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Mortality 10 Years After Percutaneous or Surgical Revascularization in Patients With Total Coronary Artery Occlusions

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ABSTRACT

BACKGROUND The long-term clinical benefit after percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) in patients with total occlusions (TOs) and complex coronary artery disease has not yet been clarified.

OBJECTIVES The objective of this analysis was to assess 10-year all-cause mortality in patients with TOs undergoing PCI or CABG.

METHODS This is a subanalysis of patients with at least 1 TO in the SYNTAXES (Synergy Between PCI With Taxus and Cardiac Surgery Extended Survival) study, which investigated 10-year all-cause mortality in the SYNTAX (Synergy Between PCI With Taxus and Cardiac Surgery) trial, beyond its original 5-year follow-up. Patients with TOs were further stratified according to the status of TO recanalization or revascularization.

RESULTS Of 1,800 randomized patients to the PCI or CABG arm, 460 patients had at least 1 lesion of TO. In patients with TOs, the status of TO recanalization or revascularization was not associated with 10-year all-cause mortality, irrespective of the assigned treatment (PCI arm: 29.9% vs. 29.4%; adjusted hazard ratio [HR]: 0.992; 95% confidence interval [CI]: 0.474 to 2.075; p = 0.982; and CABG arm: 28.0% vs. 21.4%; adjusted HR: 0.656; 95% CI: 0.281 to 1.533; p = 0.330). When TOs existed in left main and/or left anterior descending artery, the status of TO recanalization or revascularization did not have an impact on the mortality (34.5% vs. 26.9%; adjusted HR: 0.896; 95% CI: 0.314 to 2.555; p = 0.837).

CONCLUSIONS At 10-year follow-up, the status of TO recanalization or revascularization did not affect mortality, irrespective of the assigned treatment and location of TOs. The present study might support contemporary practice among high-volume chronic TO-PCI centers where recanalization is primarily offered to patients for the management of angina refractory to medical therapy when myocardial viability is confirmed. (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)
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ABBREVIATIONS AND ACRONYMS

3VD = 3-vessel disease

AF = angina frequency

CABG = coronary artery bypass grafting

CAD = coronary artery disease

CI = confidence interval

CK = creatine kinase

CK-MB = creatine kinase-myocardial band

CTO = chronic total occlusion

HR = hazard ratio

LAD = left anterior descending artery

LM = left main disease

PCI = percutaneous coronary intervention

SAQ = Seattle Angina Questionnaire

TO = total occlusion

Chronic total occlusions (CTOs) are a common observation in patients with stable coronary artery disease (CAD) who are undergoing coronary angiography with a point-prevalence between 15% and 30% (1–3). The American College of Cardiology/American Heart Association/Society for Cardiovascular Angiography and Interventions guidelines (4) recommend that in patients with appropriate clinical indications and suitable anatomy percutaneous coronary intervention (PCI) of a CTO is reasonable when performed by operators with appropriate expertise. The recommendation by the current European guidelines is that percutaneous revascularization of CTO should be considered in patients with angina resistant to medical therapy or with a large area of documented ischemia in the territory of the occluded vessel (5). However, the results from previous cohort studies have been inconsistent with regard to the potential survival benefit of successful versus failed CTO-PCI (6–9). Coronary artery bypass grafting (CABG) for total occlusion (TO) showed that failed revascularization of a non-left anterior descending artery (LAD) TO was not associated with increased risk of long-term mortality, whereas in the study, all the TOs in LAD were bypassed (10). Therefore, the clinical benefit of recanalization or revascularization of TO is still debated. In patients with TO and complex CAD undergoing PCI or CABG, the benefit of the 2 respective revascularization approaches on the long-term (10-year) outcome has not yet been clarified. Furthermore, the impact of successful treatment of TO on 10-year all-cause mortality in PCI- or CABG-treated patients with 3-vessel disease (3VD) and/or left main disease (LM) also remains undefined.

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The aim of the present subanalysis of the SYNTAXES (Synergy between PCI with Taxus and Cardiac Surgery Extended Survival) study is to investigate the 10-year mortality in patients with TOs and complex CAD after PCI or CABG stratified according to the status of TO recanalization or revascularization and 3VD and/or LM.

METHODS

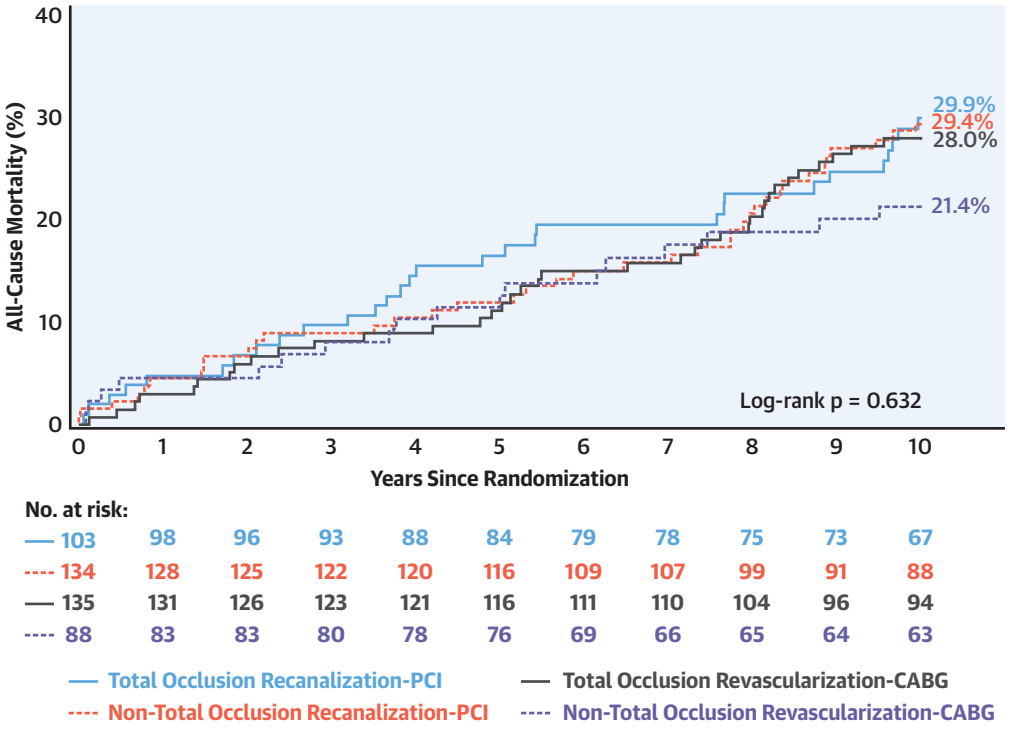
STUDY DESIGN AND PATIENT POPULATION. The present study is a post hoc subgroup analysis of the SYNTAXES study (NCT03417050), which was an investigator-driven extended 10-year follow-up of the SYNTAX (Synergy between PCI with Taxus and Cardiac Surgery) trial (NCT00114972) beyond its originally planned final follow-up at 5 years (11–13). In brief, the SYNTAX trial was a multicenter, randomized controlled trial done in 85 hospitals across 18 North American and European countries, which adopted an "all-comer" design with minimum exclusion criteria (11). A total of 1,800 patients with de novo 3VD and/or LM, 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 default use of Taxus Express paclitaxel drug-eluting stents (Boston Scientific, Marlborough, Massachusetts) or CABG (n = 897).

The main result of the SYNTAXES study in terms of vital status up to 10 years has been recently reported (14). 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 (14). The SYNTAX and SYNTAXES trials were approved by the ethics committees at each investigating center, and all patients provided their written informed consent prior to 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.

STUDY ENDPOINT. The primary endpoint of this study was all-cause mortality at 10 years. The secondary endpoint was all-cause mortality at maximum available follow-up. All analyses were performed according to the intention-to-treat principle. Vital status was confirmed by (electronic) health care record review and national death registries. Patients with missing vital status were included in the analysis and censored at the last date of contact or observation. Two hospitals, which included 5 patients in total, decided not to participate in the SYNTAXES study.

TOTAL OCCLUSION AND SYNTAX SCORE. In the SYNTAX trial, the calculation of the anatomical SYNTAX score was performed by the study sites and by an independent core laboratory blinded to the treatment assignment (15–18). The age and angiographic characteristics of TO were specified as part of the anatomical SYNTAX score calculation; both the age of the TO ≤3 months and >3 months were specified, but both were considered as TO (15). The definition of the TO required that there was absolutely no flow through the lesion (TIMI [Thrombolysis In Myocardial Infarction] flow grade 0). Antegrade flow beyond the TO maintained by bridging collaterals and/or ipsi-collaterals did not invalidate the definition of TO.

CENTRAL ILLUSTRATION **All-Cause Mortality at 10 Years According to the Status of Total Occlusion Recanalization or Revascularization and Randomized Treatment of Percutaneous Coronary Intervention or Coronary Artery Bypass Grafting**



Kawashima, H. et al. J Am Coll Cardiol. 2021;77(5):529–40.

Kaplan-Meier curves of all-cause mortality at 10 years according to the status of total occlusion (TO) recanalization or revascularization and randomized treatment of percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) (TO population in SYNTAXES [Synergy Between PCI With Taxus and Cardiac Surgery Extended Survival] study, n = 460). TO recanalization–PCI **(blue line)** versus non-TO recanalization–PCI **(red dotted line)** versus TO revascularization–CABG **(gray line)** versus non-TO revascularization–CABG **(purple dotted line).**

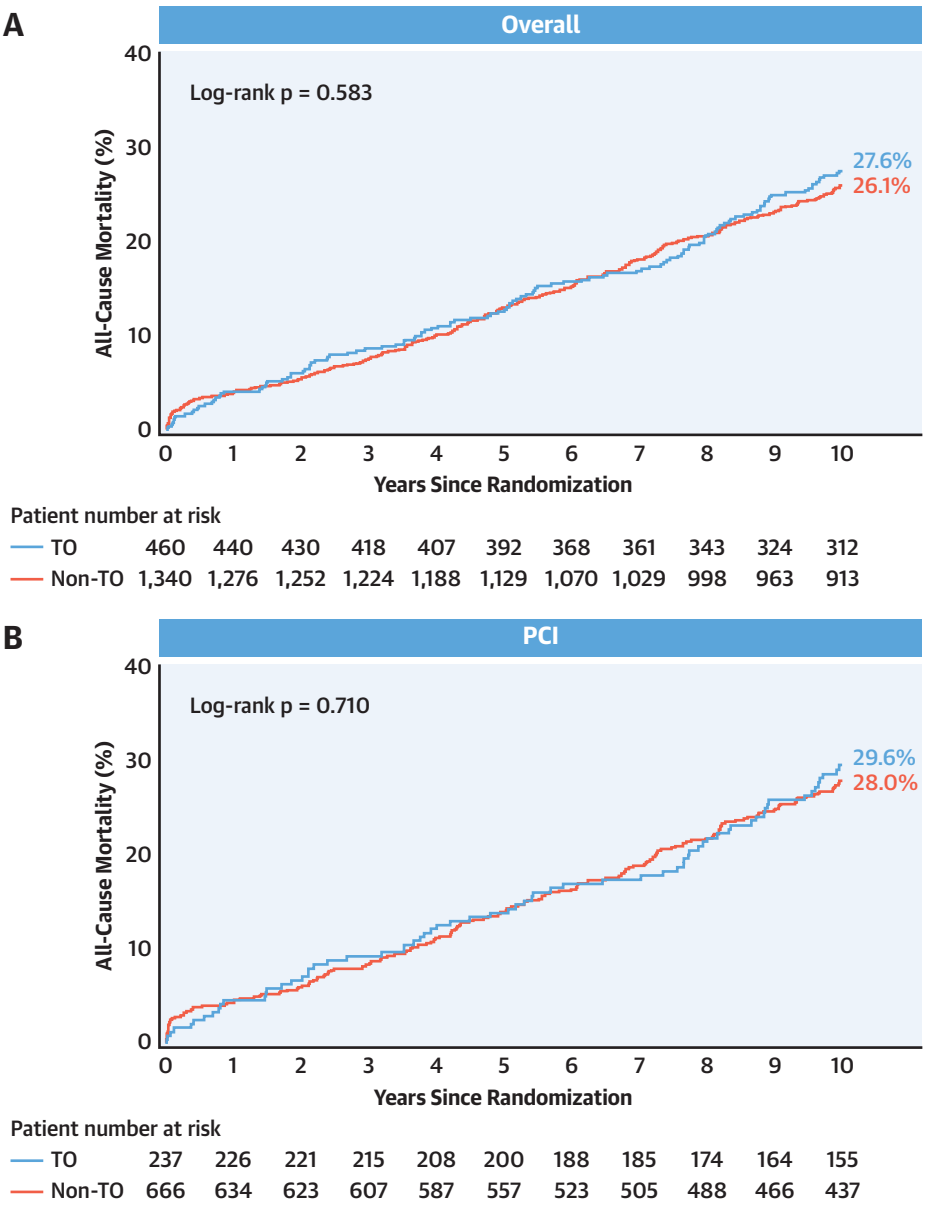
Pre-procedure, the presence of TO was evaluated by the study sites as a part of site-reported anatomical SYNTAX score calculation. Post-procedural status of TO recanalization or revascularization was also assessed by the sites according to the site-reported anatomical SYNTAX score on an intention-to-treat basis; the data were available in the electronic case records of the SYNTAX population (19,20). To maintain the consistency of TO assessment, the site-reported anatomical SYNTAX score was described and tabulated in this paper.

In the present study, the total randomized patients were stratified according to the presence or absence of a TO, and those with TO were further stratified according to the post-procedural status of recanalized or revascularized TOs and 3VD and/or LM. Patients were stratified as recanalized or revascularized TO whenever all TOs were recanalized or revascularized according to the sites.

In the PCI arm, the residual SYNTAX score was quantified by an independent core laboratory unaware of, and blind to, patient's revascularization outcome (21). This score was calculated as the sum of the individual scores of coronary lesions with ≥50% diameter stenosis in vessel ≥1.5 mm that were left without PCI (19,21,22).

MEASUREMENT OF ANGINA STATUS. In the SYNTAX trial, health status was assessed in all patients at baseline; at 1 and 6 months; and 1, 3, and 5 years after randomization (23). In the present study, disease-specific health status was assessed using the Seattle Angina Questionnaire (SAQ) (24). The SAQ is a 19-item questionnaire that measures 5 domains of health status related to CAD: angina frequency (AF); physical

FIGURE 1 All-Cause Mortality at 10 Years According to Randomized Treatments of PCI or CABG in Patients With or Without TO



Kaplan-Meier curves of all-cause mortality at 10 years according to randomized treatments of percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) in patients with or without total occlusion (TO) (total SYNTAXES [Synergy Between PCI With Taxus and Cardiac Surgery Extended Survival] population, n = 1,800): **(A)** overall; **(B)** PCI arm; and **(C)** CABG arm. TO **(blue line)** versus non-TO **(red line).**

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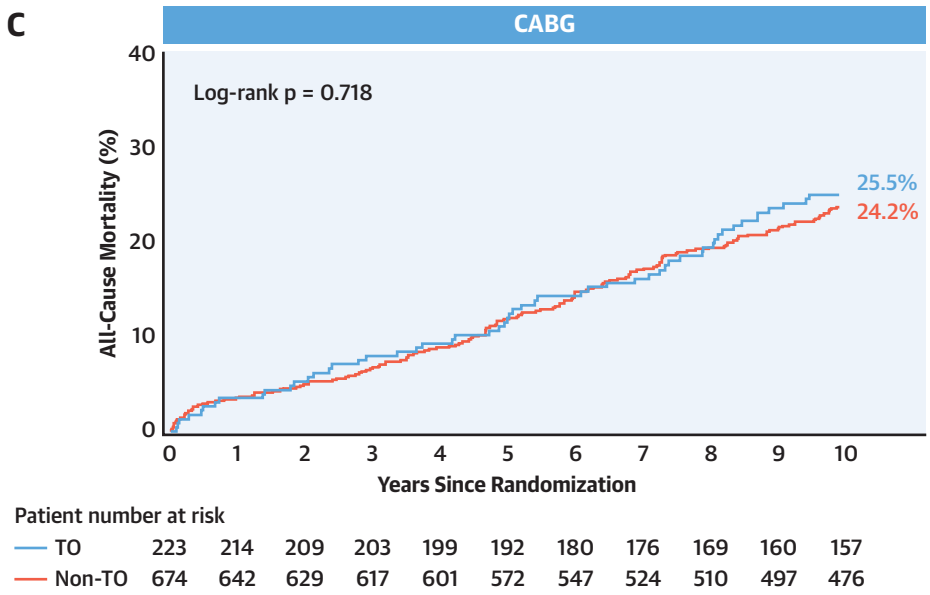
limitations; disease perception and/or quality of life; angina stability; and treatment satisfaction (24,25). The SAQ-AF score ranges from 0 to 100, with higher scores indicating fewer symptoms and better health status. Consistent with previous studies, patients were categorized as being angina-free (i.e., SAQ-AF score of 100) or as having monthly angina (SAQ-AF score: 70 to 90), weekly angina (SAQ-AF score: 40 to 60), or daily angina (SAQ-AF score: ≤30) (23).

STATISTICAL ANALYSIS. The mean ± SD for continuous variables were compared using the Student's *t*-test. Binary variables were reported as counts

FIGURE 1 Continued



and/or percentages and compared with the chi-square or Fisher exact test as appropriate. The cumulative incidence of the 10-year all-cause mortality up to 10 years was assessed using the Kaplan-Meier method and compared using the log-rank test. Hazard ratio (HR) with 95% confidence interval (CI) was assessed by a Cox proportional regression model. To adjust for potential confounding factors, the following variables were entered into a multivariable Cox regression model: age; sex; body mass index; medically treated diabetes; hypertension; dyslipidemia; current smokers; previous myocardial infarction; previous cerebrovascular disease; peripheral vascular disease; chronic obstructive pulmonary disease; chronic kidney disease (defined as creatinine clearance <60 ml/min); left ventricular ejection fraction; clinical presentation (silent ischemia, stable angina, or unstable angina); disease type (3VD or LM); and anatomical SYNTAX score. A p value <0.05 was considered to be statistically significant. All data were processed using SPSS version 26.0 (IBM Inc., Armonk, New York).

RESULTS

COMPARISON OF PATIENTS WITH AND WITHOUT TO UNDERGOING PCI OR CABG. Of 1,800 randomized patients (7,739 lesions), 460 patients (25.6%; 543 lesions) had at least 1 lesion of TO and 1,340 patients (74.4%; 7,196 lesions) did not have any TO lesion. Baseline characteristics of patients with or without TO are shown in Supplemental Table 1. There was no significant difference in the 10-year mortality between patients with and without TO (27.6% vs. 26.1%; unadjusted HR: 1.060; 95% CI: 0.862 to 1.302; p = 0.583) (**Figure 1**, Supplemental Table 2). The results remained consistent after statistical adjustment for the confounding factors (adjusted HR: 1.018; 95% CI: 0.810 to 1.280; p = 0.877) (Supplemental Table 2).

COMPARISON OF PATIENTS WITH OR WITHOUT RECANALIZED/REVASCULARIZED TOs. Baseline characteristics in patients with TO undergoing PCI and CABG are shown in **Table 1**. As baseline characteristics, the PCI arm had a higher prevalence of history of hypertension than the CABG arm did. All TOs were successfully recanalized in 43.5% of patients after PCI and revascularized in 60.5% with CABG (p < 0.001).

The all-cause mortality estimates up to 10 years according to the status of TO recanalization or revascularization are shown in the **Central Illustration and Table 2**. In the PCI arm, there was no significant difference in the 10-year all-cause mortality between patients with successfully recanalized TO and those without (TO recanalization 29.9% vs. non-TO recanalization 29.4%; unadjusted HR: 1.041; 95% CI: 0.645 to 1.681; p = 0.868). Similarly, in the CABG arm, the mortality of patients with revascularized TO did not differ from those without revascularized TO (TO revascularization 28.0% vs. non-TO revascularization 21.4%; unadjusted HR: 1.311; 95% CI: 0.746 to 2.303; p = 0.346).

After multivariate analysis, the 10-year all-cause mortality in patients with successfully recanalized

TABLE 1 Baseline Characteristics and Medical Therapy in Patients With TO Undergoing PCI or CABG

	Overall (N = 460)	PCI (n = 237)	CABG (n = 223)	p Value
Age, yrs	64.6 ± 10.4	64.7 ± 10.3	64.5 ± 10.5	0.822
Body mass index, kg/m^2	28.3 ± 4.6	28.4 ± 4.7	28.2 ± 4.5	0.667
Male	378 (82.2)	188 (79.3)	190 (85.2)	0.100
Medically treated diabetes	134 (29.1)	77 (32.5)	57 (25.6)	0.102
On insulin	49 (10.7)	27 (11.4)	22 (9.9)	0.596
Hypertension	302 (65.7)	167 (70.5)	135 (60.5)	0.025
Dyslipidemia	367 (80.5)	194 (82.9)	173 (77.9)	0.180
Current smokers	89 (19.4)	41 (17.3)	48 (21.6)	0.242
Previous myocardial infarction	181 (39.8)	83 (35.5)	98 (44.3)	0.053
Previous cerebrovascular disease	69 (15.1)	33 (14.0)	36 (16.2)	0.504
Previous stroke	22 (4.8)	814 (6.0)	8 (3.6)	0.236
Previous TIA	29 (6.3)	12 (5.1)	17 (7.7)	0.263
Previous carotid artery disease	41 (8.9)	19 (8.0)	22 (9.9)	0.487
Peripheral vascular disease	46 (10.0)	24 (10.1)	22 (9.9)	0.926
Chronic obstructive pulmonary disease	35 (7.6)	21 (8.9)	14 (6.3)	0.296
Chronic kidney disease	82 (19.3)	46 (20.7)	36 (17.7)	0.436
Creatinine clearance, ml/min	87.6 ± 32.1	86.9 ± 32.4	88.3 ± 31.8	0.652
Left ventricular ejection fraction, %	55.7 ± 13.2	55.6 ± 13.3	55.7 ± 13.1	0.984
Congestive heart failure	30 (6.6)	13 (5.5)	17 (7.7)	0.346
Clinical presentation				0.101
Silent ischemia	76 (16.5)	31 (13.1)	45 (20.2)	
Stable angina	257 (55.9)	135 (57.0)	122 (54.7)	
Unstable angina	127 (27.6)	71 (30.0)	56 (25.1)	
EuroSCORE	3.7 ± 2.7	3.8 ± 2.7	3.7 ± 2.8	0.670
Parsonnet score	8.7 ± 6.9	8.8 ± 6.8	8.5 ± 7.0	0.605
Disease type				0.862
3VD	349 (75.9)	176 (74.3)	173 (77.6)	
LM				
LM only	0	0	0	
LM + 1VD	9 (2.0)	5 (2.1)	4 (1.8)	
LM + 2VD	39 (8.5)	23 (9.7)	16 (7.2)	
LM + 3VD	63 (13.7)	33 (13.9)	30 (13.5)	
Number of lesions	4.6 ± 1.5	4.6 ± 1.5	4.7 ± 1.6	0.429
Anatomical SYNTAX score	30.8 ± 10.6	31.3 ± 11.6	30.3 ± 9.5	0.315
Any bifurcation	336 (73.0)	173 (73.0)	163 (73.1)	0.981
All TOs recanalization or revascularization	238 (51.7)	103 (43.5)	135 (60.5)	<0.001
Number of stents	–	5.0 ± 2.2	–	–
Total stent length, mm	–	95.9 ± 48.1	–	–
Off-pump CABG	–	–	38 (17.0)	–
LAD with LIMA	–	–	197 (88.3)	–
LAD with arterial graft	–	–	214 (96.0)	–
Total number of graft conduits	–	–	2.8 ± 0.7	–
Number of artery graft conduits	–	–	1.4 ± 0.7	–
Number of vein graft conduits	–	–	1.3 ± 0.9	–

Values are mean ± SD or n (%). Dashes indicate that data were not available.

CABG = coronary artery bypass grafting; EuroSCORE = European System for Cardiac Operative Risk Evaluation; LAD = left anterior descending artery; LIMA = left internal mammary artery; LM = left main disease; PCI = percutaneous coronary intervention; SYNTAX = Synergy Between PCI With Taxus and Cardiac Surgery; TIA = transient ischemic attack; TO = total occlusion; VD = vessel disease.

or revascularized TOs was also similar to those without, in the PCI arm (adjusted HR: 0.992; 95% CI: 0.474 to 2.075; p = 0.982) and in the CABG arm (adjusted HR: 0.656; 95% CI: 0.281 to 1.533; p = 0.330), and these results were consistent in the mortality at maximum available follow-up (Table 2).

When TOs existed in left main coronary artery and/or LAD, the status of TO recanalization or revascularization did not have an impact on the 10-year all-cause mortality (TO recanalization or revascularization 34.5% vs. non-TO recanalization or revascularization 26.9%; adjusted HR: 0.896; 95% CI: 0.314 to 2.555; p = 0.837) (Table 2).

TABLE 2 Association Between the Status of TO Recanalization or Revascularization and All-Cause Mortality at 10 Years and at Maximum Available Follow-up

	TO Recanalization or Revascularization (n = 238)	Non-TO Recanalization or Revascularization (n = 222)	Unadjusted HR (95% CI)	p Value	Adjusted HR (95% CI)	p Value
At 10 yrs						
Overall (N = 460)	67 (28.9)	56 (26.3)	1.112 (0.780–1.586)	0.557	0.900 (0.545–1.485)	0.680
PCI (n = 237)	30 (29.9)	38 (29.4)	1.041 (0.645–1.681)	0.868	0.992 (0.474–2.075)	0.982
CABG (n = 223)	37 (28.0)	18 (21.4)	1.311 (0.746–2.303)	0.346	0.656 (0.281–1.533)	0.330
Patients with at least 1 TO in LM and/or LAD (n = 140)	23 (34.5)	19 (26.9)	1.404 (0.765–2.579)	0.274	0.896 (0.314–2.555)	0.837
Patients with at least 1 TO except in LM and/or LAD (n = 320)	44 (26.6)	37 (25.8)	1.002 (0.647–1.552)	0.992	0.883 (0.454–1.715)	0.713
At maximum available follow-up						
Overall (N = 460)	75 (35.6)	71 (39.6)	0.951 (0.687–1.317)	0.762	0.894 (0.559–1.429)	0.640
PCI (n = 237)	32 (34.0)	45 (39.8)	0.936 (0.595–1.473)	0.775	1.003 (0.488–2.061)	0.994
CABG (n = 223)	43 (36.7)	26 (39.1)	0.986 (0.603–1.613)	0.955	0.621 (0.288–1.337)	0.223
Patients with at least 1 TO in LM and/or LAD (n = 140)	23 (34.5)	26 (56.3)	1.013 (0.578–1.776)	0.964	0.842 (0.300–2.366)	0.744
Patients with at least 1 TO except in LM and/or LAD (n = 320)	52 (39.5)	45 (33.5)	0.939 (0.62–-1.403)	0.759	0.940 (0.514–1.719)	0.841

Values are n (%) unless otherwise indicates. Number of deaths are the percentage based on Kaplan-Meier estimates. The HR show the risk of all-cause mortality in patients with versus without recanalized or revascularized TOs.

CI = confidence interval; HR = hazard ratio; other abbreviations as in Table 1.

COMPARISON OF PATIENTS WITH TO STRATIFIED ACCORDING TO LM OR 3VD. When patients with TO were stratified according to the disease type (LM or 3VD), there were no significant differences in the 10-year all-cause mortality between PCI and CABG (LM: PCI 30.5% vs. CABG 40.9%; HR: 1.539; 95% CI: 0.814 to 2.911; p = 0.185; and 3VD: PCI 29.3% vs. 21.0%; HR: 0.673; 95% CI: 0.437 to 1.037; p = 0.073) (Figure 2, Table 3).

COMPARISON OF PATIENTS WITH OR WITHOUT TO WHO UNDERWENT PCI ACCORDING TO THE RESIDUAL SYNTAX SCORE. Table 4 shows the association between the residual SYNTAX score and all-cause mortality at 10 years and at maximum available follow-up. Irrespective of the status of TOs, patients with the residual SYNTAX >8 (TO: 45.5% and non-TO: 54.7%) had worse survival up to 10 years compared with the residual SYNTAX score ≤8 (TO: 22.4% and non-TO: 24.6%) (Figure 3, Table 4). These results were consistent in the mortality at maximum available follow-up (Table 4).

ANGINA FREQUENCY IN PATIENTS WITH TO. The SAQ-AF score per each time point in patients with at least 1 TO is presented in Supplemental Figure 1. Both CABG and PCI improved the ratios of patients who were angina-free at all follow-up points.

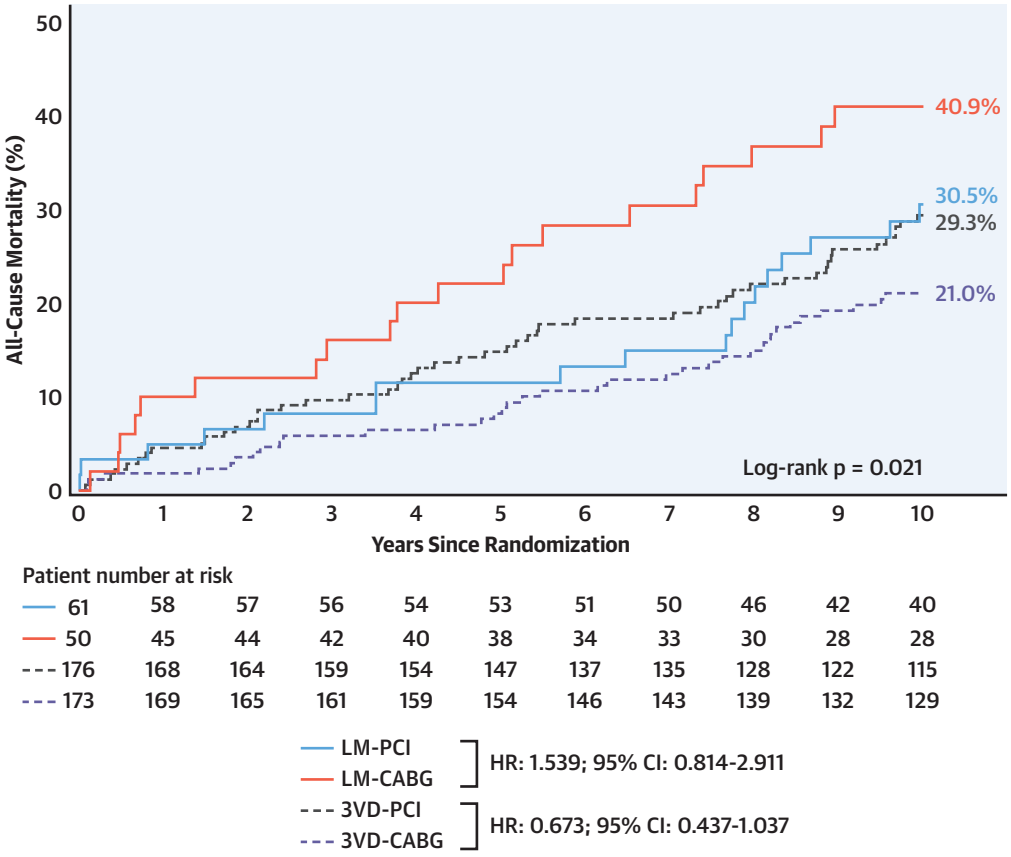
DISCUSSION

The main findings of this study are summarized as follows:

1. Among patients with TOs (n = 460), there were no significant differences in the all-cause mortality at 10 years between patients with successfully recanalized or revascularized TOs and those without, irrespective of the assigned treatment (PCI or CABG) and location of TOs (left main coronary artery and/or LAD or other vessels).
2. When patients with TO were stratified according to the type of disease (3VD or LM), there was no difference between the PCI and CABG arm in terms of the 10-year mortality.

In the present study, among patients with TOs, the success of revascularization approach was less frequent with PCI than with CABG (43.5% vs. 60.5%; p < 0.001). This relatively low TO success rate with PCI may be due to the complexity of the TO lesion or the unavailability of contemporary devices and techniques during the SYNTAX trial enrollment (2005 to 2007). At that time, dedicated contemporary TO classifications such as the J-CTO (Multicenter CTO Registry in Japan) score (26), PROGRESS CTO (Prospective Global Registry for the Study of Chronic Total Occlusion Intervention) score (27), and EuroCTO (CASTLE [previous CABG; Age >70 years; Stump anatomy, blunt or no; severe Tortuosity; Length of CTO >20 mm; Extent of calcification, >50% of the segment) score (28) did not exist, and therefore these scores were not used, although the anatomical SYNTAX score incorporated some components of abovementioned scores. The SYNTAX II trial enrolled patients approximately 1 decade later between 2014 and 2017 and investigated the impact of a contemporary PCI strategy on clinical outcomes in patients with 3VD; the procedural success rate of TO recanalization was as high as 87% (29,30), presumably

FIGURE 2 All-Cause Mortality at 10 Years According to Randomized Treatments of PCI or CABG in Patients With TO Stratified Into LM or 3VD



Kaplan-Meier curves of all-cause mortality at 10 years according to randomized treatments of PCI or CABG in patients with TO stratified into left main disease (LM) or 3-vessel disease (3VD) (TO population in SYNTAXES study, n = 460). LM-PCI **(blue line)** versus LM-CABG **(red line)** versus 3VD-PCI **(gray dotted line)** versus 3VD-CABG **(purple dotted line).** CI = confidence interval; HR = hazard ratio; other abbreviations as in Figure 1.

because of improvements in technology and technique of PCI for a TO such as the diversity of guidewires to cross a TO and the combination of antegrade and retrograde approach (31,32).

To the best of our knowledge, this is the first study evaluating the impact of TO recanalization or revascularization on long-term (≥10-year) mortality in patients with complex CAD undergoing PCI or CABG. Regardless of the assigned treatment and location of TOs, the status of TO recanalization or revascularization did not influence the all-cause mortality at 10 years and at maximum available follow-up. The randomized EuroCTO trial demonstrated a higher rate of freedom from angina in the CTO patients undergoing PCI at 1 year as compared to a conservative strategy, although major adverse cardiac events were comparable between the 2 groups (33). In the DECISION-CTO (Drug-Eluting Stent Implantation Versus Optimal Medical Treatment in Patients With Chronic Total Occlusion) trial, which is the largest randomized trial of the CTO-PCI, during a median follow-up of 4.0 years, there was also no significant difference in the incidence of major adverse cardiovascular events with the CTO-PCI compared with incidence with the conservative strategy (34). Our findings seem to corroborate these results and suggest that long-term all-cause mortality is similar between patients with successful TO recanalization or revascularization and those without, and these results persist beyond 5 years.

The lack of association between recanalization or revascularization status of TOs and long-term benefit in the mortality might be related to the indiscriminate selection of TOs treated in the absence of myocardium viability assessment prior to treatment of TO lesions. In the SYNTAX trial, there was no mandated viability assessment, so that the revascularization strategy was based on anatomic findings without taking into consideration the extent of viable and ischemic myocardium. To assess myocardium viability subtended by a TO lesion, cardiac magnetic resonance imaging with late gadolinium enhancement can be used for assessing the presence of scar in the myocardium (35). The assessment of myocardium viability by cardiac magnetic resonance imaging might be helpful to decide whether recanalization or revascularization of TOs should be attempted.

Finally, in our analysis, PCI improved the ratio of patients who were angina-free from 18.6% (baseline) to 63.8% (1 month), 63.6% (6 months), 67.6% (1 year), 68.2% (3 years), and 70.3% (5 years) (Supplemental Figure 1). The present study might support contemporary practice among high-volume CTO-PCI centers where recanalization is primarily offered to patients for the management of angina refractory to medical therapy when myocardial viability is confirmed.

STUDY LIMITATIONS. The present study is a post hoc analysis and should be considered only as hypothesis-generating (36). By protocol design of the SYNTAX trial, patients with acute myocardial infarction were excluded. In 1,800 patients randomized in the SYNTAX trial, 260 presented with silent coronary ischemia, 1,027 presented with stable angina, and 513 presented with unstable angina. At the time of recruitment (March 2005 through April 2007), preprocedure, creatine kinase (CK) and creatine kinase-myocardial band (CK-MB) were used as primary cardiac enzymes to rule out patients presented with acute myocardial infarction. CK-MB was required only if CK was ≥2× the upper limit of normal before the procedure. Of 1,800 patients, 9 patients (6 patients with stable angina and 3 patients with unstable angina) had pre-procedural elevated CK-MB values (37). The rest of the patients (1,791 of 1,800; 99.5%) did not have the elevated cardiac enzyme. In patients with at least 1 TO (460 patients), only 2 patients fulfilled the criteria of the pre-procedural elevated CK-MB value. We could not completely exclude the possibility where the TOs were "recent" occlusion with or without the elevation of the cardiac enzyme. Due to the unavailability of pre-procedural angiographies 3 months prior to the procedure and specific anamnesis pertaining to a sudden episode of chest pain possibly due to vessel occlusion, the age of TOs could not be clearly defined, with most cases being unknown. Furthermore, the low frequency of TO recanalization or revascularization might dilute a

TABLE 3 Association Between the Randomized Treatments of PCI or CABG and All-Cause Mortality at 10 Years and at Maximum Available Follow-Up According to the Disease Type (3VD or LM) in Patients With TO

	PCI (n = 237)	CABG (n = 223)	HR (95% CI)	p Value
At 10 yrs				
Patients with 3VD (n = 349)	50 (29.3)	35 (21.0)	0.673 (0.437–1.037)	0.073
Patients with LM (n = 111)	18 (30.5)	20 (40.9)	1.539 (0.814–2.911)	0.185
At maximum available follow-up				
Patients with 3VD (n = 349)	57 (37.4)	45 (32.4)	0.750 (0.507–1.108)	0.149
Patients with LM (n = 111)	20 (37.1)	24 (55.7)	1.641 (0.906–2.975)	0.102

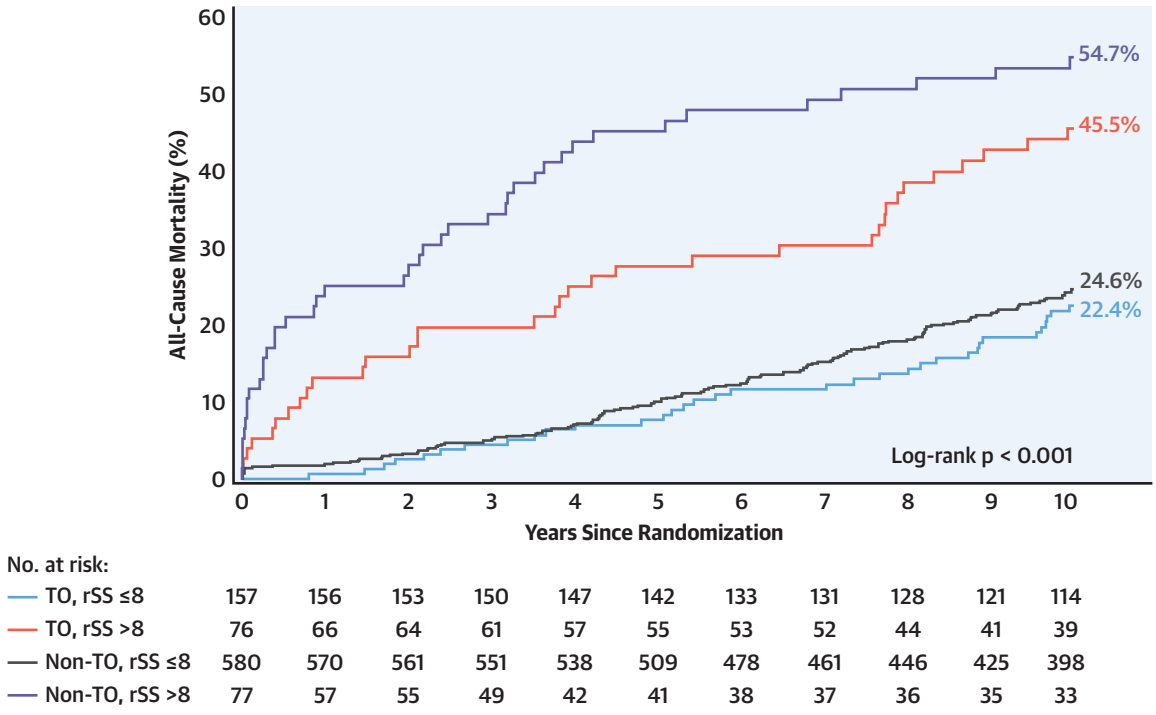
Values are n (%) unless otherwise indicated. Number of deaths are percentage based on Kaplan-Meier estimates. The HR show the risk of all-cause death in patients undergoing PCI versus CABG.
Abbreviations as in Tables 1 and 2.

TABLE 4 Association Between the Residual SYNTAX Score and All-Cause Mortality at 10 Years and at Maximum Available Follow-Up

	Death/Patients	Unadjusted HR (95% CI)	p Value	Adjusted HR (95% CI)	p Value
At 10 yrs					
Patients with TO and rSS ≤8	34/157 (22.4)	Reference	—	Reference	—
Patients with TO and rSS >8	34/76 (45.5)	2.539 (1.578–4.084)	<0.001	1.683 (1.011–2.802)	0.045
Patients without TO and rSS ≤8	137/580 (24.6)	1.125 (0.773–1.683)	0.539	1.245 (0.837–1.850)	0.279
Patients without TO and rSS >8	41/77 (54.7)	3.798 (2.409–5.987)	<0.001	4.100 (2.531–6.642)	<0.001
At maximum available follow-up					
Patients with TO and rSS ≤8	39/157 (27.1)	Reference	—	Reference	—
Patients with TO and rSS >8	38/76 (54.9)	2.600 (1.663–4.066)	<0.001	1.774 (1.105–2.848)	0.018
Patients without TO and rSS ≤8	181/580 (38.9)	1.311 (0.927–1.853)	0.125	1.366 (0.948–1.967)	0.094
Patients without TO and rSS >8	43/77 (59.1)	3.624 (2.348–5.593)	<0.001	4.035 (2.554–6.374)	<0.001

Values are n/N (%) unless otherwise indicated. Number of deaths are percentage based on Kaplan-Meier estimates.
rSS = residual SYNTAX score; other abbreviations as in Tables 1 and 2.

FIGURE 3 All-Cause Mortality at 10 Years According to the Residual SYNTAX Score in Patients With or Without TO Who Underwent PCI



Kaplan-Meier curves of all-cause mortality at 10 years according to the residual SYNTAX (Synergy Between PCI With Taxus and Cardiac Surgery) score (rSS) in patients with or without TO who underwent PCI. TO, rSS ≤8 **(blue line)** versus TO, rSS >8 **(red line)** versus non-TO, rSS ≤8 **(gray line)** versus non-TO, rSS >8 **(purple line).** Abbreviations as in Figure 1.

potential benefit on mortality. Moreover, beyond the initial 5 years of follow up, there are no data on the prevalence of myocardial infarction, rehospitalization, and no information on quality of life including angina status. In addition, the recanalization or revascularization of TOs was assessed based on the site decision. However, in the SYNTAX trial, the heart team was obliged to state before the randomization process took place which vessel needed to be revascularized. Procedural success rates of recanalization or revascularization of TOs were available in the electronic case records of the SYNTAX population. Moreover, viability assessment was not part of the protocol. In addition, the SYNTAX trial was conducted between 2005 and 2007, with a predominant use of first-generation paclitaxel-eluting stents for treatment with PCI, which may limit the generalizability of our findings to current practices. However, it is unavoidable that the findings stemming from long-term follow-up data are based on partially outdated technology, whereas the evidence for contemporary technology can be only derived from short-term follow-up studies. Finally, the endpoint in the SYNTAXES study was all-cause mortality alone. However, the SYNTAXES study provides randomized data that was meticulously collected and achieved a high follow-up rate of 93.8% for 10-year vital status (1,689 of 1,800 enrolled patients) (14).

CONCLUSIONS

At 10-year follow-up, the status of TO recanalization or revascularization did not affect mortality, irrespective of the assigned treatment (PCI or CABG) and location of TOs (left main coronary artery and/or LAD or other vessels). The present study might support contemporary practice among high-volume CTO-PCI centers where recanalization is primarily offered to patients for the management of angina refractory to medical therapy when myocardial viability is confirmed.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS:

All-cause mortality is unrelated to coronary artery patency 10 years following revascularization, irrespective of initial revascularization strategy (percutaneous or surgical) or anatomical location of total coronary artery occlusions.

TRANSLATIONAL OUTLOOK:

Further studies are needed to identify the factors that determine long-term clinical outcomes in patients undergoing revascularization of completely occluded coronary arteries.

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