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Impact of Optimal Medical Therapy on 10-Year Mortality After Coronary Revascularization

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ABSTRACT

BACKGROUND The benefit of optimal medical therapy (OMT) on 5-year outcomes in patients with 3-vessel disease and/or left main disease after percutaneous coronary intervention or coronary artery bypass grafting (CABG) was demonstrated in the randomized SYNTAX (Synergy Between PCI With Taxus and Cardiac Surgery) trial.

OBJECTIVES The objective of this analysis is to assess the impact of the status of OMT at 5 years on 10-year mortality after percutaneous coronary intervention or CABG.

METHODS This is a subanalysis of the SYNTAXES (Synergy Between PCI With Taxus and Cardiac Surgery Extended Survival) study, which evaluated for up to 10 years the vital status of patients who were originally enrolled in the SYNTAX trial. OMT was defined as the combination of 4 types of medications: at least 1 antiplatelet drug, statin, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker, and beta-blocker. After stratifying participants by the number of individual OMT agents at 5 years and randomized treatment, a landmark analysis was conducted to assess the association between treatment response and 10-year mortality.

RESULTS In 1,472 patients, patients on OMT at 5 years had a significantly lower mortality at 10 years compared with those on ≤2 types of medications (13.1% vs 19.9%; adjusted HR: 0.470; 95% CI: 0.292-0.757; $P = 0.002$) but had a mortality similar to those on 3 types of medications. Furthermore, patients undergoing CABG with the individual OMT agents, antiplatelet drug and statin, at 5 years had lower 10-year mortality than those without.

CONCLUSIONS In patients with 3-vessel and/or left main disease undergoing percutaneous coronary intervention or CABG, medication status at 5 years had a significant impact on 10-year mortality. Patients on OMT with guideline-recommended pharmacologic therapy at 5 years had a survival benefit. (Synergy Between PCI With Taxus and Cardiac Surgery: SYNTAX Extended Survival [SYNTAXES]; NCT03417050; Taxus Drug-Eluting Stent Versus Coronary Artery Bypass Surgery for the Treatment of Narrowed Arteries [SYNTAX]; NCT00114972) (J Am Coll Cardiol 2021;78:27-38)

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ABBREVIATIONS AND ACRONYMS

3VD = 3-vessel disease

ACE = angiotensin-converting enzyme

ARB = angiotensin receptor blocker

CABG = coronary artery bypass graft

CAD = coronary artery disease

LM = left main disease

OMT = optimal medical therapy

PCI = percutaneous coronary intervention

Evidence-based use of optimal medical therapy (OMT) is recommended for all patients with coronary artery disease (CAD) and is the initial treatment strategy for patients with chronic coronary syndrome (1–4). Several observational studies and subanalyses of randomized controlled trials have demonstrated that OMT use in patients with CAD is associated with favorable short- to medium-term clinical outcomes after revascularization with either percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG), despite the fact that the patient population and definitions of OMT have varied among studies (5–9). In the SYNTAX (Synergy Between PCI With Taxus and Cardiac Surgery) trial, OMT use was associated with significant reduction in all-cause mortality up to 5 years in patients with de novo 3-vessel disease (3VD) and/or left main disease (LM) undergoing PCI or CABG (7). Furthermore, all the individual OMT agents (antiplatelet drug, statin, angiotensin-converting enzyme [ACE] inhibitor/angiotensin receptor blocker [ARB], beta-blocker) reduced mortality at 5 years (7). However, the clinical benefit of OMT and its individual components on the mortality at very long term (10 years) in patients with de novo 3VD and/or LM has not yet been investigated.

SEE PAGE 39

The SYNTAXES (Synergy Between PCI With Taxus and Cardiac Surgery Extended Survival) study followed up the vital status of patients enrolled in SYNTAX for up to 10 years (10). The aim of the present subanalysis of the SYNTAXES study is to investigate the impact of OMT maintenance on the all-cause mortality beyond the 5-year original follow-up of the SYNTAX trial.

METHODS

STUDY DESIGN AND PATIENT POPULATION. The present study is a post hoc subgroup analysis of the SYNTAXES study (NCT03417050) (11), which was an investigator-driven extended 10-year follow-up of the SYNTAX trial (NCT00114972) beyond its originally planned final follow-up at 5 years (11–14). In brief, the SYNTAX trial was a multicenter, randomized controlled trial done in 85 hospitals across 18 North American and European countries, which adopted 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 paclitaxel-drug eluting stents (TAXUS Express, Boston Scientific Corporation) or CABG (n = 897). The main result of the SYNTAXES study in terms of vital status up to 10 years has been recently reported as well as the redevelopment of the SYNTAX score II 2020 (10,15). The ethics committees approved the SYNTAX and SYNTAXES trials at each investigating center, and all patients provided their written informed consent prior to participation in the SYNTAX trial. Follow-up was performed under local law and regulations of each participating institution and complied with the Declaration of Helsinki.

STUDY MEDICATION AND DEFINITION. In the SYNTAX trial, detailed drug history was collected for all patients at discharge and at 1-month, 6-month, 1-year, 3-year, and 5-year follow-ups (12). Cardiac medication was recorded by the investigators. The investigators were encouraged to review all routine medications carefully at every outpatient clinic visit. OMT was defined as the combination of the following 4 types of medications: 1) at least 1 antiplatelet drug (aspirin, clopidogrel, or ticlopidine); 2) statin; 3) ACE inhibitor/ARB; and 4) beta-blocker—that are included in current practice guidelines for the management of ischemic heart disease (16) and are consistent with published reports (6,7,17,18). According to the SYNTAX trial protocol, OMT was strongly recommended for patients enrolled in the trial. However, the usage of medications was left to the discretion of the investigators and was not randomized.

OUTCOMES. The primary endpoint of this study was all-cause mortality at 10 years. 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 (10). Two hospitals, which included 5 patients in total, decided not to participate in the SYNTAXES study (10). The LM subgroup consisted of patients with any LM, either isolated, or in combination with single-vessel, 2-vessel, or 3-vessel CAD. The 3VD subgroup consisted of patients with 3VD in the absence of LM (10,13). The anatomical complexity of CAD was graded according to the anatomical SYNTAX score during pre-randomization heart team meetings, with higher SYNTAX scores indicating more complex CAD (19). The anatomical SYNTAX scores, according to independent core laboratory analyses, were defined according to tertiles, with scores of 22 or lower defined as low, 23 to 32 as intermediate,

and 33 or higher as high (10,12). Furthermore, in the PCI arm, the residual SYNTAX score was quantified by an independent core laboratory unaware of, and blind to, patient's revascularization outcome (20). This score was calculated as the sum of the individual scores of coronary lesions with ≥50% diameter stenosis in vessels ≥1.5 mm that were left without PCI (20-22). By design and according to protocol, patients with acute myocardial infarction were excluded from the SYNTAX trial, whereas patients who presented with silent ischemia, stable, and unstable angina were included in the trial. In the present study, patients who presented with silent ischemia or stable angina were defined as having stable ischemic heart disease. Similarly, patients who presented with unstable angina were defined according to the definition prevailing at the time of the trial design (11).

STATISTICAL ANALYSIS. Quantitative variables are reported as mean ± SD or median and interquartile range (25%-75%). Categorical variables are expressed as numeric values and percentages. A comparison of quantitative variables was performed using the unpaired Student's *t*-test or Mann-Whitney *U* test depending on the variable distribution. The chi-square test was used to compare categorical variables. The cumulative incidences were estimated by using the Kaplan-Meier method, and the comparisons among patients stratified according to the medication status and randomized treatment were performed using the log-rank test. Between 5 and 10 years after PCI or CABG, the landmark analyses according to the medication status at 5 years based on the electronic case report form and randomized treatment were performed. In this study, patients were stratified according to the number of individual OMT agents at 5 years; the 10-year all-cause mortality was compared between patients on OMT (4 types of medications) and those on 3 or ≤2 types of medications using the unadjusted and adjusted Cox regression hazards models. Patients were further stratified according to the randomized treatment of PCI or CABG. The Kaplan-Meier curves were also constructed in propensity matched cohorts, and the details of the propensity score and results (Supplemental Figure 1) were included in the Supplemental Appendix. The covariates in the adjusted model included age, sex, body mass index, medically treated diabetes, hypertension, dyslipidemia, current smoking, 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, congestive heart failure, clinical presentation (silent ischemia, stable angina, or unstable angina), disease type (3VD or LM), and the anatomical SYNTAX score that had been selected based on prior knowledge of the association of these covariates with the outcomes (23). A 2-sided *P* value <0.05 was considered to be statistically significant. All data were processed using SPSS version 26.0 (IBM Inc, Armonk, New York) and R version 3.6.0 (R Foundation for Statistical Computing, Vienna, Austria).

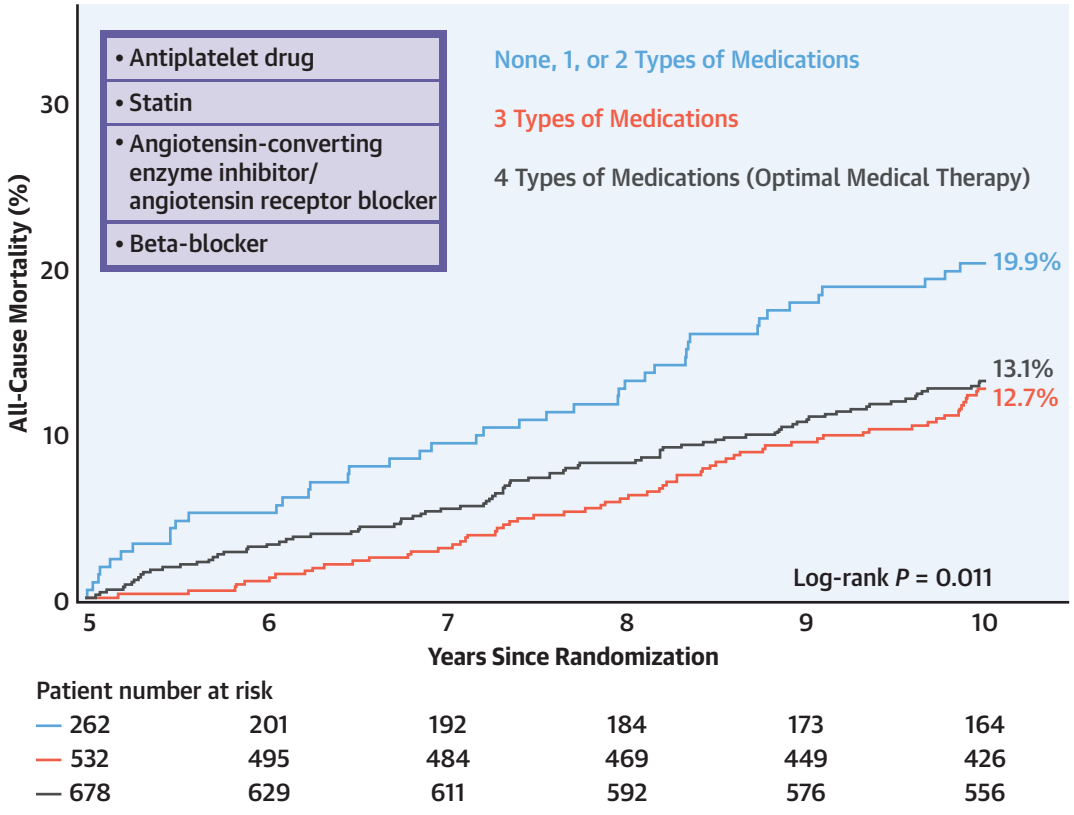
TABLE 1 Baseline Characteristics According to the OMT Status at 5 Years

	OMT (n = 678)	Non-OMT (n = 794)	*P* Value
Age, y	64.0 ± 9.3	64.9 ± 9.8	0.063
Body mass index, kg/m^2	28.2 ± 4.8	28.0 ± 4.4	0.192
Male	539 (79.5)	624 (78.6)	0.669
Diabetes	172 (25.4)	171 (21.5)	0.083
On Insulin	56 (8.3)	78 (9.8)	0.298
Hypertension	450 (66.4)	527 (66.4)	1.000
Dyslipidemia	546 (81.5)	610 (77.3)	0.050
Current smoking	126 (18.6)	155 (19.6)	0.641
Previous myocardial infarction	243 (36.2)	215 (27.5)	<0.001
Previous cerebrovascular disease	72 (10.7)	112 (14.2)	0.044
Previous stroke	22 (3.3)	35 (4.4)	0.244
Previous transient ischemic attack	28 (4.2)	36 (4.6)	0.707
Previous carotid artery disease	39 (5.8)	67 (8.4)	0.047
Peripheral vascular disease	42 (6.2)	71 (8.9)	0.048
Chronic obstructive pulmonary disease	41 (6.0)	69 (8.7)	0.055
Chronic kidney disease	101 (16.0)	126 (17.2)	0.552
Creatinine clearance, mL/min	89.0 ± 33.9	86.3 ± 30.7	0.128
Left ventricular ejection fraction, %	59.0 ± 11.8	59.5 ± 13	0.524
Congestive heart failure	33 (4.9)	23 (2.9)	0.052
Clinical presentation			0.937
Silent ischemia	89 (13.1)	107 (13.5)	
Stable angina	400 (59.0)	472 (59.4)	
Unstable angina	189 (27.9)	215 (27.1)	
EuroSCORE	3.4 ± 2.4	3.6 ± 2.4	0.235
Parsonnet score	7.7 ± 6.1	8.0 ± 6.8	0.417
Disease type			0.014
3-vessel disease	432 (63.7)	456 (57.4)	
Left main disease	246 (36.3)	338 (42.6)	
Number of lesions	4.6 ± 1.8	4.2 ± 1.8	<0.001
Anatomical SYNTAX score	29.4 ± 11.7	27.8 ± 11.2	0.009
Randomized treatment			0.329
PCI	358 (52.8)	399 (50.3)	
CABG	320 (47.2)	395 (49.7)	
Any bifurcation	487 (72.0)	570 (72.2)	0.932
Total occlusion	193 (28.5)	184 (23.2)	0.020
Complete revascularization	396 (58.4)	486 (61.5)	0.225
Residual SYNTAX score (only PCI population)	5.8 ± 0.3	5.0 ± 0.3	0.033
Clinical events between revascularization and 5-year follow-up			
Myocardial infarction	40 (5.9)	35 (4.4)	0.195
Any revascularization	144 (21.2)	137 (17.3)	0.053

Values are mean ± SD or n (%).

CABG = coronary artery bypass graft; EuroSCORE = European System for Cardiac Operative Risk Evaluation; OMT = optimal medical therapy; PCI = percutaneous coronary intervention; SYNTAX = Synergy Between PCI With Taxus and Cardiac Surgery.

CENTRAL ILLUSTRATION **Kaplan-Meier Curves of All-Cause Mortality From 5 to 10 Years**



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The Kaplan-Meier curves were stratified according to the number of individual optimal medical therapy agents at 5 years. Patients on none, 1, or 2 types of medications **(blue line)** versus patients on 3 types of medications **(red line)** versus patients on 4 types of medications **(black line).**

RESULTS

PATIENT CHARACTERISTICS. Baseline characteristics according to the status of OMT at 5-year follow-up are shown in Table 1. Of 1,800 randomized patients, drug information at 5 years after PCI or CABG was obtained in 1,472 patients. Of these, 678 patients (46.1%) took OMT, and 794 patients (53.9%) were not taking OMT.

The OMT group had a higher prevalence of a history of myocardial infarction than the non-OMT group did. In contrast, previous cerebrovascular disease and peripheral vascular disease were less frequently observed in the OMT group. The frequencies of 3VD and total occlusion were higher in the OMT group than in the non-OMT group. The total number of lesions was more extensive, and the anatomical SYNTAX score was higher in the OMT group than in the non-OMT group (29.4 ± 11.7 vs 27.8 ± 11.2; $P = 0.009$). Furthermore, the residual SYNTAX score was significantly higher in the OMT group than in the non-OMT group (5.8 ± 0.3 vs 5.0 ± 0.3; $P = 0.033$). This is a post hoc analysis of the SYNTAXES study, in which medication usage was not part of randomization.

IMPACT OF THE NUMBER OF INDIVIDUAL OMT AGENTS AT 5 YEARS ON 10-YEAR MORTALITY. The Central Illustration shows Kaplan-Meier curves of the all-cause mortality from 5 to 10 years according to the number of the individual OMT agents at 5 years (none, 1, or 2 types of medications: 19.9%; 3 types of medications: 12.7%; and 4 types of medications [OMT]: 13.1%; log-rank $P = 0.011$). After adjusting the confounding factors, patients on OMT at 5 years had a significantly lower mortality at 10 years than did those on ≤2 types of medications (13.1% vs 19.9%; adjusted HR: 0.470; 95% CI: 0.292-0.757; $P = 0.002$) but had a mortality similar to those on 3 types of medications (Table 2).

TABLE 2 Impact of the Number of the Individual OMT Agents on the All-Cause Mortality Between 5 and 10 Years

	Death	Unadjusted HR (95% CI)	*P* Value	Adjusted HR (95% CI)	*P* Value
Patients on OMT (n = 678) vs patients on none, 1, or 2 types of medications (n = 262)	85 (13.1) vs 43 (19.9)	0.614 (0.425-0.886)	0.009	0.470 (0.292-0.757)	0.002
Patients on OMT (n = 678) vs patients on 3 types of medications (n = 532)	85 (13.1) vs 63 (12.7)	1.059 (0.764-1.466)	0.732	0.953 (0.617-1.473)	0.830
Patients on 3 types of medications (n = 532) vs patients on none, 1, or 2 types of medications (n = 262)	63 (12.7) vs 43 (19.9)	0.580 (0.393-0.854)	0.006	0.493 (0.299-0.813)	0.006

Values are n (%) unless otherwise indicated. Data are percentages based on Kaplan-Meier estimates.
Abbreviation as in Table 1.

The combination pattern of the number of individual OMT agents up to 5 years after the revascularization is shown in Supplemental Table 1. The most frequent combination pattern of the number of individual OMT agents was patients on 4 types (OMT) of medications at discharge and 1-month, 6-month, 1-year, 3-year, and 5-year follow-ups (244 of 1,472 patients, 16.6%).

VARIOUS COMBINATIONS OF INDIVIDUAL OMT AGENTS AT 5 YEARS AND 10-YEAR MORTALITY. The breakdown of the combination of individual OMT agents at 5 years and the 10-year all-cause mortality are shown in Supplemental Table 2. The mortality in patients without any medication, with 1 type of medication, and with 2 types of medications were 36.4%, 25.1%, and 17.0%, respectively.

IMPACT OF INDIVIDUAL MEDICATION STATUS AT 5 YEARS ON 10-YEAR MORTALITY. The Kaplan-Meier curves of all-cause mortality from 5 to 10 years according to the individual OMT agents at 5 years are presented in **Figure 1**. In both the univariate and multivariate analyses, patients with the individual OMT agents, antiplatelet drug and statin, had lower mortality than those without did (antiplatelet drug: 13.2% vs 22.6%; adjusted HR: 0.484; 95% CI: 0.287-0.816; $P = 0.006$, and statin: 13.1% vs 20.3%; adjusted HR: 0.556; 95% CI: 0.351-0.912; $P = 0.020$, respectively) (**Figure 1, Table 3**).

The pattern of individual OMT agent prescription up to 5 years after the revascularization is presented in Supplemental Table 3. The most frequent patterns of individual OMT agent prescription were patients on each medication at discharge and 1-month, 6-month, 1-year, 3-year and 5-year follow-up, respectively.

IMPACT OF MEDICATION STATUS AT 5 YEARS AND MODE OF REVASCULARIZATION ON 10-YEAR MORTALITY. **Figure 2** shows the Kaplan-Meier curves of all-cause mortality from 5 to 10 years according to the individual OMT agents and the randomized treatment. In the CABG arm, patients prescribed antiplatelet drug and statin had lower mortality both by the univariate and multivariate analyses (antiplatelet drug: 10.4% vs 25.0%; adjusted HR: 0.283; 95% CI: 0.137-0.585; $P = 0.001$, and statin: 9.8% vs 27.6%; adjusted HR: 0.246; 95% CI: 0.123-0.493; $P < 0.001$, respectively) (**Figure 2, Table 3**).

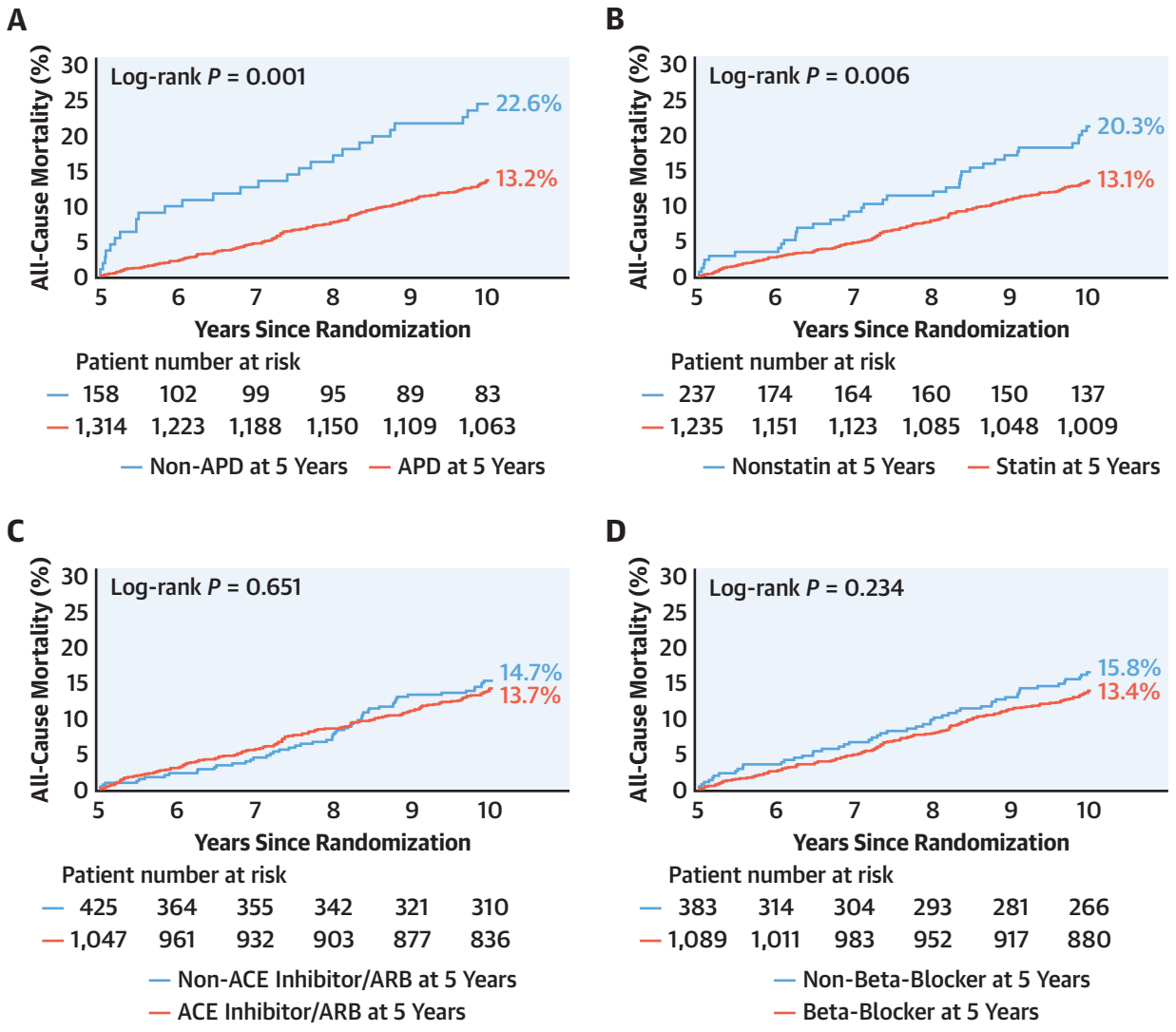
Supplemental Figure 2 shows the Kaplan-Meier curves of all-cause mortality from 5 to 10 years according to the OMT status at 5 years and randomized treatment. The mortality in patients with and without OMT undergoing CABG were 9.7% vs 14.1%, and those undergoing PCI were 16.2% vs 15.6%. Supplemental Figure 3 shows the Kaplan-Meier curves of all-cause mortality from 5 to 10 years according to the OMT status at 5 years and disease type (LM or 3VD). The mortality in patients with and without OMT having LM were 14.7% versus 16.3%, and those having 3VD were 12.2% vs 13.8%. Supplemental Figure 4 shows the Kaplan-Meier curves of all-cause mortality from 5 to 10 years according to the OMT status at 5 years and SYNTAX score tertiles (≤22: low; 23-32: intermediate; ≥33: high). The mortality in patients with and without OMT and the SYNTAX score ≤22 were 12.8% vs 10.9%, those and the SYNTAX score 23 to 32 were 8.9% versus 15.1%, and those and the SYNTAX score ≥33 were 16.3% versus 19.7%. Furthermore, as shown in Supplemental Table 4, there was no significant treatment interaction effect of OMT versus non-OMT on the mortality in the stable ischemic heart disease and unstable angina groups, and there were no significant differences between the OMT and non-OMT groups (stable ischemic heart disease: 13.5% vs 14.2%; adjusted HR: 0.843; 95% CI: 0.531-1.338; $P = 0.468$, and unstable angina: 12.0% vs 16.7%; adjusted HR: 0.583; 95% CI: 0.282-1.205; $P = 0.145$).

DISCUSSION

The main findings of this study can be summarized as follows:

1. Patients who were successfully maintained on OMT (4 types of medications) up to 5 years after their revascularization had a survival benefit at 10 years comparable to that of those patients who

FIGURE 1 Kaplan-Meier Curves of All-Cause Mortality From 5 to 10 Years



The Kaplan-Meier curves were stratified according to the individual optimal medical therapy agent at 5 years. **(A)** Non-antiplatelet drug (APD) **(blue line)** versus APD **(red line)**. (APD means at least 1 antiplatelet drug [aspirin, clopidogrel, or ticlopidine] prescription.) **(B)** Nonstatin **(blue line)** versus statin **(red line)**. **(C)** Non-angiotensin-converting enyme (non-ACE) inhibitor/angiotensin receptor blocker (ARB) **(blue line)** versus ACE inhibitor/ARB **(red line)**. **(D)** Non-beta-blocker **(blue line)** versus beta-blocker **(red line)**.

were on ≤2 types of medications but had a mortality similar to those on 3 types of medications.

2. Overall, patients on antiplatelet drug and statin therapy at 5 years were associated with lower all-cause mortality at 10 years than patients not on those drugs were. This association was emphasized in patients treated with CABG.

Our study evaluated the impact of OMT and individual OMT agents on the 10-year all-cause mortality in patients with de novo 3VD and/or LM undergoing PCI or CABG. The post hoc analysis from the COURAGE (Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation) trial demonstrated all-cause mortality in 52% of the original trial population during a median 11.9-year follow-up, and it showed no late mortality benefit of PCI + OMT versus OMT alone, although the use of bare-metal stents in 97% of patients may have contributed to the neutral outcome (24).

TABLE 3 Impact of Medication Status at 5 Years on the All-Cause Mortality Between at 5 and 10 Years

Drug	Group	Using Drug Death/Patients	Omitting Drug Death/Patients	Unadjusted HR (95% CI) Using Drug vs Omitting Drug	*P* Value	Adjusted HR (95% CI) Using Drug vs Omitting Drug	*P* Value
APD	Overall	164/1314 (13.2)	27/158 (22.6)	0.500 (0.333-0.752)	0.001	0.484 (0.287-0.816)	0.006
	PCI	102/692 (15.7)	8/65 (19.2)	0.818 (0.399-1.681)	0.585	0.918 (0.346-2.438)	0.864
	CABG	62/622 (10.4)	19/93 (25.0)	0.334 (0.200-0.558)	<0.001	0.283 (0.137-0.585)	0.001
Statin	Overall	154/1235 (13.1)	37/237 (20.3)	0.606 (0.423-0.868)	0.006	0.566 (0.351-0.912)	0.020
	PCI	97/631 (16.3)	13/126 (13.8)	1.224 (0.686-2.184)	0.493	1.420 (0.598-3.376)	0.427
	CABG	57/604 (9.8)	24/111 (27.6)	0.306 (0.190-0.494)	<0.001	0.246 (0.123-0.493)	<0.001
ACE inhibitor/ARB	Overall	136/1047 (13.7)	55/425 (14.7)	0.930 (0.680-1.272)	0.651	0.830 (0.555-1.240)	0.363
	PCI	79/539 (15.7)	31/218 (16.3)	0.969 (0.639-1.468)	0.881	0.883 (0.498-1.567)	0.671
	CABG	57/508 (11.7)	24/207 (13.1)	0.883 (0.548-1.423)	0.609	0.693 (0.377-1.273)	0.237
Beta-blocker	Overall	139/1089 (13.4)	52/383 (15.8)	0.824 (0.559-1.134)	0.234	0.598 (0.392-0.912)	0.017
	PCI	82/565 (15.4)	28/192 (17.6)	0.879 (0.572-1.349)	0.554	0.553 (0.306-0.997)	0.049
	CABG	57/524 (11.4)	24/191 (14.2)	0.753 (0.467-1.213)	0.234	0.617 (0.324-1.174)	0.141

Values are n/N (%) unless otherwise specified. Values are percentages based on Kaplan-Meier estimates. APD means at least 1 antiplatelet drug (aspirin, clopidogrel, or ticlopidine) prescription.
APD = antiplatelet drug; ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; other abbreviations as in Table 1.

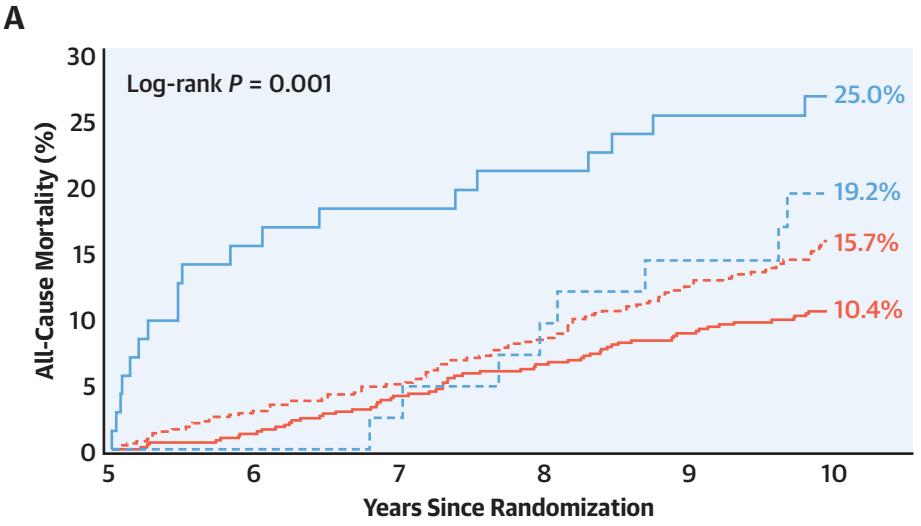
The present study suggests that at least 3 types of OMT medications should be maintained at 5 years following revascularization. In our analysis, patients with OMT had more comorbidities and more coronary artery complexity than those without OMT did (Table 1). Furthermore, the residual SYNTAX score was significantly higher in the OMT group than in the non-OMT group (Table 1). However, the 10-year all-cause mortality in patients who received all 4 types of OMT medications (mortality: 13.1%) represents a nearly 7% absolute difference, compared with 10-year all-cause mortality in those who received ≤2 types of medications (mortality: 19.9%). These findings suggest that the 7% absolute treatment difference may have actually been an underestimation of the impact of OMT on the mortality.

All the individual OMT agents (antiplatelet medication, statin, ACE inhibitor/ARB, and beta-blocker) as secondary prevention therapy have been shown to improve long-term clinical outcomes and are recommended in patients with clinically evident CAD (25-27), including patients who have undergone PCI or CABG (28-31). In the SYNTAX trial, Iqbal et al (7) demonstrated the impact of time-dependent use of all the individual OMT agents on the 5-year all-cause mortality. In this study, the use of antiplatelet drug and statin at 5 years was associated with the lower mortality at 10 years than the omission of those drugs was (antiplatelet drug: HR: 0.20; 95% CI: 0.15-0.27; $P < 0.001$, statin: HR: 0.31; 95% CI: 0.24-0.41; $P < 0.001$, ACE inhibitor/ARB: HR: 0.70; 95% CI: 0.54-0.91; $P = 0.010$, and beta-blocker: HR: 0.47; 95% CI: 0.36-0.62; $P < 0.001$). In general, antiplatelet agent and statin are generally prescribed to patients with CAD. However, the use of beta-blocker and ACE inhibitor/ARB is not universal and is largely limited to patients with additional risk factors, such as hypertension, previous myocardial infarction, or heart failure.

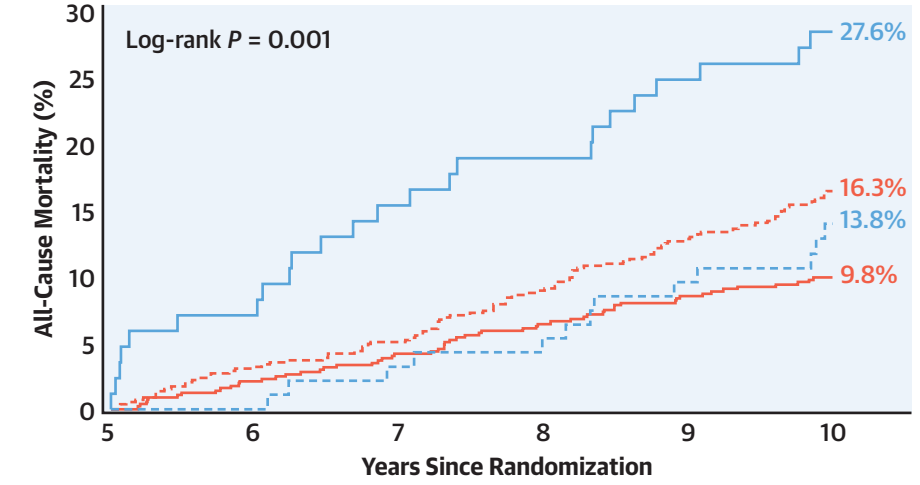
This study highlights the importance of continuous secondary prevention medication with antiplatelet drug and statin after CABG to improve the 10-year all-cause mortality. Patients are often referred for CABG because they are not so compliant to the drug prescription. Furthermore, this population not on OMT may represent the actual clinical practice. In the CABG cohort of the SYNTAX trial, lack of acetylsalicylic acid prescription at hospital discharge was identified as the strongest predictor of the mortality at 4 years (HR: 3.56; 95% CI: 2.04-6.21; $P < 0.001$) (32). Statin has also been shown to improve survival in patients after CABG (33-36). In the present study, patients post-CABG with antiplatelet medication and statin therapy at 5 years had the lower mortality at 10 years than those without similar therapy (approximately 60% mortality reduction vs omitting drugs) (Figure 2). Importantly, patients undergoing CABG had more beneficial effect on the mortality than did patients after PCI. Both in the CABG and PCI arms, the usage rates of antiplatelet agent and statin at 5 years were high (CABG: 87.0% and 84.5%; PCI: 91.4% and 83.4%) (Table 3). It is recommended that patients undergoing CABG continue antiplatelet medication and statin beyond 5 years to avail themselves of the survival benefit of such therapy observed in this analysis. These findings might serve as an essential source of data to advise future updates of perioperative medication guidelines in CABG (37).

The present analysis investigated the impact of the medication status at 5 years on the 10-year mortality without the documentation of the medication status

FIGURE 2 Kaplan-Meier Curves of All-Cause Mortality From 5 to 10 Years



Patient number at risk						
Non-APD-CABG at 5 Years	93	60	58	56	53	51
APD-CABG at 5 Years	622	588	570	556	542	528
Non-APD-PCI at 5 Years	65	42	41	39	36	32
APD-PCI at 5 Years	692	635	618	594	567	535



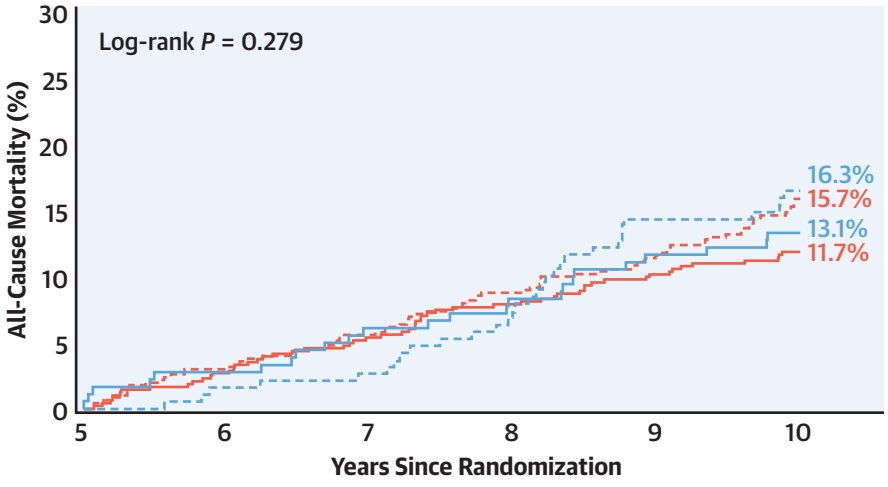
Patient number at risk						
Non-Statin-CABG at 5 Years	111	79	72	69	64	59
Statin-CABG at 5 Years	604	569	556	543	531	520
Non-Statin-PCI at 5 Years	126	95	92	91	86	78
Statin-PCI at 5 Years	631	582	567	542	517	489

The Kaplan-Meier curves were stratified according to the individual optimal medical therapy agent at 5 years and randomized treatment of percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG). **(A)** Non-APD-CABG **(blue line)** versus APD-CABG **(red line)** versus non-APD-PCI **(blue dotted line)** versus APD-PCI **(red dotted line)**. (APD means at least 1 antiplatelet drug [aspirin, clopidogrel, or ticlopidine] prescription.) **(B)** Non-statin-CABG **(blue line)** versus statin-CABG **(red line)** versus non-statin-PCI **(blue dotted line)** versus statin-PCI **(red dotted line)**. **(C)** Non-ACE inhibitor/ARB-CABG **(blue line)** versus ACE inhibitor/ARB-CABG **(red line)** versus non-ACE inhibitor/ARB-PCI **(blue dotted line)** versus ACE inhibitor/ARC-PCI **(red dotted line)**. **(D)** Non-beta-blocker-CABG **(blue line)** versus beta-blocker-CABG **(red line)** versus non-beta-blocker-PCI **(blue dotted line)** versus beta-blocker-CABG **(red dotted line)**. Abbreviations as in Figure 1.

Continued on the next page

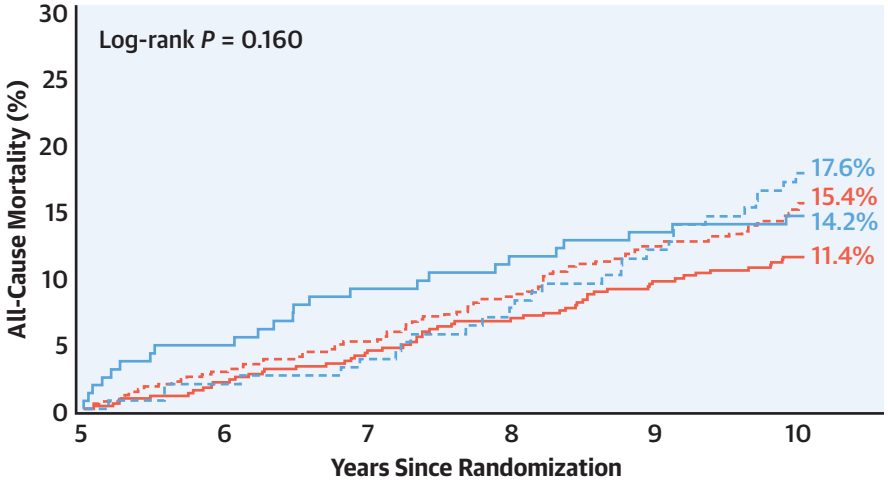
FIGURE 2 Continued

C



Patient number at risk						
Non-ACE Inhibitor/ ARB-CABG at 5 Years	207	176	170	166	160	156
ACE Inhibitor/ ARB-CABG at 5 Years	508	472	458	446	435	423
Non-ACE Inhibitor/ ARB-PCI at 5 Years	218	188	185	176	161	154
ACE Inhibitor/ ARB-PCI at 5 Years	539	489	474	457	442	413

D



Patient number at risk						
Non-Beta Blocker-CABG at 5 Years	191	157	150	146	143	139
Beta Blocker-CABG at 5 Years	524	491	478	466	452	440
Non-Beta Blocker-PCI at 5 Years	192	157	154	147	138	127
Beta Blocker-PCI at 5 Years	565	520	505	486	465	440

between 5 and 10 years. Our analysis lacks precise data on the extent to which OMT was used beyond 5 years, as well as patient adherence with OMT between 5 and 10 years, and thus, we implicitly assume that continued adherence to OMT over time has occurred in all subjects. To mitigate such a bold assumption about the medication status between 5 and 10 years, we did not resort to time-dependent analysis. Instead, the population was stratified simply according to the medication status at 5 years. As presented in Supplemental Tables 1 and 3, the medication status varied in the first 5 years. However, we assumed that patients on 3 or 4 medications up to 5 years were motivated to continue their medical treatment. For example, in these patients on OMT at 5 years, the majority (93%) were continuously on 3 or 4 medications from 1-year to 5-year follow-ups, whereas in patients on 3 medications at 5 years, 78% were on 3 or 4 medications from 1-year to 5-year follow-ups. These populations adherent to multiple medications may have contributed to the improved outcomes observed in the current analysis.

STUDY LIMITATIONS. This is a post hoc study and has limitations inherent to any such analysis (38). First, in the current analysis, drug assessment was no longer recorded after 5 years (12). However, up to 5 years, the data of medication at serial time points were available in this all-comer clinical trial of patients with 3VD and/or LM undergoing PCI or CABG (Supplemental Tables 1 and 3). Second, the SYNTAX trial was conducted between 2005 and 2007, with a predominant use of first-generation paclitaxel drug-eluting stents for treatment with PCI, which may limit the generalizability of our findings to current practices. Furthermore, there have been profound changes and improvements in medical therapy with many newer treatments (high-intensity statin, proprotein convertase subtilisin/kexin type 9 inhibitors, more powerful $P2Y_{12}$ inhibitors, low-dose rivaroxaban, and newer diabetic agents such as sodium-glucose cotransporter-2 inhibitors and glucagon-like peptide-1 receptor agonists), which continue to improve the overall prognosis of our patients. However, it is unavoidable that the findings stemming from long-term follow-up data are based on partially outdated technology and/or medications. Given that PCI and CABG for the treatment of complex CAD are rapidly evolving, the evidence for contemporary technology can only be derived from short-term follow-up studies. In addition, this observational study only assessed medications and did not refer to comprehensive secondary prevention that encompasses lifestyle and pharmacologic intervention. There was no serial collection of data on diet and physical activity. Third, in the present study, biologic and physiologic measurements such as low-density lipoprotein-cholesterol, hemoglobin A1c, and blood pressure were only available at baseline. Fourth, we acknowledged that the results from the analysis of individual drugs (antiplatelet drugs, statins, and beta-blockers) could be a spurious or chance finding and not a causal association, caused by relatively small sample sizes and restricted power, hampering the demonstration of significant differences in those subgroup analyses. 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) (10).

CONCLUSIONS

In patients with 3VD and/or LM undergoing PCI or CABG, medication status at 5 years had a significant impact on the 10-year all-cause mortality. Patients on OMT with guideline-recommended pharmacologic therapy at 5 years had a survival benefit. These findings suggest the importance of maintenance OMT over the long term in extending life span after coronary revascularization.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: Medication therapy for 5 years has a significant impact on 10-year mortality. Guideline-recommended pharmacologic therapy for 5 years after percutaneous or surgical coronary revascularization is associated with survival benefit at 10 years, and the benefit was greater among those undergoing CABG surgery compared with those undergoing PCI.

TRANSLATIONAL OUTLOOK: Although these observations strengthen the evidence favoring OMT after coronary revascularization, further research is needed to understand the differential impact based on method of revascularization.

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KEY WORDS coronary artery bypass graft, optimal medical therapy, percutaneous coronary intervention, survival, SYNTAX

APPENDIX For supplemental figures and tables, as well as details about propensity score matching, please see the online version of this paper.