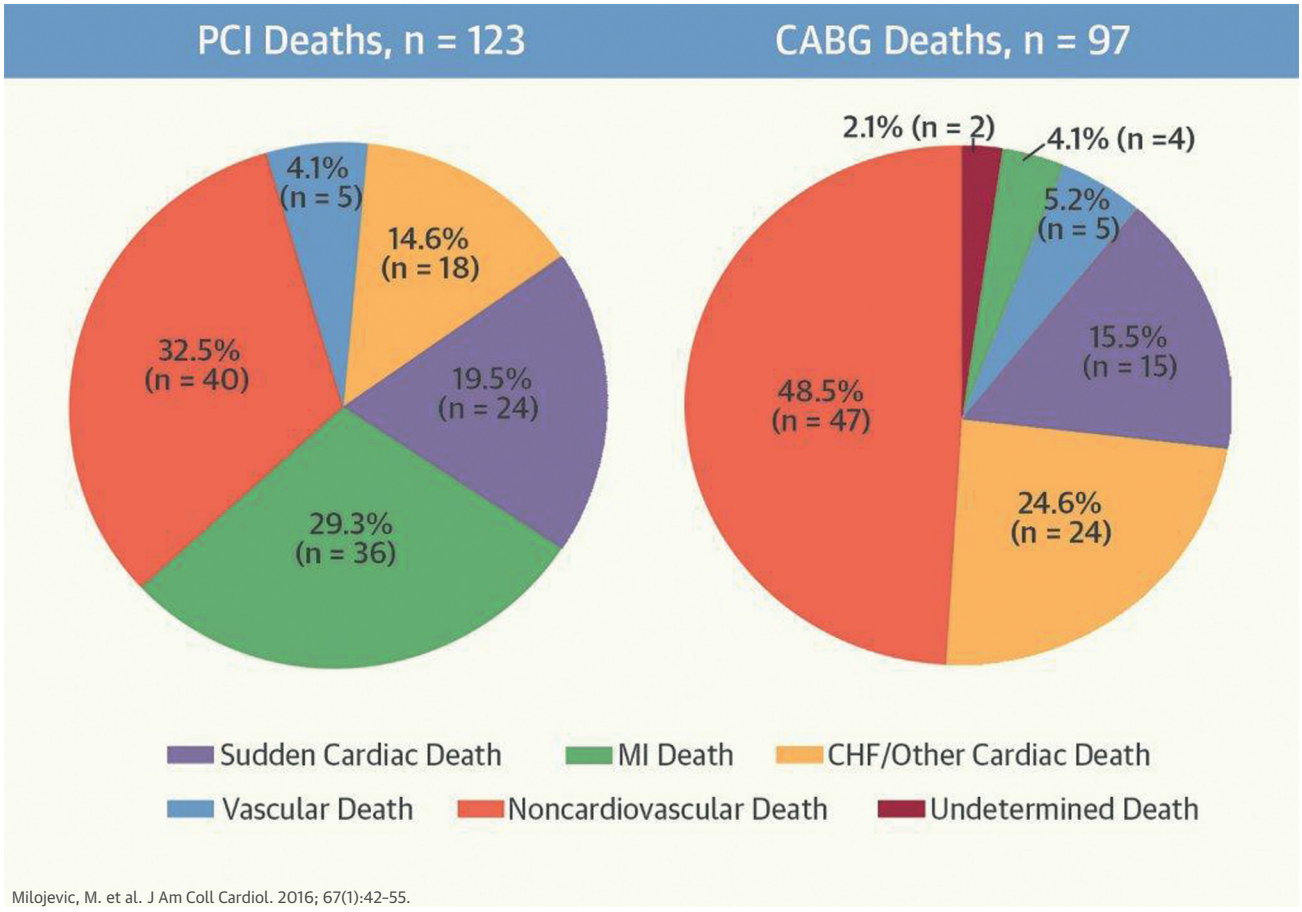
Abbreviations as in Tables 1 to 3.

of a higher risk profile (e.g., diabetes, hypertension, and so on) that furthermore increases the risk of adverse events (31). These considerations contributed to the selection of less complex LM disease in the EXCEL (Evaluation of the Xience Everolimus-Eluting Stent Versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization) randomized comparison between CABG and LM stenting with current generation DES.

In subgroups according to diabetes, the difference between PCI and CABG in cardiac death was greater in diabetic patients than in nondiabetic patients, whereas the difference in all-cause death was not significant in diabetic patients (32). This is notable in the BARI publication (33), but not in the results of the recent FREEDOM (Future Revascularization Evaluation in Patients with Diabetes Mellitus: Optimal Management of Multivessel Disease) trial, which results were in favor of CABG in terms of all-cause death and comparable outcomes in cardiovascular death (34). This may reflect the relatively low number of events of cardiac or cardiovascular death and the play of chance that may play a role. In other subgroup analyses, the significant increases in cardiac deaths that were observed after PCI in patients with 3VD strengthens the finding that these patients particularly benefited from CABG (35). Conversely, consistent with other studies of patients with LM diseases, cardiac death was not different between PCI and CABG (25,36), justifying the hypothesis on which the current EXCEL trial is based (NCT01205776).

Multivariate models identified several distinct variables associated with long-term all-cause and cardiac death that may aid decisions regarding revascularization strategies. In comparison with previously published studies that identified predictors of long-term mortality (33,37,38), our results add significantly to the current body of evidence. Long-term analyses of all-cause mortality may lose accuracy in determining the relevance of myocardial revascularization to the occurrence of death, whereas analysis of cardiac death as adjudicated by a CEC may provide a more clear distinction between death as a result of comorbidities or as the consequence of CAD. Furthermore, the majority of models to predict death included only preoperative values. The present analyses also emphasized the importance of nonfatal adverse events (stroke and MI) as predictors of future fatal events. We identified that a nonfatal stroke was a significant predictor of death, which corresponds with the association between stroke and subsequent increased risk not only of repeated stroke, but also of the combined risk of stroke and MI (39). In addition, a nonfatal MI was associated with an increased risk of all-cause and cardiac mortality. This might be the result of progressive heart failure because our findings also showed that patients with a moderate or poor left ventricular ejection fraction and a history of MI are at an increased risk of MI-related death. Therefore, prevention of MI after treatment with PCI, but also after CABG, is of critical importance for survival. As shown in our multivariate analyses, as well as in several other studies, the importance of secondary prevention medication is essential in this regard. Iqbal et al. (40) recently showed that the impact of secondary prevention medication was even larger than the impact of performing PCI or CABG in patients with complex CAD. Guideline-directed medical therapy should be a principal strategy for all patients with CAD, as also recently shown in an analysis of BARI 2D data (41). This information on predictors may be particularly useful for the Heart Team currently when both PCI and CABG are excellent treatment options; the Heart Team should not only determine the most optimal

CENTRAL ILLUSTRATION **Causes of Deaths in the SYNTAX Randomized Cohort: PCI and CABG Comparison**



Milojevic, M. et al. J Am Coll Cardiol. 2016; 67(1):42–55.

After percutaneous coronary intervention (PCI), the leading cause of cardiovascular death was myocardial infarction (MI)-related death. After coronary artery bypass grafting (CABG), the leading cause of cardiovascular death was congestive heart failure (CHF), arrhythmia, or other causes (e.g., arrhythmia and all other cardiac deaths).

revascularization strategy, but which strategy might also be useful when integrated into the post-procedural phase (7).

STUDY LIMITATIONS. The present study represents a post-hoc analysis; therefore, the results should be regarded as exploratory and hypothesis-generating. Moreover, a great number of subgroup analyses have been reported, so results should be interpreted with caution because some differences may be the results of chance (42). Although the SYNTAX trial was an all-comers randomized trial, inclusion of patients in a randomized trial is limited to specific inclusion and exclusion criteria; therefore, the external validity, which reflects actual patients in the real-world, may be suboptimal.

Despite the primarily used SYNTAX trial classifications, the determination of cause-specific death could not always be established. This is particularly relevant to the subcategories of cardiac death in which absolute precision may not always be possible. However, bias was limited by event adjudication by a blinded committee of physician experts using previous standardized definitions.

Autopsy was performed in a low number of cases (n = 38, 10.7%); therefore, the rate of death related to MI could be underestimated, considering that MI might be involved in the process of heart failure and cardiac rupture, as well as sudden cardiac death.

We did not have information on post-procedural occurrence of additional co-morbidities, which could affect the established groups of predictors.

Although medication use was recorded throughout different time points during follow-up, there were no data on compliance rates or on reasons for

discontinuation of medication. Moreover, at later follow-up with longer periods between collection of medication data (e.g., 2 years), we were unable to determine the exact date of medication discontinuation. Therefore, we could not assess the impact of medication use during follow-up on death rates.

CONCLUSIONS

For patients with complex CAD, CABG compared with PCI did not reduce all-cause death, but was shown to be associated with a significantly reduced rate of cardiac death that was driven primarily by a reduction of death as a consequence of MI. This reduction was greatest in patients with diabetes, 3VD, or a SYNTAX score ≥33. Although PCI is becoming a more acceptable revascularization strategy for patients with LM or 3VD, treatments following PCI should target reducing post-revascularization spontaneous MI, because this remains the leading cause of death after PCI.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: For patients with complex coronary disease, CABG was associated with a lower rate of cardiac death after 5 years than PCI, and patients who underwent PCI with first-generation DES were at higher risk of fatal MI than those managed with CABG.

TRANSLATIONAL OUTLOOK: Additional randomized studies in patients undergoing PCI with newer generation DES should examine predictors of MI-related death.

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KEY WORDS cardiac death, cause of death, coronary artery bypass grafting, heart failure, myocardial infarction, percutaneous coronary intervention, stroke, sudden death, SYNTAX

APPENDIX For supplemental tables and materials, please see the online version of this article.