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ORIGINAL INVESTIGATIONS

10-Year Follow-Up After Revascularization in Elderly Patients With Complex Coronary Artery Disease

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ABSTRACT

BACKGROUND The optimal revascularization strategy for the elderly with complex coronary artery disease remains unclear.

OBJECTIVES The goal of this study was to investigate 10-year all-cause mortality, life expectancy, 5-year major adverse cardiac or cerebrovascular events (MACCE), and 5-year quality of life (QOL) after percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG) in elderly individuals (>70 years old) with 3-vessel disease (3VD) and/or left main disease (LMD).

METHODS In the present pre-specified analysis on age of the SYNTAX Extended Survival study, 10-year all-cause death and 5-year MACCE were compared with Kaplan-Meier estimates and Cox proportional hazards models among elderly or nonelderly patients. Life expectancy was estimated by restricted mean survival time within 10 years, and QOL status according to the Seattle Angina Questionnaire up to 5 years was assessed by linear mixed-effects models.

RESULTS Among 1,800 randomized patients, 575 patients (31.9%) were elderly. Ten-year mortality did not differ significantly between PCI and CABG in elderly (44.1% vs. 41.1%; hazard ratio [HR]: 1.08; 95% confidence interval [CI]: 0.84 to 1.40) and nonelderly patients (21.1% vs. 16.6%; HR: 1.30; 95% CI: 1.00 to 1.69; $p_{interaction} = 0.332$). Among elderly patients, 5-year MACCE was comparable between PCI and CABG (39.4% vs. 35.1%; HR: 1.18; 95% CI: 0.90 to 1.56), whereas it was significantly higher in PCI over CABG among nonelderly patients (36.3% vs. 23.0%; HR: 1.69; 95% CI: 1.36 to 2.10; $p_{interaction} = 0.043$). There were no significant difference in life expectancy (mean difference: 0.2 years in favor of CABG; 95% CI: −0.4 to 0.7) and 5-year QOL status between PCI and CABG among elderly patients.

CONCLUSIONS Elderly patients with 3VD and/or LMD had comparable 10-year all-cause death, life expectancy, 5-year MACCE, and 5-year QOL status irrespective of revascularization mode. (Synergy Between PCI With TAXUS and Cardiac Surgery: SYNTAX Extended Survival [SYNTAXES]; NCT03417050) (SYNTAX Study: TAXUS Drug-Eluting Stent Versus Coronary Artery Bypass Surgery for the Treatment of Narrowed Arteries [SYNTAX]; NCT00114972) (J Am Coll Cardiol 2021;77:2761–73) © 2021 by the American College of Cardiology Foundation.

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ABBREVIATIONS AND ACRONYMS

3VD = 3-vessel disease

CABG = coronary artery bypass grafting surgery

CAD = coronary artery disease

LMCAD = left main coronary artery disease

MACCE = major adverse cardiac or cerebrovascular events

PCI = percutaneous coronary intervention

QOL = quality of life

SAQ = Seattle Angina Questionnaire

The average life expectancy is increasing worldwide. In the United States, average life expectancy at birth was 76.9 years in the year 2000 (1), 78.7 years in 2018 (2), and is expected to reach 80 years in approximately 2030 (3). Coronary artery disease (CAD) is the leading cause of death among elderly patients, who tend to have more complex and severe CAD compared with younger patients. Therefore, in the era of a global aging, discussions on the optimal treatment strategy for elderly patients with complex CAD, taking into account long-term outcomes, are essential and inevitable. Unfortunately these debates are hampered because numerous trials have excluded elderly patients because of age itself, or their comorbidities, resulting in a dearth of evidence on the optimal treatment strategy for these patients (4,5).

SEE PAGE 2774

In this context, current guidelines do not provide sufficient evidence-based recommendations for the management of elderly patients with complex CAD such as 3-vessel disease (3VD) or left main coronary artery disease (LMCAD) (4,6,7). Older patients are frequently more frail than younger patients, and consequently practitioners may be reluctant to recommend an invasive surgical strategy to treat their complex CAD (8). Although risk models incorporating age and patient comorbidities are advocated to quantify overall risk, and may assist the Heart Team in deciding the most appropriate revascularization strategy, these models were developed from studies including mainly younger patients (9,10).

Furthermore, to date, no randomized trials have evaluated the full range of relevant outcomes including an elderly patient's life expectancy and quality of life (QOL), all of which are essential aspects of the decision-making process for elderly patients (11).

The SYNTAX (Synergy between PCI with Taxus and Cardiac Surgery) trial, which compared percutaneous coronary intervention (PCI) versus coronary artery bypass graft (CABG) in patients with 3VD or LMCAD, had minimum exclusion criteria, and therefore provides the opportunity to analyze the outcome of elderly subjects more appropriately than other trials with stricter exclusion criteria (12). The aim of the present prespecified subgroup analysis of the SYNTAXES (Synergy between PCI with Taxus and Cardiac Surgery Extended Survival) study was to investigate the impact of revascularization modality on 10-year all-cause death and life expectancy, as well as major adverse cardiac or cerebrovascular events (MACCE) rates and QOL up to 5 years among elderly and non-elderly patients with 3VD and/or LMCAD.

METHODS

STUDY DESIGN AND PATIENT POPULATION. The present study is a prespecified analysis of patients ≤ or >70 years old, conceived as part of the SYNTAXES study (NCT03417050) (13), which was an investigator-driven extended 10-year follow-up of the randomized SYNTAX trial (NCT00114972) beyond its original follow-up of 5 years (12,14). In brief, the SYNTAX trial was a multicenter, randomized controlled trial done in 85 hospitals across 18 North American and European countries, which adopted minimum exclusion criteria except for those presenting with myocardial infarction. A total of 1,800 patients with de novo 3VD and/or LMCAD, who were deemed eligible for both PCI and CABG based on clinical judgment and the consensus of a Heart Team, were enrolled and randomized in a 1:1 fashion either to receive PCI (n = 903) with the uniform use of TAXUS Express paclitaxel drug-eluting stents (Boston Scientific Corporation, Marlborough, Massachusetts) or CABG (n = 897). If patients were deemed ineligible for either PCI or CABG, they were entered into the nested CABG (PCI-ineligible patients) or PCI (CABG-ineligible patients) registries.

The main result of the SYNTAXES study in terms of vital status up to 10 years has been reported (13). The median duration of follow-up was 11.2 years (interquartile range: 7.7 to 12.1 years) overall and 11.9 years (interquartile range: 11.2 to 12.3 years) in survivors (13). The SYNTAX and SYNTAXES trials were

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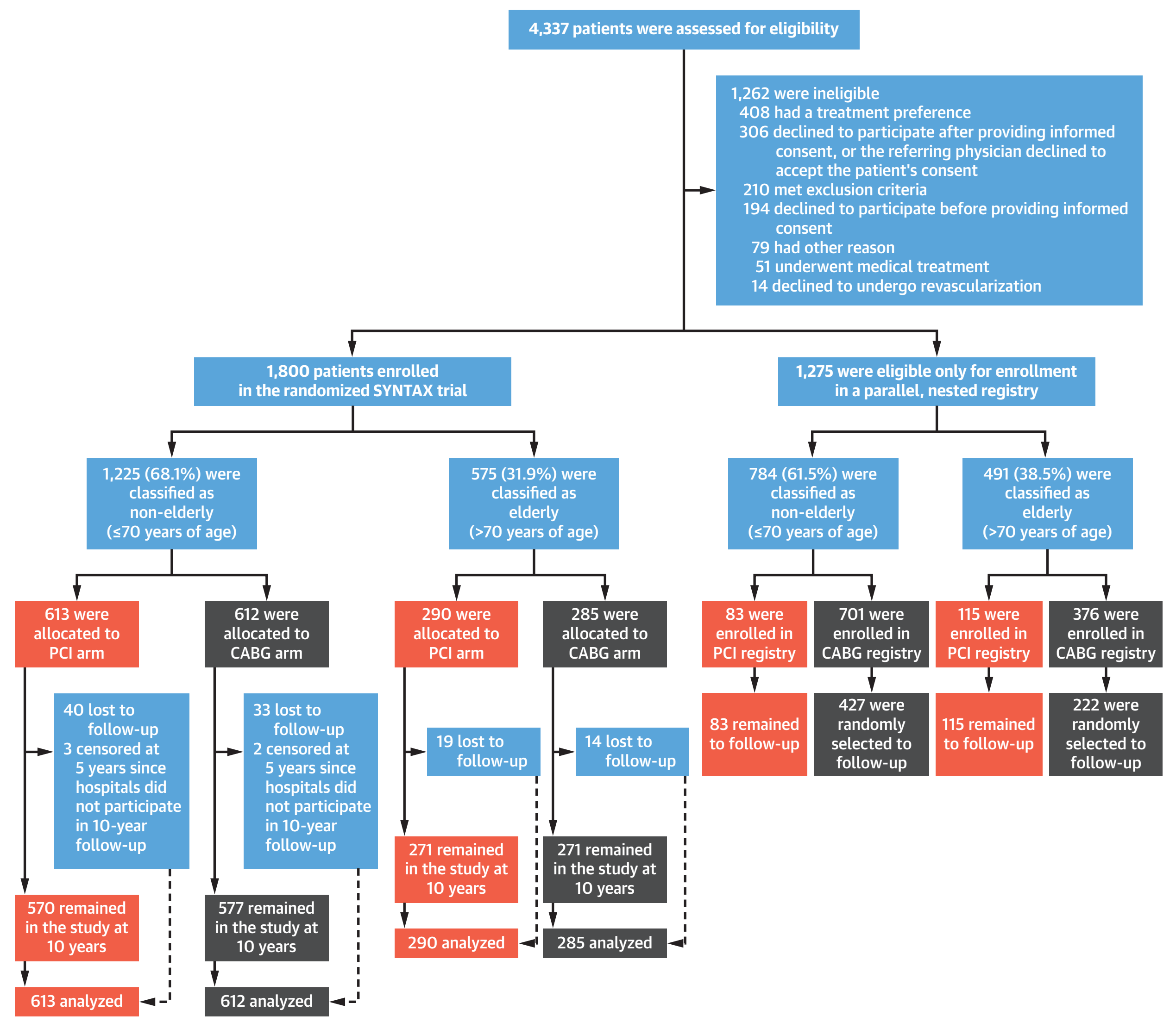
FIGURE 1 Consort Flowchart of the Present Study



CABG = coronary artery bypass graft; PCI = percutaneous coronary intervention; SYNTAX = Synergy between PCI with Taxus and Cardiac Surgery.

approved by the ethics committees at each investigating center, and all patients provided written informed consent before participation in the SYNTAX trial. Follow-up was performed in accordance with local law and regulations of each participating institution and complied with the Declaration of Helsinki.

ELDERLY SUBGROUP. Patients were divided into 2 groups according to their age at the time of randomization with the prespecified threshold of 70 years old; elderly patients (>70 years old) or nonelderly patients (≤70 years old).

STUDY ENDPOINT. The primary endpoint of this study was all-cause death at 10 years. Vital status was confirmed by using electronic healthcare record review and national death registries. Patients with missing vital status were included in the analysis and censored at the time of "lost to follow-up" or at 5 years when recruiting centers did not participate in the SYNTAXES study for 10-year extended follow-up (a total of 5 patients in 2 centers).

We also assessed major adverse cardiac and cerebrovascular events (MACCE: defined as the composite of all-cause death, myocardial infarction [MI], stroke, and any repeat revascularization) at 5 years and its components, which were adjudicated by an independent clinical events committee.

TABLE 1 Baseline Characteristics in Patients >70 or ≤70 Years

	Patients >70 Years (n = 575)	Patients ≤70 Years (n = 1,225)	p Value
Randomization			0.880
PCI	50.4 (290/575)	50.0 (613/1,225)	
CABG	49.6 (285/575)	50.0 (612/1,225)	
Age, yrs	75.8 ± 3.6	60.1 ± 7.4	**<0.001**
Octogenarian ≥80 yrs	16.3 (94/575)	-	
Sex			
Male	66.4 (382/575)	82.9 (1,016/1,225)	**<0.001**
Female	33.6 (193/575)	17.1 (209/1,225)	**<0.001**
Body mass index, kg/m^2	27.1 ± 4.1	28.4 ± 4.8	**<0.001**
<20 kg/m^2	1.7 (10/575)	1.3 (16/1224)	0.526
Diabetes	24.7 (142/575)	25.3 (310/1,225)	0.816
On insulin	9.4 (54/575)	10.4 (128/1,225)	0.504
Metabolic syndrome	41.9 (189/451)	47.6 (467/982)	0.052
Hypertension	69.2 (398/575)	65.1 (798/1,225)	0.097
Dyslipidemia	69.5 (398/573)	81.9 (993/1,212)	**<0.001**
Current smoking	6.7 (38/570)	26.6 (325/1,223)	**<0.001**
Previous MI	31.4 (178/566)	33.5 (407/1,214)	0.416
Previous cerebrovascular disease	20.2 (115/569)	11.3 (138/1,222)	**<0.001**
Previous stroke	5.4 (31/569)	3.9 (47/1,220)	0.136
Previous transient ischemic attack	5.8 (33/568)	4.2 (51/1,221)	0.149
Previous carotid artery disease	13.4 (77/575)	5.8 (71/1,225)	**<0.001**
Peripheral vascular disease	12.3 (71/575)	8.7 (106/1,225)	**0.017**
Chronic obstructive pulmonary disease	9.9 (57/575)	7.9 (97/1,225)	0.175
Chronic kidney disease	43.4 (228/525)	7.9 (88/1,113)	**<0.001**
Creatinine clearance, ml/min	64.7 ± 19.4	96.2 ± 32.9	**<0.001**
LVEF, %	58.7 ± 12.9	58.6 ± 13.1	0.857
Congestive heart failure	6.5 (37/567)	3.8 (46/1,211)	**0.015**
Clinical presentation			
Silent ischemia	15.5 (89/575)	14.0 (171/1,225)	0.389
Stable angina	53.2 (306/575)	58.9 (721/1,225)	**0.025**
Unstable angina	31.3 (180/575)	27.2 (333/1,225)	0.073
EuroSCORE	6.0 ± 2.2	2.7 ± 2.1	**<0.001**
Parsonnet SCORE	16.3 ± 5.8	4.8 ± 3.5	**<0.001**
Disease type			0.070
3VD	57.7 (332/575)	62.3 (763/1,225)	
LMCAD	42.3 (243/575)	37.7 (462/1,225)	
Disease type			**0.024**
LMCAD only	4.0 (23/574)	5.6 (68/1,225)	
LMCAD+1VD	8.4 (48/574)	7.3 (90/1,225)	
LMCAD+2VD	15.3 (88/574)	10.6 (130/1,225)	
LMCAD+3VD	14.6 (84/574)	14.2 (174/1,225)	
2VD (No LMCAD)	1.2 (7/574)	2.4 (29/1,225)	
3VD (No LMCAD)	56.4 (324/574)	59.9 (734/1,225)	
Number of lesions	4.4 ± 1.7	4.3 ± 1.8	0.211
SYNTAX score	30.2 ± 11.8	28.0 ± 11.2	**<0.001**
SYNTAX score tercile			
Low	25.4 (144/568)	35.2 (430/1,221)	**<0.001**
Intermediate	36.8 (209/568)	32.8 (401/1,221)	0.108
High	37.9 (215/568)	31.9 (390/1,221)	**0.016**
Any total occlusion	21.7 (123/568)	24.0 (292/1,219)	0.307
Any bifurcation	76.6 (435/568)	71.0 (865/1,219)	**0.014**
Number of stents	4.5 ± 2.1	4.7 ± 2.3	0.263
Total stent length per patient, mm	82.9 ± 43.7	87.0 ± 49.9	0.223
Off pump CABG	15.9 (43/271)	14.7 (87/593)	0.682

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Health status was assessed directly from patients by self-reported survey questions using the Seattle Angina Questionnaire (SAQ), a 19-item questionnaire that measures 5 domains of health status related to CAD: angina frequency, physical limitations, disease perception/QOL, angina stability, and treatment satisfaction (15). Scores range from 0 to 100, with higher scores indicating fewer symptoms and better health status. The questionnaires were completed in person at the time of scheduled follow-up visits or were sent by mail at baseline and at 1, 6, 12, 36, and 60 months after randomization.

NESTED REGISTRIES. For exploratory purposes, risk of all-cause death at 10 years was also assessed among elderly (>70 years old) or nonelderly (≤70 years old) patients included in the nested CABG or PCI registries (12). In the nested CABG registry (N = 1,077), 649 (60%) patients were randomly selected by the central allocation service for clinical follow-up, whereas in the nested PCI registry (N = 198), all patients were followed-up for 10-year survival (**Figure 1**) (12).

STATISTICAL ANALYSIS. All the analyses were performed on the intention-to-treat population. Continuous variables are expressed as mean ± SD and were compared using independent Student's *t*-tests. Categorical variables are presented as counts and percentages and are compared using the chi-square test or Fisher exact test as appropriate. Kaplan-Meier method was used to estimate the cumulative rates of events over time, and the log-rank test was performed to examine the differences between groups.

The incidence of all-cause death up to 10 years was assessed in comparison between PCI and CABG using the unadjusted Cox proportional hazards model to calculate hazard ratios (HRs) and 95% confidence intervals (CIs) in elderly and nonelderly patients, with treatment-by-subgroup interaction. The impact of age on the primary endpoint was assessed as a continuous variable by depicting restricted cubic spline curves derived from the adjusted proportional hazards model with the reference of 70 years in either the PCI or CABG arm. The risk-difference in all-cause death at 10 years between the nested PCI and CABG registries was assessed by using the unadjusted and adjusted Cox proportional hazards models taking into account the nonrandomized fashion. The adjusted covariates had been selected based on prior knowledge of the association of these covariables with the outcomes (16).

As for the life expectancy analysis for elderly patients, restricted mean survival time within 10 years after PCI or CABG was estimated from the area under the Kaplan-Meier curve (17).

For QOL status assessments in elderly patients, linear mixed-effects models were used to estimate the differences between the PCI and CABG arms in terms of angina frequency, physical limitation, QOL, and treatment satisfaction according to the SAQ subscales as continuous variables during the 5-year follow-up, including age, sex, and each baseline SAQ subscale scores as covariates. In the linear mixed-effects models, it was assumed that any missing data were missing at random.

For exploratory purposes, the risk-differences in all-cause death at 10 years and MACCE at 5 years between PCI and CABG in elderly or nonelderly patients were further stratified by several subgroups; sexes, medically treated diabetes, disease type (3VD or LMCAD), anatomic SYNTAX score terciles (≤22, 23 to 32, or ≥33), and left ventricular ejection fraction (LVEF: >40% or ≤40%).

Statistical significance was defined as a 2-sided p value ≤0.05. All analyses were performed using SPSS Statistics version 26 (IBM Corp., Armonk, New York) and R software version 3.5.1 (R Foundation for Statistical Computing, Vienna, Austria).

TABLE 1 Continued

	Patients >70 Years (n = 575)	Patients ≤70 Years (n = 1,225)	p Value
Number of total conduits	2.7 ± 0.7	2.8 ± 0.7	0.069
Number of arterial conduits	1.2 ± 0.5	1.5 ± 0.7	**<0.001**
Number of venous conduits	1.5 ± 0.8	1.3 ± 0.9	**0.028**
Complete revascularization	58.2 (329/565)	60.7 (729/1,201)	0.323
Residual SYNTAX score*	4.7 ± 7.0	4.4 ± 6.8	0.470
Residual SYNTAX score >8*	19.5 (56/287)	16.1 (97/603)	0.217
Medication at discharge			
Any antiplatelet therapy			
Aspirin	89.7 (507/565)	93.8 (1,126/1,201)	**0.004**
Thienopyridine	58.1 (328/565)	59.0 (709/1,201)	0.717
Statin	77.3 (437/565)	82.3 (988/1,201)	**0.017**
Beta blockers	76.1 (430/565)	81.8 (982/1,201)	**0.006**
ACE inhibitor	48.3 (273/565)	50.7 (609/1,201)	0.359
ARB	10.1 (57/565)	10.2 (123/1,201)	1.000

Values are % (n/N) or mean ± SD. **Bold** p values are statistically significant. *Residual SYNTAX score was available only post-PCI due to lack of post-CABG angiography.

ACE = angiotensin-converting enzyme; ARB = angiotensin II receptor blocker; CABG = coronary artery bypass graft; LMCAD = left main coronary artery disease; LVEF = left ventricular ejection fraction; MI = myocardial infarction; PCI = percutaneous coronary intervention; SYNTAX = Synergy between PCI with Taxus and Cardiac Surgery; 3VD = 3-vessel disease; 2VD = 2-vessel disease.

RESULTS

BASELINE CHARACTERISTICS. Of 1,800 patients enrolled in the SYNTAX trial, 575 patients (31.9%) were elderly (>70 years). Among those, vital status was available in 538 patients (93.6%) after 10 years (Figure 1). Baseline characteristics of elderly and nonelderly patients are summarized in Table 1. The mean age of elderly and nonelderly patients, at the time of randomization, was 75.8 ± 3.6 years and 60.1 ± 7.4 years, respectively. Compared with nonelderly patients, elderly patients were more frequently women (33.6% vs. 17.1%, p < 0.001) and had lower body mass index; higher prevalences of cerebrovascular disease, PVD, CKD, and congestive heart failure; had higher EuroSCORE, Parsonnet SCORE, and anatomic SYNTAX score; and had more bifurcation lesions. Elderly patients were less likely to be discharged on aspirin, statins, and beta blockers compared with nonelderly patients. Among patients undergoing CABG, the elderly group used fewer arterial conduits but more venous conduits compared with the nonelderly group. The prescription rates of the medications up to 5 years are presented in Supplemental Table 1, demonstrating overall lower prescription rates in elderly patients than those in nonelderly patients.

Baseline characteristics stratified by the randomized revascularization strategies in elderly or nonelderly groups are presented in Supplemental Table 2, in which most baseline variables were well balanced between 2 randomized groups.

CLINICAL OUTCOMES OF ELDERLY (>70 YEARS) AND NONELDERLY PATIENTS. The comparison of the cumulative incidence of all-cause death up to 10 years or MACCE up to 5 years between the PCI and CABG arms among elderly and nonelderly patients is shown in Figure 2 and Table 2.

At 10 years of follow-up, there was no significant difference in the risk of all-cause death between PCI and CABG in elderly patients (44.0% vs. 41.5%; HR: 1.08; 95% CI: 0.84 to 1.40; p = 0.530). In nonelderly patients, PCI was associated with a numerically higher risk of all-cause death at 10 years compared with CABG (21.1% vs. 16.6%; HR: 1.30; 95% CI:1.00 to 1.69; p =0.052; p for interaction = 0.332).

Among elderly patients, the risk of MACCE at 5 years did not differ between PCI and CABG (39.4% vs. 35.1%; HR: 1.18; 95% CI: 0.90 to 1.56; p = 0.233). In contrast, among nonelderly patients, PCI was associated with a significantly higher risk of 5-year MACCE compared with CABG (36.3% vs. 23.0%; HR: 1.69; 95% CI: 1.36 to 2.10; p <0.001; p for interaction = 0.043).

The adjusted risks of 10-year mortality or 5-year MACCE according to continuous age at the randomization in each revascularization strategy are illustrated in the Central Illustration. The risk-difference between PCI and CABG of 10-year all-cause mortality and 5-year MACCE became smaller as age increased.

In the subgroup analyses among elderly patients, significant treatment-by-subgroup interactions were observed in terms of 5-year MACCE in the SYNTAX score terciles and LVEF subgroups, whereas no interaction was observed in any subgroups in terms of 10-year mortality (Supplemental Figures 1 and 2).

NESTED REGISTRIES. At 10 years, elderly patients included in the nested PCI registry had a significantly higher risk of all-cause death compared with those included in the nested CABG registry (67.7% vs. 42.1%; adjusted HR: 2.32; 95% CI: 1.39 to 3.89; p = 0.001, Supplemental Table 3). In contrast, among nonelderly patients, there was no significant difference in the adjusted risk of all-cause death at 10 years between the nested PCI and CABG registries (37.5% vs. 20.6%; adjusted HR: 1.73; 95% CI: 0.76 to 3.94; p = 0.191, Supplemental Table 3).

LIFE EXPECTANCY. The restricted mean survival times of the elderly patients within 10 years after their index procedure were similar between those treated with PCI and CABG with mean estimates of 7.9 years (95% CI: 7.5 to 8.3 years) for those undergoing PCI and 7.7 years (95% CI: 7.4 to 8.1 years) for those undergoing CABG with a mean difference of 0.2 years (95% CI: −0.4 to 0.7 years; p = 0.524). Differences in the estimated life expectancy between the 2 revascularization strategies among septuagenarians (70 to 80 years of age) or octogenarians (80 to 90 years of age) were also small, with mean differences of 0.2 years (95% CI: −0.4 to 0.8 years) and 0.0 years (95% CI: −1.4 to 1.4 years), respectively.

QUALITY OF LIFE. According to the linear mixed effects models of SAQ subscales, all disease-specific health status was similar between PCI and CABG up to 5 years, with mean differences of −1.8 (95% CI: −3.8 to 0.3), 0.5 (95% CI: −2.6 to 3.7), 1.3 (95% CI: −1.4 to 4.1), and 0.0 (95% CI: −1.8 to 1.8) in angina frequency, physical limitation, treatment satisfaction, and QOL, respectively (**Figure 3**). Results of other health status subscales are shown in Supplemental Table 4.

DISCUSSION

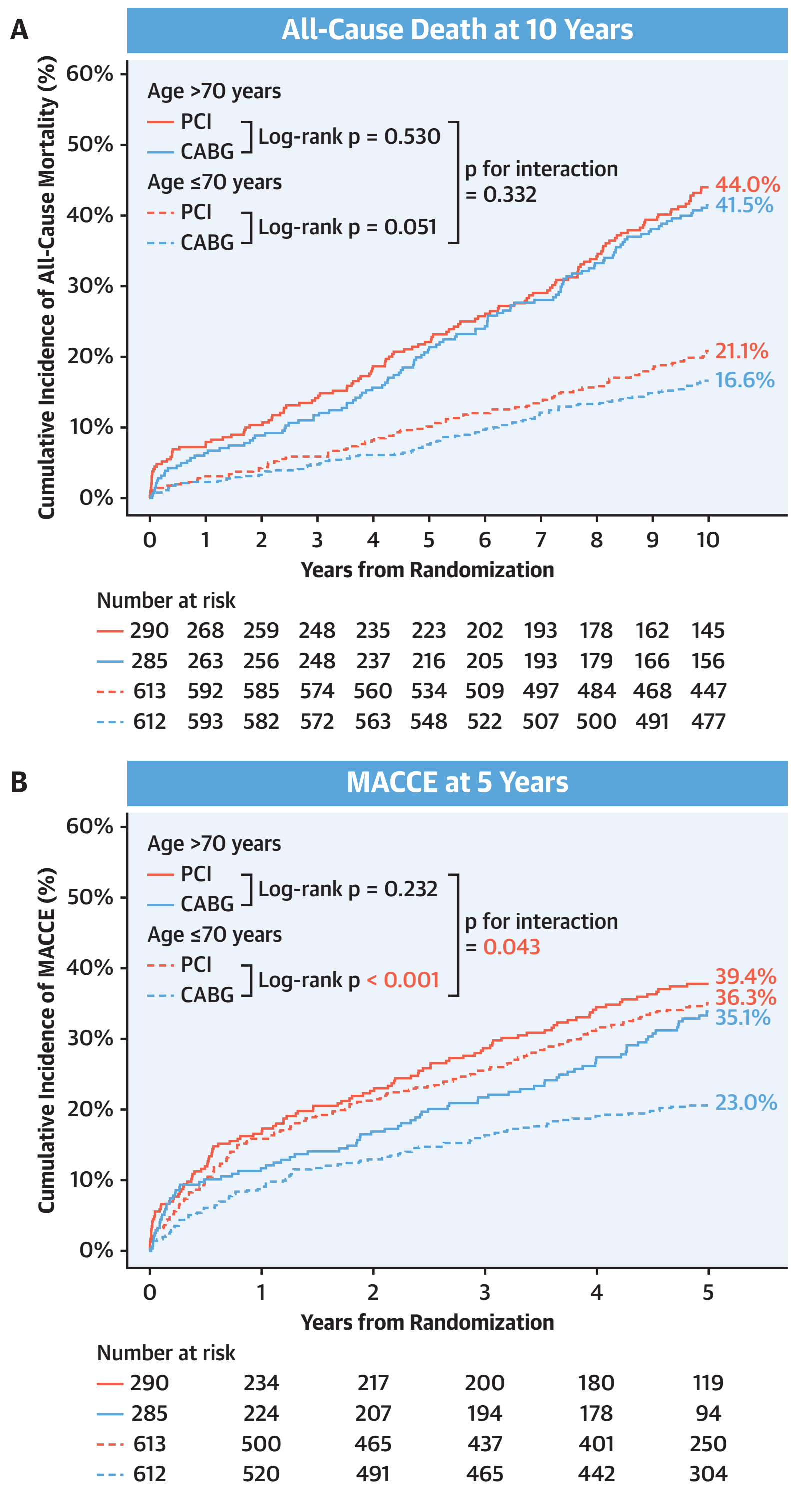
FINDINGS OF THE CURRENT STUDY. The present analysis demonstrates that among elderly patients (>70 years of age) with complex CAD, the risk of all-cause death at 10 years or MACCE at 5 years did not differ significantly between PCI versus CABG. In contrast, among nonelderly patients (≤70 years of age), the risk of MACCE at 5 years was significantly higher with PCI than CABG, suggesting that the beneficial effects of CABG over PCI on clinical outcomes observed in younger patients would not apply to elderly individuals. In fact, the adjusted HR for all-cause death steadily increases with age in both PCI and CABG arms, whereas for MACCE, the HR in the PCI arm seems to plateau with older age, and in the CABG arm the MACCE risk steadily increases as age becomes higher (**Central Illustration**).

ADVANCED AGE, COMPLEX CAD, AND MORTALITY RISK. Age is one of the strongest risk factors in the pathogenesis of atherosclerosis, and it follows that older patients tend to have more complex and severe CAD compared with younger patients. Indeed, in the present study, patients older than 70 years had significantly higher SYNTAX scores than younger patients. Higher prevalence of concomitant diseases such as renal impairment and congestive heart failure in the elderly, as reflected by their significantly higher EuroSCORE and Parsonnet SCORE, may increase the risk of other adverse events related to a highly invasive strategy, such as delirium and cognitive decline.

It is notable that a significant interaction exists between age (elderly or nonelderly) and treatment effect of PCI and CABG in terms of 5-year MACCE. The 5-year MACCE was significantly higher in PCI than in CABG for nonelderly population; however, it was not significant in elderly individuals. This was mainly because in elderly individuals the mortality differences between PCI and CABG were not significant (HR: 1.08; 95% CI: 0.75 to 1.55), whereas the risk-difference in MI was significant (HR: 2.08; 95% CI: 1.10 to 3.91) but not as much as the one observed in nonelderly individuals (HR: 2.76; 95% CI: 1.63 to 4.66). It would be hypothesized that because of the limited life expectancy for elderly individuals, the beneficial effect of CABG over PCI in preventing recurrent events (e.g., MI or repeat revascularization) and cardiac-related mortality would be underestimated (18).

Recently, Gaudino et al. (19) reported that bilateral internal thoracic arteries (BITAs) had the potential to improve 10-year prognosis compared with single internal thoracic arteries (SITAs), particularly in younger patients undergoing CABG, suggesting the age-dependent effect of BITA on long-term survival (19). Observational studies, including an analysis of 26,124 patients, also suggested that the long-term benefit of BITA compared with SITA, observed in younger patients, was not evident in those older than 70 (20). The reason for fewer benefits of BITA over SITA among elderly patients remains unclear: on one hand it may be less plausible in elderly individuals to derive a long-

FIGURE 2 Cumulative Incidence of All-Cause Death at 10 Years or MACCE at 5 Years in Elderly or Nonelderly Patients Undergoing PCI or CABG



Kaplan-Meier curves show a cumulative incidence of all-cause death at 10 years **(A)** or MACCE at 5 years **(B)** in CABG **(blue curves)** or PCI **(red curves)** arms stratified by 70 years of age. MACCE = major adverse cardiac or cerebrovascular events; other abbreviations as in Figure 1.

TABLE 2 **Relative Hazard Risks of PCI Versus CABG on Clinical Outcomes in Elderly or Nonelderly Patients**

	Elderly (>70 Years)		Nonelderly (≤70 Years)		
Clinical Outcomes	HR (95% CI) PCI/CABG	p Value	HR (95% CI) PCI/CABG	p Value	p for Interaction
All-cause death at 10 years	1.08 (0.84–1.40)	0.530	1.30 (1.00–1.69)	0.052	0.332
MACCE at 5 years	1.18 (0.90–1.56)	0.233	1.69 (1.36–2.10)	**<0.001**	**0.043**
All-cause death	1.08 (0.75–1.55)	0.678	1.46 (0.98–2.18)	0.064	0.272
MI	2.08 (1.10–3.91)	**0.024**	2.76 (1.63–4.66)	**<0.001**	0.486
Stroke	0.78 (0.35–1.73)	0.534	0.48 (0.22–1.08)	0.075	0.413
Revascularization	2.11 (1.35–3.31)	**0.001**	2.04 (1.57–2.67)	**<0.001**	0.896

Bold p values are statistically significant.
MACCE = major adverse cardiac or cerebrovascular events; other abbreviations as in Table 1.

term benefit because of their limited life expectancy, and on the other hand it might be less attractive in these elderly individuals to perform a more invasive and complex surgical approach. The present study showed more use of venous conduits in elderly patients compared with nonelderly patients (**Table 1**), exemplifying the complexity and technical challenge of multiple arterial grafting in this population.

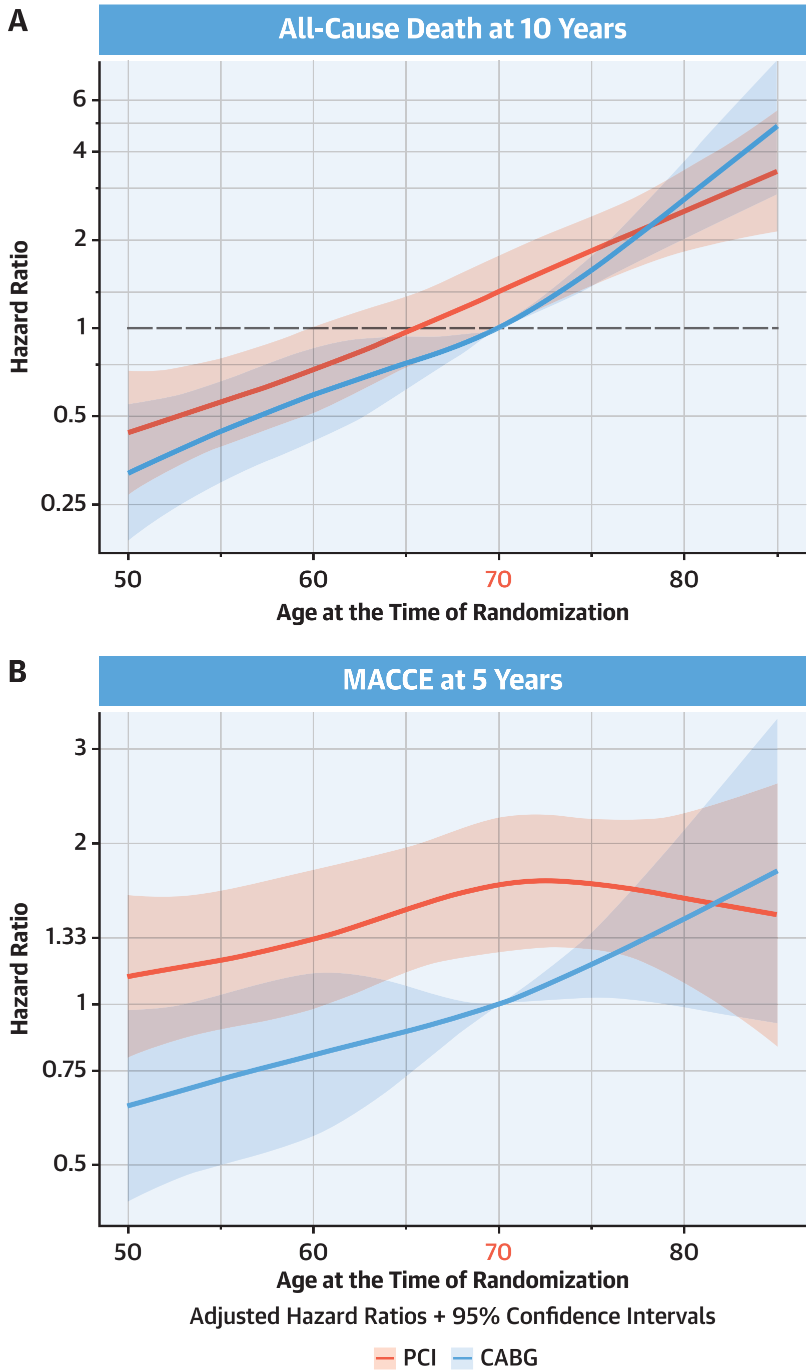
DIFFERENCE BETWEEN RANDOMIZED STUDY AND REGISTRY. Thus far, there are no randomized trials comparing PCI with CABG specifically in the elderly population with complex CAD (3VD or LMCAD). Several observational studies have reported favorable results for CABG compared with PCI in elderly patients with complex CAD (21-23). However, potential confounding factors related to the selection of the revascularization strategy cannot be excluded in these cohort studies. In fact, in contrast to the randomized cohort, the 10-year mortality risk was significantly higher in elderly patients included in the nested PCI registry than those included in the nested CABG registry even after adjustment for potential confounders (Supplemental Table 3), indicating that a substantial number of elderly patients who were too high risk for surgery underwent PCI instead. Therefore, compared with registry data, a subgroup analysis of a large randomized trial may provide less biased evaluation of the actual impact of revascularization strategy on clinical outcomes as well as QOL status in elderly patients.

A number of large randomized controlled trials comparing PCI with CABG in patients with complex CAD reported long-term results after revascularization stratified by age (24-28). However, those studies used a relatively younger age threshold for stratification (63 to 67 years). Hence, these results would be insufficient to provide insights into the issues specifically related to elderly individuals. Among those trials, only the FREEDOM study demonstrated age-by-treatment interaction with respect to all-cause death using the threshold of 63.3 years of age, in which the beneficial treatment effect of CABG over PCI was observed in younger patients but not in older patients (27).

CLINICAL IMPLICATIONS. In the current study, the very long-term follow-up over 10 years and the high follow-up rate (94.3% in elderly patients) enabled the estimation of life expectancy after PCI or CABG in elderly patients with complex CAD. Although the sample size might be insufficient to demonstrate a difference in life expectancy, the upper bound of the 95% CI was 0.7 years in favor of CABG (**Table 3**). For elderly individuals, QOL may be more important than a maximum 0.7 years (8.4 months) prolongation of life expectancy during 10 years of follow-up (29). In the current analysis, all disease-specific health status according to the SAQ up to 5 years were similar between the PCI and CABG arms, and the upper and lower bounds of the 95% CI for the mean difference in any SAQ subscales did not reach clinically important difference of 10 points (15) (**Figure 3**). Given the equivalent long-term survival risk and QOL status between PCI and CABG, a less invasive strategy using PCI instead of CABG may be favored for elderly patients, and actually preferred by them. Of course, the final treatment decision should be made on an individual basis integrating the difference of any clinical risks and life expectancy in the context of QOL (4,6,29). Our results may facilitate the patient's understanding, and be useful for both the patient and the Heart Team during the decision-making process (4).

MEDICAL THERAPY FOR ELDERLY PATIENTS WITH COMPLEX CAD. As recently suggested by the ISCHEMIA trial, guideline-directed medical therapy (GDMT) alone could be an alternative strategy to revascularization for the management of patients with moderate-severe myocardial ischemia, although

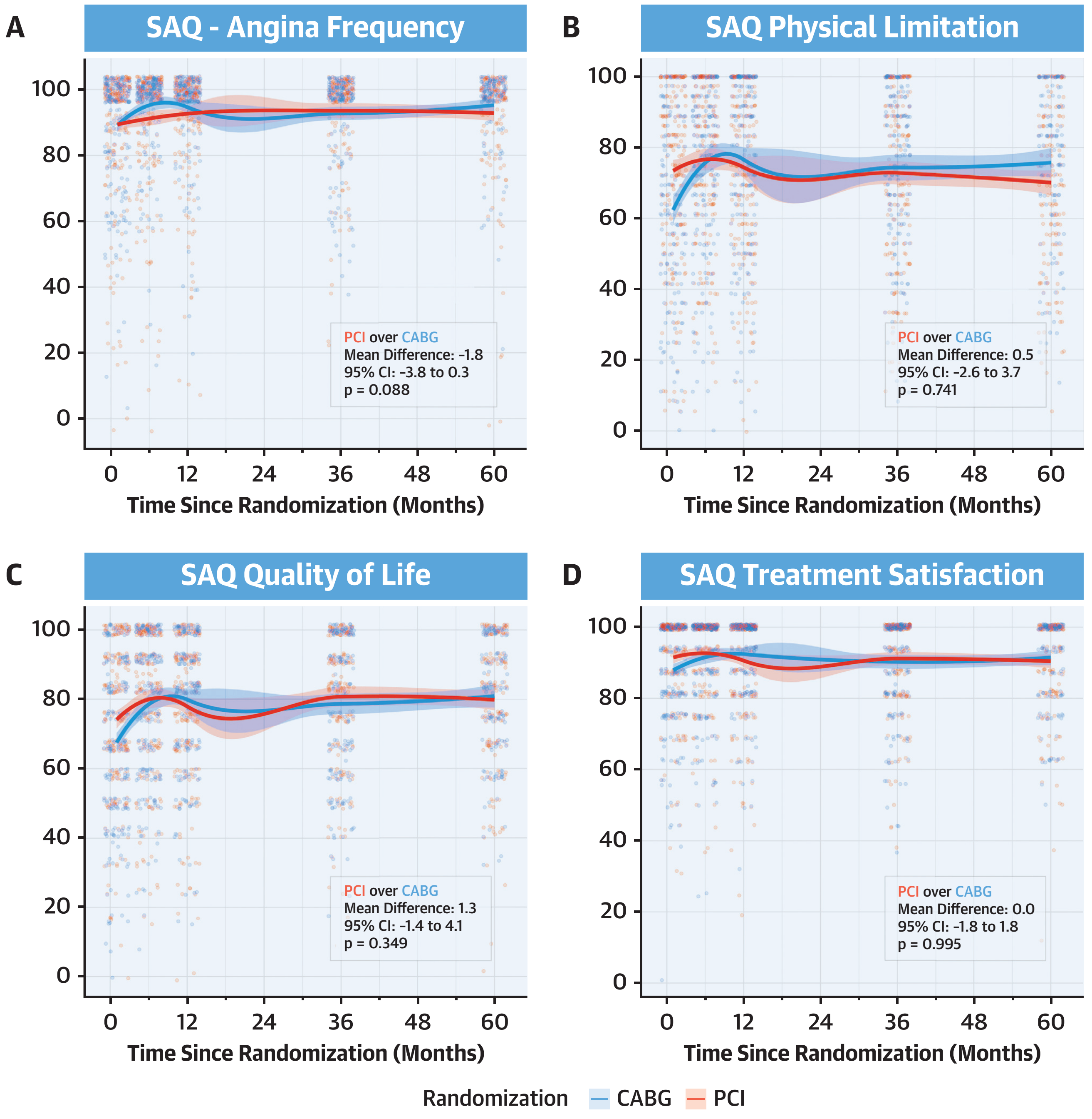
CENTRAL ILLUSTRATION Adjusted Hazard Ratio for 10-Year All-Cause Death and 5-Year Major Adverse Cardiac or Cerebrovascular Event According to Age at the Time of Randomization



Ono, M. et al. J Am Coll Cardiol. 2021;77(22):2761–73.

The risk-differences between percutaneous coronary intervention (PCI) and coronary artery bypass graft (CABG) of **(A)** 10-year all-cause mortality and **(B)** 5-year major adverse cardiac or cerebrovascular events (MACCE) crossed over as age increased. The restricted cubic-spline curves were depicted from the adjusted Cox regression model. The reference (i.e., hazard ratio [HR]: 1) is the risk on 70 years of age in the CABG arm. Solid lines indicate the HRs and translucent areas indicate the 95% confidence intervals. The HRs are adjusted by sexes. The p values for nonlinearity of the 2 curves with age were 0.351 and 0.352 for all-cause mortality at 10 years and MACCE at 5 years, respectively.

FIGURE 3 Adjusted Effect of PCI Versus CABG on Disease-Specific Health Status as Measured by the SAQ Among Elderly Patients



The difference in the angina frequency **(A)**, physical limitation **(B)**, quality of life **(C)**, and treatment satisfaction **(D)** according to the SAQ as a continuous variable between PCI and CABG arms during the 5 years of follow-up are estimated, using a linear mixed effects model, including age, sex, and baseline SAQ scores as covariates. Red and blue dots indicate the distribution of each SAQ subscale. CI = confidence interval; SAQ = Seattle Angina Questionnaire; other abbreviations as in **Figure 1**.

no age-specific result has been reported thus far (30). However, the efficacy of GDMT principally depends on the patient's compliance and adherence to it. In fact, in the present study, elderly patients less frequently used medications compared with younger patients (Table 1 and Supplemental Table 1), implying poor adherence or intolerance to medical therapy possibly because of numerous other medications or lack of social support. Indeed, in the TIME trial (31), a higher number of major adverse cardiac events occurred at 6 months in the GDMT alone group compared with the invasive strategy group among patients older than 75 years; the compliance to medical therapy was modest even in the GDMT group (lipid-lowering drug was prescribed only in 22% of the GDMT group). Needless to say, the adherence to GDMT is also of paramount importance after revascularization (32). The lower prescription rate of GDMT (especially statins) in the CABG arm compared with the PCI arm might partially negate the potential benefit of CABG (Supplemental Table 2).

STUDY STRENGTHS AND LIMITATIONS. The present study has several strengths. The minimum exclusion criteria of the SYNTAX study allowed assessment of the elderly population with complex CAD more appropriately than other randomized trials with stricter exclusion criteria. The SYNTAXES study achieved a high follow-up rate of 93.8% for 10-year vital status (1,689 of 1,800 enrolled patients) (Figure 1), which enabled the potential bias of lost-to-follow-up among elderly patients as well as younger patients to be minimized. The QOL assessments, which are of crucial importance for the decision-making process in elderly patients, were also incorporated in the present study.

Our study also has several limitations. First, although the current age threshold of 70 years is the prespecified threshold documented in the protocol of the SYNTAX study, there is no universal definition on the threshold of age to define elderly. Therefore, other trials addressing the elderly population could have a different threshold. Second, the SYNTAX trial was conducted between 2005 and 2007 with a universal use of first-generation paclitaxel drug-eluting stents for treatment with PCI. The technological improvements of PCI devices as well as medical treatment strategies may limit the generalizability of our findings to current practice. It is, however, unavoidable that the findings from long-term follow-up data are based on outdated technology, whereas the evidence for contemporary technology can be derived only from short-term follow-up studies. Third, the SYNTAX trial enrolled patients with clinical indication for revascularization either by PCI or CABG. Therefore, the results might not be applicable to elderly patients with less severe CAD who have symptoms amenable to optimal medical therapy (30,33). Fourth, although the SYNTAX trial applied a minimum of exclusion criteria, patients who were considered as ineligible for either PCI or CABG by a Heart Team were excluded from the randomization and were entered into the nested CABG or PCI registries. Therefore, it should be acknowledged that our findings of equipoise long-term outcomes between PCI and CABG in elderly patients would be applicable only for those who are eligible for both PCI and CABG. Finally, the extended follow-up of the SYNTAXES trial up to 10 years was only for survival status, and the data of other clinical endpoints with independent adjudication and health status according to SAQ were limited up to 5 years.

TABLE 3 Restricted Mean Survival Time (Within 10-Years) After PCI or CABG in Elderly Patients (>70 Years) With Complex CAD

	PCI	CABG	Difference CABG Over PCI	
	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)	p Value
Elderly >70 yrs	7.7 (7.4 to 8.1)	7.9 (7.5 to 8.3)	0.2 (−0.4 to 0.7)	0.524
70–80 yrs	7.9 (7.5 to 8.4)	8.1 (7.8 to 8.5)	0.2 (−0.4 to 0.8)	0.478
≥80 yrs	6.7 (5.8 to 7.7)	6.8 (5.8 to 7.8)	0.0 (−1.4 to 1.4)	0.973

CAD = coronary artery disease; CI = confidence interval; other abbreviations as in Table 1.

CONCLUSIONS

Among elderly patients older than 70 years with 3VD and/or LMCAD, MACCE rates and QOL status at 5 years did not significantly differ between the 2 revascularization strategies. At 10 years, there was no significant difference in all-cause death and estimated life expectancy between PCI and CABG. Although the final treatment decision should be selected on an individual basis integrating all the factors, including life expectancy and QOL, PCI might be a reasonable alternative to CABG for elderly patients with 3VD and/or LMCAD.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Among patients older than 70 years with 3-vessel and/or left main CAD undergoing revascularization, MACCE at 5 years and all-cause mortality after 10 years did not differ significantly differ between PCI and CABG, in contrast to patients, in whom the 5-year MACCE rate was higher after PCI than CABG. PCI may therefore represent a reasonable alternative to CABG for elderly patients with complex CAD.

TRANSLATIONAL OUTLOOK: Further studies incorporating newer generation drug-eluting stents, contemporary clinical management, and carefully defined patient characteristics are needed to determine the best treatment strategy for elderly patients with complex CAD, taking into account life expectancy and QOL.

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KEY WORDS CABG, elderly, life expectancy, long-term outcome, PCI, SYNTAX

APPENDIX For supplemental tables and figures, please see the online version of this paper.