JACC: CARDIOVASCULAR INTERVENTIONS VOL. 16, NO. 3, 2023

PUBLISHED BY ELSEVIER

NEW RESEARCH PAPER

CORONARY

Outcomes of Medical Therapy Plus PCI for Multivessel or Left Main CAD Ineligible for Surgery

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ABSTRACT

BACKGROUND Percutaneous coronary intervention (PCI) is increasingly used to revascularize patients ineligible for CABG, but few studies describe these patients and their outcomes.

OBJECTIVES This study sought to describe characteristics, utility of risk prediction, and outcomes of patients with left main or multivessel coronary artery disease ineligible for coronary bypass grafting (CABG).

METHODS Patients with complex coronary artery disease ineligible for CABG were enrolled in a prospective registry of medical therapy + PCI. Angiograms were evaluated by an independent core laboratory. Observed-to-expected 30-day mortality ratios were calculated using The Society for Thoracic Surgeons (STS) and EuroSCORE (European System for Cardiac Operative Risk Evaluation) II scores, surgeon-estimated 30-day mortality, and the National Cardiovascular Data Registry (NCDR) CathPCI model. Health status was assessed at baseline, 1 month, and 6 months.

RESULTS A total of 726 patients were enrolled from 22 programs. The mean SYNTAX (Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery) score was 32.4 ± 12.2 before and 15.0 ± 11.7 after PCI. All-cause mortality was 5.6% at 30 days and 12.3% at 6 months. Observed-to-expected mortality ratios were 1.06 (95% CI: 0.71-1.36) with The Society for Thoracic Surgeons score, 0.99 (95% CI: 0.71-1.27) with the EuroSCORE II, 0.59 (95% CI: 0.42-0.77) using cardiac surgeons' estimates, and 4.46 (95% CI: 2.35-7.99) using the NCDR CathPCI score. Health status improved significantly from baseline to 6 months: SAQ summary score (65.9 ± 22.5 vs 86.5 ± 15.1; $P < 0.0001$), Kansas City Cardiomyopathy Questionnaire summary score (54.1 ± 27.2 vs 82.6 ± 19.7; $P < 0.0001$).

CONCLUSIONS Patients ineligible for CABG who undergo PCI have complex clinical profiles and high disease burden. Following PCI, short-term mortality is considerably lower than surgeons' estimates, similar to surgical risk model predictions but is over 4-fold higher than estimated by the NCDR CathPCI model. Patients' health status improved significantly through 6 months. (J Am Coll Cardiol Intv 2023;16:261–273) © 2023 by the American College of Cardiology Foundation.

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

Manuscript received August 22, 2022; revised manuscript received December 9, 2022, accepted January 2, 2023.

ISSN 1936-8798/$36.00 https://doi.org/10.1016/j.jcin.2023.01.003

JACC: CARDIOVASCULAR INTERVENTIONS VOL. 16, NO. 3, 2023
FEBRUARY 13, 2023:261–273

ABBREVIATIONS AND ACRONYMS

AF = angina frequency

CABG = coronary artery bypass grafting

CAD = coronary artery disease

GDMT = guideline-directed medical therapy

KCCQ = Kansas City Cardiomyopathy Questionnaire

KCCQ SS = Kansas City Cardiomyopathy Questionnaire overall summary score

NCDR = National Cardiovascular Data Registry

PCI = percutaneous coronary intervention

SAQ = Seattle Angina Questionnaire

STS = The Society for Thoracic Surgeons

Current societal guidelines endorse coronary artery bypass grafting (CABG) as the preferred revascularization strategy for patients with complex multivessel or left main coronary disease.[1,2] However, patients with significant comorbidity burden or high-risk surgical anatomy are frequently determined to be prohibitive risk candidates for CABG and are increasingly referred for complex, higher-risk percutaneous coronary intervention (PCI), although several studies have indicated that they are also at high risk for mortality after PCI.[3-6] Because this population has not been prospectively studied and has been systematically excluded from prior trials of revascularization strategy, there is an absence of data in both medical literature and clinical practice guidelines to inform management of these challenging patients. Importantly, revascularization strategy and the utility of existing risk prediction tools designed to identify patients' risk of mortality when these patients are treated with PCI have not been described. Further, estimates of clinical outcome following PCI are uncertain, and no prior studies have described the burden of patients' symptoms, physical function and quality of life at diagnosis and following PCI.

To inform clinical decision making for this high-risk population, we enrolled patients with multivessel and/or left main coronary artery disease (CAD) who were determined to be at prohibitive risk for CABG after heart team evaluation from 22 U.S. centers in the OPTIMUM (Outcomes of Percutaneous RevascularizaTIon for Management of SUrgically Ineligible Patients with Multivessel or Left Main Coronary Artery Disease; NCT02996877) registry. The study had several objectives. First, we sought to identify the clinical characteristics driving surgeons' risk assessments, and the correlations between predicted 30-day mortality using contemporary risk assessment tools and observed mortality. Second, we aimed to describe the patient and procedural characteristics of participants undergoing PCI who were at prohibitive risk for CABG, including completeness of revascularization after PCI as assessed by an angiographic core laboratory. Finally, we sought to understand patients' symptoms in follow-up, with baseline and follow-up patient-reported health status assessed using established health-related quality-of-life measures in order to define trajectories of health status among patients with complex CAD who were considered to be at prohibitive risk for bypass surgery.[7,8] These foundational insights are critical to inform contemporary practice, patient consent, and future clinical trials for patients with surgical CAD who are not candidates for bypass surgery.

METHODS

PATIENT POPULATION. Eligible patients were ≥18 years of age and were diagnosed with significant multivessel and/or left main CAD at the time of elective coronary angiography, as previously described.[9] Eligible coronary anatomy was defined angiographically consistent with American College of Cardiology/American Heart Association Appropriate Use Criteria guidelines as an unprotected left main stenosis of ≥50%, 3-vessel disease with stenoses ≥70%, or 2-vessel coronary disease (≥70%) with 1 lesion involving the proximal left anterior descending artery.[10] If coronary stenoses of ≥40% were evaluated with fractional flow reserve or instantaneous wave-free ratio, a lesion was determined to be hemodynamically significant if fractional flow reserve was ≤0.80 or instantaneous wave-free ratio was ≤0.89.[11,12] Participants with prior bypass surgery were included if they presented with ≥2 epicardial coronary distributions subtended by a severe native coronary stenosis with either no bypass graft supplying the vessel or an occluded or severely diseased (≥70% angiographic stenosis) bypass graft supplying the affected vessel.

The intent of the OPTIMUM study was to assess treatment strategies and outcomes after careful heart team evaluation, which is advised by contemporary society guidelines.[1,2] Accordingly, patients presenting for emergency revascularization in the setting of ST-segment elevation myocardial infarction, cardiogenic shock, and unstable arrhythmias in addition to patients presenting for staged revascularization after recent PCI were excluded from enrollment. Patients treated with an initial strategy of guideline-directed medical therapy (GDMT) alone and those treated with GDMT + PCI were enrolled. Given low proportion of patients managed with GDMT alone, the protocol was amended by the steering committee during enrollment to focus only on enrollment of GDMT + PCI patients, and this analysis represents only those treated with a strategy of GDMT + PCI.[9]

Institutional Review Board approval was obtained for the OPTIMUM registry via a central Institutional Review Board (Advarra). Institutional Review Board approval of the OPTIMUM registry protocol was also obtained at each participating center.

BASELINE CLINICAL AND ANGIOGRAPHIC CHARACTERISTICS. After surgical evaluation, treatment was advised based on the recommendation of

treating cardiovascular clinicians. Baseline characteristics, clinical indications, and health status were documented by trained study coordinators at each site. All data were entered into an electronic data management system (REDCap).

All index diagnostic angiograms, index procedure angiograms, and angiograms for planned, staged interventional procedures in follow-up were obtained for review by an independent core laboratory (Cardiovascular Research Foundation). At baseline, SYNTAX (Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery) scores were calculated for each patient.[13] For patients previously treated with CABG, SYNTAX scores were calculated with consideration of patent bypass grafts to vessels previously treated with bypass.[9] For analysis purposes, reasonably complete revascularization was defined as achievement of a residual SYNTAX score ≤8 points.[14]

MORTALITY RISK ASSESSMENT. The participating cardiac surgeon documented the primary criterion defining prohibitive risk for CABG, along with all factors contributing to this decision in the assessment.[9] Risk for surgical perioperative morbidity and mortality was calculated for each patient using The Society of Thoracic Surgeons (STS) and EuroSCORE (European System for Cardiac Operative Risk Evaluation) II 30-day mortality risk scores.[15,16] To identify any discordance between evaluating surgeons' surgical risk assessments and risk scores calculated using the STS and EuroSCORE II models, each evaluating cardiac surgeon was also asked to provide a personal assessment of the individual patient's perioperative mortality if treated with CABG. Finally, the risk of in-hospital mortality when treated with PCI was calculated using the most recent version of the National Cardiovascular Data Registry (NCDR) CathPCI risk model.[17] The integer risk score and corresponding mortality rate was calculated for each patient using the bedside risk prediction tool.[17]

CLINICAL OUTCOMES AND HEALTH STATUS ASSESSMENT. Vital status was assessed at hospital discharge, 30 days after enrollment and at 6-month follow-up. Any death occurring during a hospitalization including treatment with an index or staged PCI procedure was defined as an in-hospital death. Clinical events were documented with source verification and adjudicated by an independent committee.

CAD-specific health status was assessed using the Seattle Angina Questionnaire (SAQ). The SAQ is a valid and reliable 19-item questionnaire with a 4-week recall period that measures 5 domains of health in patients with CAD: angina frequency (AF), angina stability, quality of life, physical limitation, and treatment satisfaction.[7,18] Domain scores range from 0 to 100, with higher scores indicating fewer symptoms and better quality of life. To assess heart failure related health status, we also administered the 12-item version of the Kansas City Cardiomyopathy Questionnaire (KCCQ).[8] This validated, reliable and responsive instrument uses 12 questions to assess 7 domains of heart failure-related health status, and can be summarized using the Kansas City Cardiomyopathy Questionnaire overall summary score (KCCQ SS). Following baseline assessment at the time of enrollment, health status was reassessed at 1- and 6-month follow-up via telephone calls conducted centrally at Saint Luke's Mid America Heart Institute. All interviews were conducted by staff trained in administration of health status interview techniques.

To further refine insights into follow-up health status, we also conducted an analysis stratified by baseline angina burden. Consistent with prior research, this analysis compared those with baseline SAQ AF >80 (no or minimal angina) to participants with more frequent angina at baseline (SAQ AF ≤80).[19,20] We also performed a responder analysis to quantify the proportion of patients who reported "clinically significant" and "moderate-to-large" health status improvement between baseline and 6 months using the SAQ and KCCQ. To avoid potential bias from missing follow-up health status assessment among patients who died or had extremely poor functional capacity, participants who died or were too ill to complete follow-up telephone health status interviews were considered nonresponders. Using thresholds established in prior studies,[19,20] a clinically significant change was defined as an SAQ summary score (SS) of ≥5 points, SAQ subdomain scores ≥10 points, and KCCQ scores of ≥5.7 points. Moderate-to-large change in health status was defined as a change of ≥10 points for the SAQ SS, ≥20 points for SAQ subdomains and ≥10.5 points for the KCCQ SS.[19-21] Because many participants in the OPTIMUM registry were treated because of underlying heart failure or angina equivalents of dyspnea, we further defined the clinically important and moderate-to-large improvements as either SAQ or KCCQ improvement by the magnitudes described previously.

STATISTICAL ANALYSES. Descriptive statistics were summarized as mean ± SD for continuous variables and count (percentage) for categorical variables. Baseline characteristics were compared between groups using Student's *t*-test for continuous variables and the chi-square test for categorical variables.

TABLE 1 Baseline Patient Characteristics (N = 726)

Age, y	70.0 ± 10.9
Male	497 (68.5)
White	610 (84.0)
Current smoker	132 (18.2)
Diabetes mellitus	411 (56.6)
Diabetes treated with insulin	235 (57.2)
Prior myocardial infarction	350 (48.2)
Prior percutaneous coronary intervention	238 (32.8)
Prior coronary artery bypass grafting	119 (16.4)
History of dyslipidemia	587 (80.9)
History of hypertension	662 (91.2)
Immunosuppresive treatment in the past 30 d	60 (8.3)
History of depression	134 (8.5)
History of stroke or transient ischemic attack	146 (20.1)
History of peripheral arterial disease	217 (29.9)
History of chronic kidney disease	270 (37.2)
End-stage renal disease requiring dialysis	74 (10.2)
Chronic lung disease	234 (32.2)
Chronic home oxygen	68 (9.4)
Chronic oral steroids	37 (5.1)
History of atrial fibrillation	168 (23.1)
Chronic anticoagulation	138 (19.0)
Chronic heart failure	371 (51.1)
Heart failure type	
Systolic	172 (46.4)
Diastolic	73 (19.7)
Combined	59 (15.9)
Not specified	67 (18.1)
Current NYHA functional class	
I	17 (4.6)
II	66 (17.8)
III	123 (33.2)
IV	47 (12.7)
Unknown	118 (31.8)
Left ventricular ejection fraction, %	42.6 ± 16.3
Left ventricular systolic function category	
Hyperdynamic	9 (1.3)
Normal	282 (40.7)
Mildly reduced	120 (17.3)
Moderately reduced	113 (16.3)
Severely reduced	169 (24.4)
Prior valve surgery or percutaneous valve	23 (3.2)
Total number of previous sternotomies	
None	587 (80.9)
1	113 (15.6)
2	10 (1.4)
3	3 (0.4)
Unknown	13 (1.8)
Moderate-severe mitral regurgitation	150 (23.4)
Severe mitral stenosis	2 (0.3)
Severe aortic stenosis	24 (3.3)
Angina symptoms at presentation (site reported)	
No angina	180 (26.8)
Stable (note CCS class below)	238 (35.5)
Unstable (note TIMI risk score below)	253 (37.7)
CCS classification (among patients with recognized angina)	
I	8 (3.4)
II	53 (22.4)
III	124 (52.3)
IV	52 (21.9)
ACS classification (among patients with ACS)	
Unstable angina	137 (34.6)
Non-STEMI	259 (65.4)
TIMI risk score	
Low (0-2)	12 (5.5)
Intermediate (3-4)	146 (67.3)
High (≥5)	59 (27.2)

Values are mean ± SD or n (%).

ACS = acute coronary syndrome; CCS = Canadian Cardiovascular Society; NYHA = New York Heart Association; STEMI = ST-segment elevation myocardial infarction; TIMI = Thrombolysis In Myocardial Infarction.

Comparison of observed and expected mortality was confirmed by calculating each patient's predicted risk using the tools described previously. For STS and EuroSCORE II risk models, as well as surgeons' mortality risk estimates, the ratio of observed in-hospital and 30-day mortality follow-up was calculated. In-hospital observed-to-expected mortality ratios were calculated using the NCDR CathPCI model including all deaths occurring during the index hospitalization. The 95% CIs for the observed-to-expected ratios were then calculated by bootstrapping 1,000 replicates of the OPTIMUM population using sampling with replacement.

All analyses were performed with SAS version 9.4 (SAS Institute).

RESULTS

PATIENT CHARACTERISTICS. Between December 2016 and July 2019, 726 patients treated with GDMT + PCI were enrolled from 22 centers. The clinical characteristics of these patients are presented in Table 1. Briefly, the mean age of the population was 70.0 ± 10.9 years. Prior PCI had been performed in 32.8% of participants, and 16.4% had a history of prior CABG. The mean left ventricular ejection fraction was 42.6% ± 16.3%; 51.1% had been diagnosed with chronic heart failure. Severe left ventricular systolic dysfunction

TABLE 2 Angiographic and Procedural Characteristics (N = 726)

Baseline coronary anatomy	
Number of vessels diseased	
Mean ± SD	4.2 ± 1.5
Median (IQR)	4.0 (3.0-5.0)
Baseline SYNTAX score	32.4 ± 12.2
Baseline SYNTAX score category	
Low	149 (21.8)
Intermediate	224 (32.8)
High	309 (45.3)
Severe left main stenosis	205 (28.3)
Severe left anterior descending stenosis	666 (92.0)
Severe right coronary stenosis	549 (75.8)
Severe circumflex stenosis	481 (66.4)
Any severely calcified lesion	597 (82.5)
Any bifurcation lesion	580 (80.2)
Number of bifurcation lesions	1.4 ± 1.1
Any chronic total occlusion	412 (56.9)
Number of chronic total occlusions	1.6 ± 0.8
J-CTO score	1.4 ± 0.8
Any lesion ≥20 mm	561 (78.5)
Operator-reported indications for PCI	
Symptom relief	289 (39.8)
Ischemia reduction	99 (13.6)
Treatment of cardiomyopathy	121 (24.1)
Acute coronary syndrome	197 (27.1)
Avoidance of transplant	2 (0.3)
Ventricular arrhythmia	1 (0.1)
Other or unknown	17 (2.3)
Post-PCI coronary anatomy	
SYNTAX score	15.0 ± 11.7
Low	510 (75.7)
Intermediate	101 (15.0)
High	63 (9.3)
SYNTAX score ≤8 points	231 (34.3)
SYNTAX score = 0 points	77 (11.4)
PCI treatment	
Radial access	273 (37.6)
Number vessels treated	
Mean ± SD	2.9 ± 1.4
Median (IQR)	3.0 (2.0-4.0)
Number of DES implanted	
Mean ± SD	3.2 ± 1.9
Median (IQR)	3.0 (2.0-4.0)
Number of BMS	
Mean ± SD	0.1 ± 0.4
Median (IQR)	0.0 (0.0-0.0)
Left main treated	277 (38.2)
Left anterior descending treated	538 (74.1)
Left circumflex treated	369 (50.8)
Right coronary artery treated	254 (35.0)
Any atherectomy	232 (32.0)
Any bifurcation treated	245 (33.7)
Any chronic total occlusion attempted	147 (20.3)
Chronic total occlusion PCI success	118 (80.3)
Any cutting balloon used	143 (19.7)
Any intravascular ultrasound	442 (61.0)
Any optical coherence tomography	30 (4.1)
Any FFR or iFR	29 (4.0)
Any postdilation	672 (94.4)
Max stent pressure	17.3 ± 3.6
Hemodynamic support (inclusive of all procedures)	194 (26.7)
Tandem Heart	3 (1.5)
Extracorporeal membrane oxygenation	3 (1.5)
Impella CP	125 (64.4)
Impella 2.5	18 (9.3)
Intra-aortic balloon pump	56 (28.9)
Impella RP	1 (0.1)

Values are mean ± SD, median (IQR), or n (%). Proportions for core lab variables reflect a denominator of patients with complete core lab analysis.

BMS = bare-metal stent(s); DES = drug-eluting stent(s); FFR = fractional flow reserve; iFR = instantaneous wave-free ratio; J-CTO = Multicenter Registry of CTO of Japan; PCI = percutaneous coronary intervention; SYNTAX = Synergy between Percutaneous Coronary Intervention with the Taxus and Cardiac Surgery.

Continued in the next column

(left ventricular ejection fraction ≤30%) was present in 24.4% of participants. Prevalence of additional characteristics included diabetes mellitus (56.6%), history of transient ischemic attack or stroke (20.1%), chronic kidney disease (37.2%), and severe obstructive lung disease (32.2%).

The primary determinants of prohibitive risk for CABG reported from the perspective of participants' cardiac surgeons are reported in Supplemental Table 1. The most common reasons were poor targets or conduit (18.9%), severe cardiomyopathy (14.6%), and severe lung disease (10.1%). The prevalence of supporting characteristics contributing to the assessment of prohibitive surgical risk are also described in Supplemental Table 1.

PCI PROCEDURES. Among 726 patients treated with GDMT + PCI, the majority of patients underwent a single PCI procedure (83.2%), whereas 15.4% underwent 2 procedures and 1.4% underwent 3. The most common primary indications for revascularization were treatment of ischemic symptoms (39.8%), ischemic cardiomyopathy (24.1%), and treatment of an acute coronary syndrome (27.1%).

The vessels treated and the angiographic characteristics of patients undergoing PCI are presented in Table 2. Complete angiographic data to calculate preprocedure SYNTAX scores were available in 682 (93.9%) of 726 patients. The baseline SYNTAX score was 32.4 ± 12.2 points; among these participants, 45.3% had high-complexity disease (SYNTAX score ≥33). A mean of 2.9 ± 1.4 vessels were treated per patient. Left main PCI was performed in 38.2% of patients, and 74.1% had PCI of the left anterior

TABLE 3 Procedural Complications and Mortality (N = 726)

Procedural complications	
Coronary perforation	31 (4.3)
Pericardial effusion	13 (1.8)
Hemodynamically significant pericardial effusion	9 (1.2)
Clinical periprocedural myocardial infarction	11 (1.5)
No reflow	9 (1.2)
Emergency cardiac surgery	4 (0.6)
Access site hematoma	36 (5.0)
Non-access site bleeding	31 (4.3)
Mortality	
30-d or in-hospital death	41(5.6)
In-hospital death	22 (3.0)
Death within 30 d (out of hospital)	19 (2.6)
Cardiovascular in-hospital or 30-d death	28 (82.4)[a]
Death within 6 mo	89 (12.3)

Values are n (%). [a]Records were available to adjudicate cause of death for 34 of the 41 deaths.

descending artery. Hemodynamic support was used during PCI in 26.7% of patients, most frequently with the Impella percutaneous left ventricular assist device (Abiomed). Atherectomy was performed in 32.0% of cases and intravascular imaging was utilized in 63.8%. Chronic total occlusion PCI was performed in 20.3% of patients, with a success rate of 80.3% among attempted cases.

Postrevascularization SYNTAX scores could be calculated for 674 (92.8%) patients. The average SYNTAX score postrevascularization was 15.0 ± 11.7; 75.7% had low-complexity (SYNTAX score ≤22), 15.0% had intermediate-complexity (SYNTAX score 23-32), and 9.3% had high-complexity (SYNTAX score ≥33) residual CAD. A residual SYNTAX score of ≤8 points was achieved in 34.3% of patients, and a residual SYNTAX score of zero was achieved in 11.4% of patients.

PROCEDURAL COMPLICATIONS AND MORTALITY. Vital status at 30 days was known for 698 (96.1%) patients. In-hospital major cardiac and cerebrovascular outcomes and early mortality are presented in **Table 3**. In-hospital or 30-day death occurred in 41 (5.6%) patients. Among these events, 22 (3.0%) and 19 (2.6%) deaths occurred in-hospital and between discharge and 30-days, respectively. Cardiac death was adjudicated in 28 (82.4%) of 34 of the 30-day deaths with known cause of death. The composite of myocardial infarction, contrast induced nephropathy, perforation, bleeding, or emergency surgery occurred in 71 (9.8%) patients. By 6 months, all-cause mortality occurred in 89 (12.3%) patients.

COMPARISON OF OBSERVED VS PREDICTED MORTALITY. Predicted surgical mortality through 30 days was 5.3% ± 5.7% using the STS risk score, 5.7% ± 5.4% using the EuroSCORE II score, and was estimated at a mean of 10.4% ± 12.3% by evaluating cardiac surgeons. The contemporary NCDR CathPCI beside risk score predicted in-hospital mortality to be 0.7% ± 4.1%. Observed-to-expected mortality ratios using each risk estimate are presented in the **Central Illustration**.

HEALTH STATUS OUTCOMES. Follow-up health status assessment through 6 months was complete in 501 (78.6%) of 637 living patients. Missing assessments among patients alive at 6 months were due to being too ill to complete follow-up interviews in 26 (4.1%), refusal in 83 (13.0%), and loss to follow-up in 27 (4.2%). A comparison of the clinical characteristics and health status scores of patients with and without health status follow-up is presented in Supplemental Table 2.

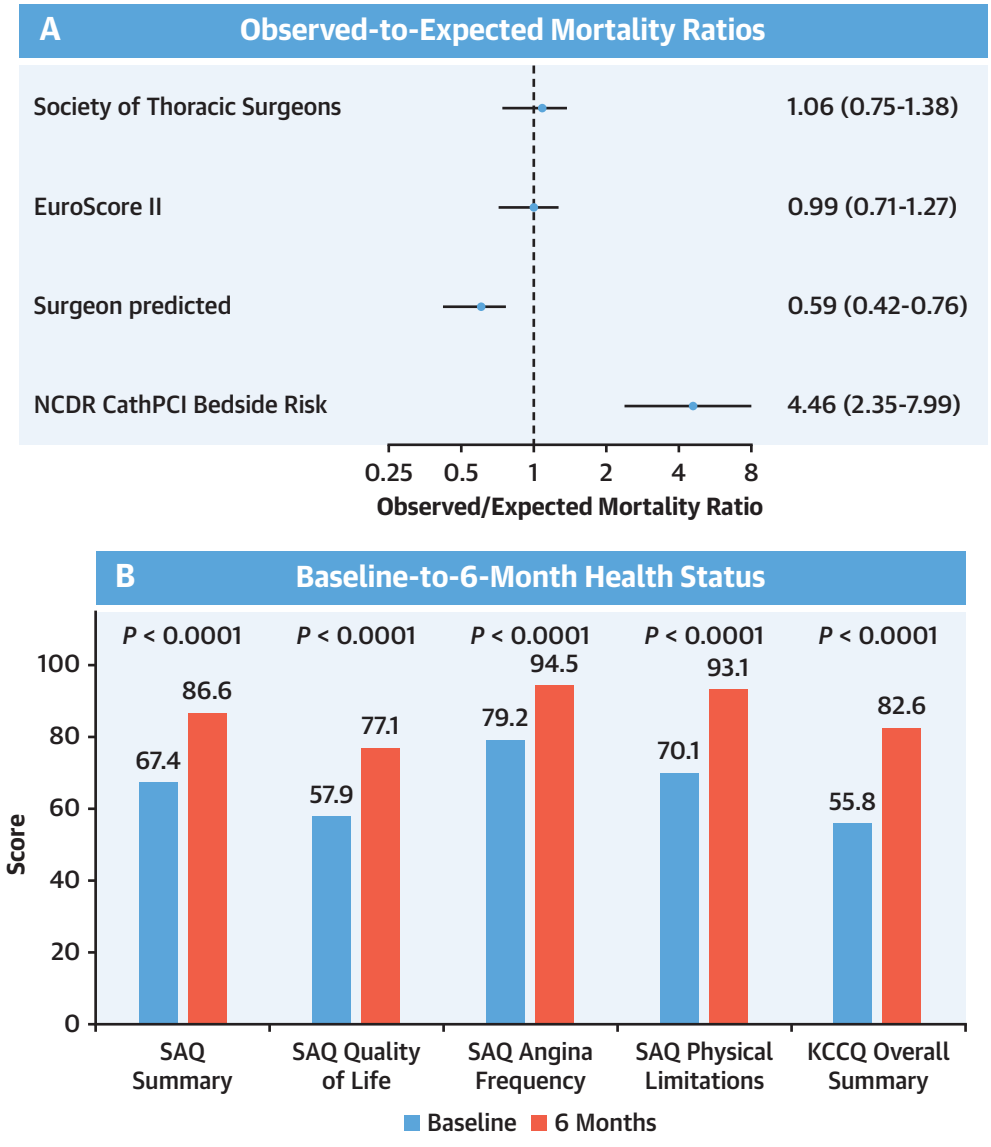
Mean baseline, 1-month, and 6-month SAQ and KCCQ scores are presented in **Table 4**. Health status at baseline and 6 months among patients' complete baseline and 6-month health status data are depicted in the **Central Illustration**. Significant improvements in mean health status were observed in each domain of the SAQ and on the KCCQ SS between baseline and 6-month follow-up. Although the majority of patients reported anginal symptoms at baseline (59.6%; 27.7% with daily/weekly angina and 31.9% with monthly angina), 82.4% reported no angina at the time of 6-month follow-up (**Figure 1**).

When stratifying the population by baseline angina status, those with more frequent baseline symptoms experienced larger improvements in CAD-specific and heart failure-specific health status. Mean SAQ SS improved in both groups, with larger improvements among those with more frequent baseline angina (6.7 ± 17.0 points among those with no or minimal baseline angina and 32.2 ± 21.3 points among those with frequent baseline angina). Mean change from baseline to 6 months exceeded 30 points on the SAQ domains of AF, quality of life, and physical limitation, and on the KCCQ SS (Supplemental Table 3) among those with more frequent baseline angina. Furthermore, among patients with no or minimal baseline angina, large health status improvement was noted on the KCCQ SS (22.4 ± 27.2 points).

The proportion of responders who reported clinically important magnitudes of baseline to 6-month health status change on the SAQ SS, SAQ domains, and KCCQ SS are presented in Supplemental Table 4. Clinically important improvements in SAQ SS were reported in 58.0% of

CENTRAL ILLUSTRATION Study Overview and Main Results

PCI Outcomes and Mortality Risk Scores for Surgically Ineligible Patients With Left Main or Multivessel CAD (N = 726)



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(A) Observed over expected mortality ratios using The Society of Thoracic Surgeons 30-day mortality risk score, EuroSCORE (European System for Cardiac Operative Risk Evaluation) II 30-day mortality risk score, the evaluating cardiac surgeon's personal estimate of risk with bypass surgery, and the in-hospital mortality estimated by the National Cardiovascular Data Registry (NCDR) CathPCI integer risk score. Values are HR (95% CI). **(B)** Mean health status scores at baseline and 6-month follow-up. Analysis restricted to patients with complete data for both baseline and 6-month health status assessments. **Error bars** represent 95% CIs. KCCQ = Kansas City Cardiomyopathy Questionnaire; SAQ = Seattle Angina Questionnaire.

TABLE 4 Baseline, 1-Month, and 6-Month Health Status

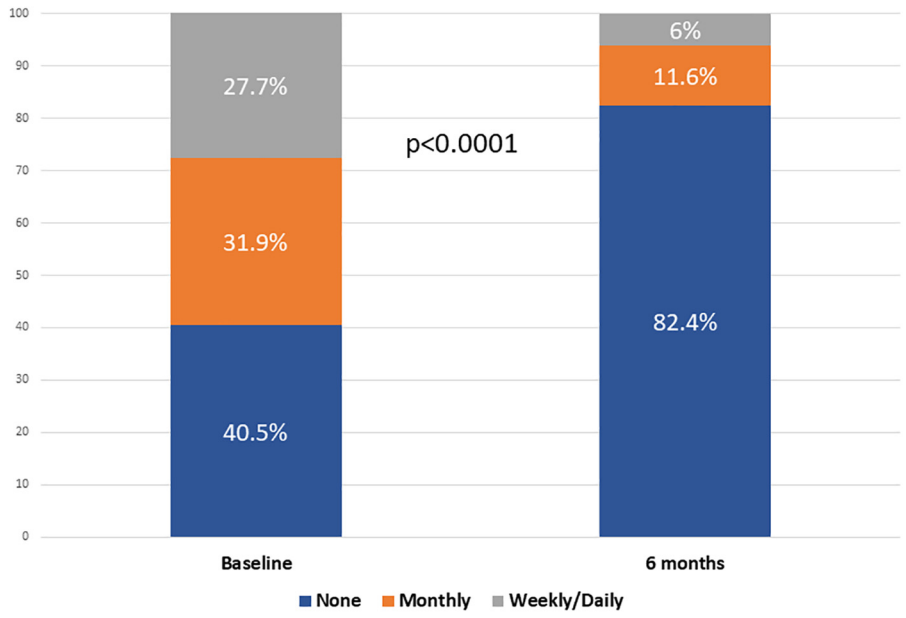
Baseline (n = 724)	
SAQ Summary Score	65.9 ± 22.5
SAQ Physical Limitation Score	60.9 ± 29.8
SAQ Angina Frequency Score	78.2 ± 23.6
SAQ Quality of Life Score	56.0 ± 27.8
KCCQ-12Summary Score	54.1 ± 27.2
1 mo (n = 551)	
SAQ summary score	84.7 ± 13.9
SAQ physical limitation score	91.4 ± 19.2
SAQ angina frequency score	95.6 ± 11.5
SAQ quality-of-life score	72.4 ± 22.7
KCCQ-12 summary score	78.5 ± 20.7
6 mo (n = 501)	
SAQ summary score	86.5 ± 15.1
SAQ physical limitation score	92.9 ± 16.9
SAQ angina frequency score	94.5 ± 14.7
SAQ quality-of-life score	77.2 ± 22.3
KCCQ-12 summary score	82.6 ± 19.7

Values are mean ± SD.
KCCQ = Kansas City Cardiomyopathy Questionnaire; SAQ = Seattle Angina Questionnaire.

participants and 62.0% of patients using the KCCQ SS. Moderate-to-large improvements were reported by 49.9% using the SAQ SS and 55.5% on the KCCQ SS. Finally, when defining a clinically important improvement by improvement in either SAQ SS or KCCQ SS, the proportion of patients reaching this threshold increased to 69.9%, and 64.0% achieved a moderate-to-large improvement.

COMPLETENESS OF REVASCULARIZATION AND OUTCOMES. Comparing patients with a residual SYNTAX score ≤8 points vs higher scores, in-hospital or 30-day mortality was numerically but not statistically significantly lower (3.9% vs 6.3%; $P = 0.19$), and by 6 months, mortality was similar between groups (10.8% among those with a SYNTAX score <8 points vs 12.2% for those with a SYNTAX score ≥8 points; $P = 0.60$). A comparison of baseline to 6-month change in SAQ domain and the KCCQ SS is presented in Supplemental Figure 1. No significant differences in SAQ SS, SAQ quality of life, and KCCQ were observed relative to completeness of revascularization.

FIGURE 1 Baseline and 6-Month Angina Burden



The proportion of the OPTIMUM (Outcomes of Percutaneous RevascularizaTIon for Management of SUrgically Ineligible Patients with Multivessel or Left Main Coronary Artery Disease) registry cohort reporting no angina (Seattle Angina Questionnaire angina frequency [SAQ AF] = 100 points), daily to weekly angina (SAQ AF = ≤60 points), and monthly angina (SAQ AF = 61 to 99 points) at baseline and at the time of 6-month follow-up health status interviews.

DISCUSSION. Patients with left main and/or multivessel CAD at prohibitive surgical risk represent the confluence of complex coexisting illness, frailty, and complex anatomy and present an increasingly common clinical dilemma. Considering the absent representation of these individuals in prior trials, there are few data to inform the development of guideline recommendations for treatment of these patients. The OPTIMUM registry was designed as a prospective, multicenter study to examine clinical decision making, contemporary management, and the clinical and health status outcomes of these challenging patients. In this study, participants who were ineligible for CABG were characterized by extensive comorbidity, complex coronary anatomy, and treatment with varied interventional strategies. Reflecting the underlying risk profile of this cohort, early mortality was considerably higher than most other PCI indications but was similar to predictions from surgical risk models and lower than the evaluating surgeons' estimates. Profound improvements in patient-reported health status in follow-up after treatment with GDMT + PCI were also observed. Mean improvements in both CAD-specific and heart failure–specific health status were large, and when examining the health status trajectory of individual patients, over two-thirds of patients experienced clinically important improvement at 6 months when considering both health status instruments.

Although a growing proportion of patients are deemed ineligible for bypass surgery despite left main or multivessel CAD in contemporary practice, few studies have rigorously characterized this population or the decision-making process at the time of selection of a revascularization strategy. Accordingly, a key goal of the OPTIMUM registry was to characterize this population using a cohort enrolled from diverse care settings across the country, and the enrollment criteria for the study were intentionally broad to capture all patients deemed ineligible for surgery, rather than focus on specific subgroups. This is the first multicenter study to demonstrate this truly complex and highly variable patient population. Furthermore, we were able to document the rationale for prohibitive surgical risk from the perspective of the evaluating clinicians. We found that the rationale for surgical ineligibility was varied, reflecting a host of anatomic characteristics, clinical risk factors, and participants' functional capacity.

Early mortality was high in this complex population, and the relationship between observed and predicted mortality merits careful consideration. We found that risk prediction models designed to identify risk of 30-day mortality with bypass surgery performed well in this population, despite their application to patients undergoing less invasive PCI procedures and lack of inclusion of surgically ineligible patients in the cohorts used to derive these models. This underscores the high-risk nature of this population, and there are several potential drivers of this observation. First, this finding suggests that the risk factors that identify high risk with bypass surgery also predict higher risk for revascularization with PCI. However, because these patients were never included in the datasets used to derive these surgical risk models, it is equally plausible that mortality may have been even higher if these patients were treated with surgical revascularization, as reflected in the surgeons' personal estimates of risk of mortality with CABG. Pending development of tools to assess risk derived from prohibitive surgical risk populations, these results suggest that instruments such as the STS and EuroSCORE scores may be more appropriate than contemporary PCI risk models to predict risk of mortality following PCI.

Furthermore, these results strongly reinforce that PCI risk among surgically ineligible patients is also not well captured by existing PCI risk prediction models, which has been described in prior studies of surgically ineligible patients.[3,22] Observed mortality in this population was nearly 4.5-fold higher than predicted by the most contemporary NCDR CathPCI bedside risk model. This finding should be considered carefully. The highly complex patients enrolled in the OPTIMUM registry represented a very small proportion of the derivation cohorts for the NCDR risk model. Accordingly, the unique outcomes trajectories experienced by these patients are incompletely represented by these models. Surgical ineligibility has been included as a variable in these models but was not retained in the final NCDR CathPCI bedside risk model given its application to a small number of patients in general practice. Mortality was lower than estimated by evaluating cardiac surgeons for treatment with bypass surgery. It is unclear whether this reflects overestimation of risk by surgeons or lower risk with a less invasive revascularization procedure when treating with PCI, and it is an important topic of future studies. It is also important to acknowledge that the impact of PCI on mortality risk is not as clearly established as surgical revascularization, consistent with a class 2A recommendations in contemporary guidelines,[1] underscoring continued need for future studies including randomized trials to evaluate the impact of PCI on key clinical endpoints in this population. These findings highlight a need to develop risk prediction tools to estimate risks and benefits derived from high-risk cohorts such as the

OPTIMUM registry to refine discussions of risk when treating these complex patients.

We observed poor baseline health status and large early health status improvement among surviving patients treated with guideline-directed GDMT and PCI that were sustained throughout 6-month follow-up. Importantly, improvements in mean angina frequency, CAD-specific quality of life, overall CAD-specific health status, and heart failure-specific health status were highly clinically relevant and statistically significant. These findings underscore that these challenging patients are frequently highly symptomatic at baseline and have potential to experience very large health status benefits. For example, participants in the invasive arm of the International Study of Comparative Health Effectiveness with Medical and Invasive Approaches trial had a mean SAQ SS of 76.0 points at baseline compared with only 67.4 points among patients in the OPTIMUM registry.[20] However, follow-up SAQ SS scores among OPTIMUM registry patients increased to a mean of 86.6 points, with resulting health status similar to that experienced by less complex ISCHEMIA (International Study of Comparative Health Effectiveness with Medical and Invasive Approaches) trial participants in early follow-up (85.2 points at 3 months), suggesting that similar follow-up health status can be achieved in an extreme-risk cohort of patients, even in comparison with those with fewer comorbidities and less complex CAD. This is further underscored by results of the responder analysis. Even with the assumption that all patients who died or were too ill to complete follow-up health status interviews had no significant health status improvement, large proportions of the population reported clinically important health status improvements with 58.0% improving using the SAQ SS and 62.0% of patients reporting clinically meaningful health status improvement using the KCCQ SS at 6-month follow-up.

The improvement in SAQ scores observed in OPTIMUM are particularly robust given that a large proportion of patients (39.2%) reported no angina at baseline. There are 2 key considerations in interpretation of this finding. First, when stratifying by baseline angina, those reporting frequent baseline symptoms experienced particularly large symptom improvements (32.2 $\pm$ 21.3 points using the SAQ SS, 31.7 $\pm$ 24.0 points using SAQ quality of life, 32.9 $\pm$ 28.3 points using SAQ AF, and 31.2 $\pm$ 26.8 points with the KCCQ SS). This large magnitude of improvement is similar in magnitude to the SAQ scores reported by patients in a highly symptomatic cohort of patients with medically refractory angina undergoing chronic total occlusion PCI in the OPEN-CTO (Outcomes, Patient Health Status, and Efficiency in Chronic Total Occlusion) registry.[23] Second, the large proportion without baseline angina likely reflects that cardiomyopathy and heart failure– frequent indications for revascularization in the OPTIMUM registry–led to dyspnea symptoms rather than to angina in in a significant proportion of the OPTIMUM cohort. Of note, when stratifying the population by baseline angina, large improvements in KCCQ scores were noted even among those with minimal to no baseline angina. Furthermore, when clinically important and moderate-to-large health status benefits were defined by magnitude of improvement on either the SAQ SS or KCCQ SS to account for the health status impact of both angina and dyspnea symptoms, the proportion reporting a clinically significant improvement at 6 months increased to 69.9% and a moderate-to-large benefit to 64.0%. This finding underscores the critical importance of assessing heart failure symptoms in these patients and including instruments to quantify heart failure symptoms when assessing patient-reported symptoms in future studies of prohibitive surgical risk patients with complex CAD. Further studies are needed to identify the predictors of health status improvement after PCI in patients at prohibitive risk for surgery to allow a more informed discussion of anticipated symptom burden, physical function, and quality of life following these procedures.

Completeness of revascularization in the OPTIMUM registry was performed at the discretion of treating clinicians. Prior observational studies of multivessel PCI have suggested improved survival among those undergoing complete revascularization,[24] though no randomized study of complete vs incomplete revascularization exists to inform clinical practice. The current study was not powered to detect a difference in mortality following complete vs incomplete revascularization and reflects the selection of patients for a complete revascularization strategy by treating operators. In total, the findings of this study support continued focus on discussion of the potential health status benefits of PCI among patients with multivessel CAD at prohibitive risk for bypass surgery. We observed robust improvements in mean 6-month health status among patients treated with both complete and incomplete revascularization. Further studies are needed to define the ideal extent of revascularization to inform treatment decisions at the time of PCI for these complex patients with multivessel CAD.

In total, these findings highlight the importance of developing novel risk prediction tools, which also predict patients' health status, derived from a population of patients with complex CAD at prohibitive surgical risk to help inform heart team decision making. Because mortality risk is high but likelihood of dramatic health status improvement is also high, incorporating both outcomes if of key importance. In contrast to younger, "healthier" CAD patients, patients at high surgical risk are often older with advanced comorbidities. For these patients, improving quality of life is often their primary goal of care. Clinical risk factors have been shown to be strongly predictive of poor outcome in a prior analysis of high-risk patients undergoing PCI.[25] Importantly, these clinical risk factors are available at the time of consideration of revascularization strategy, allowing their use to support clinical decision making.[26] Further work is necessary to build and validate a prediction tool that can be used by evaluating heart teams to discuss patients' potential outcomes after these complex procedures. Future analyses of the OPTIMUM registry will also focus on exploring the association between extent of revascularization, procedural approaches, and outcomes as initial steps to future studies to better understand how to care for these complex patients.

STUDY LIMITATIONS. First, the OPTIMUM registry was a prospective, real-world registry and not a randomized clinical trial. Randomization to surgery was not possible given lack of equipoise among the heart team, and comparison with GDMT also introduces practical challenges and bias. Enrollment in the GDMT arm of the study was slow and limited, and it is quite likely that those not offered PCI are incomparable to those selected by clinicians for the treatment with GDMT + PCI. As such, we cannot compare PCI with a GDMT alone, and we limited analyses of the cohort to patients treated with GDMT + PCI. Second, the OPTIMUM registry reflects treatment patterns of clinicians at high-volume centers incorporating heart teams and may not be applicable to all care settings. These results may not generalize to patients treated at less experienced, lower-volume centers. Enrolling centers attempted to ensure consecutive enrollment, though it is not possible to ensure that all patients reviewed by the heart team were considered for enrollment. Furthermore, these results apply to patients referred for heart team evaluation and are not generalizable to patients who are not referred for cardiac surgery and interventional cardiology evaluation following diagnostic coronary angiography. Third, as an observational study of patients treated with guideline-directed GDMT + PCI, the health status changes in follow-up reflect the importance of both interventions. It is not possible to disentangle the impact of GDMT from revascularization in the present study. Fourth, given the limited availability of some health status instruments in other languages, and the difficulty of conducting follow-up health status interviews in other languages, only patients who could speak English were included in the OPTIMUM registry, consistent with prior registries.[27] Finally, we did not mandate collection of cardiac biomarkers, creatinine, and hemoglobin after PCI procedures. Accordingly, the rates of periprocedural myocardial infarction, acute kidney injury, and bleeding may be underestimates. Finally, objective measurements of physical capacity, such as those from exercise stress testing, were not systematically available in follow-up. However, given the significant correlation between SAQ physical limitation scores and exercise duration,[7] the robust improvement in scores within this domain after successful PCI underscores improvement in functional capacity.

CONCLUSIONS

Patients with complex CAD who were deemed prohibitive risk candidates for CABG have complex clinical profiles, have high disease burden, and are at high risk for early mortality. Following treatment with complex PCI, short-term mortality is similar to predicted mortality using surgical risk models, higher than predicted using PCI risk models, and yet lower than the evaluating surgeon's estimates of mortality risk with bypass surgery, supporting the use of risk prediction tools such as the STS and EuroSCORE II scores in heart team discussions of mortality risk. Although these patients report poor health status at baseline, robust improvements in both CAD-specific and heart failure-specific health status were observed 6 months following the treatment with GDMT + PCI. These findings inform decision making and outcomes for a high-risk and largely unstudied patient population and support further efforts to refine risk stratification, inform selection and treatment strategy, and predict improvement in functional capacity and quality of life.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

This work was supported by Boston Scientific Corporation (grant number ISROTH10299). Dr Salisbury has received consulting and advisory board fees from Medtronic; and institutional grant support from Boston Scientific and Abiomed. Dr Grantham has received speaking fees, honoraria, and travel expense reimbursement from Asahi, Boston Scientific, Abbott, and Corindus; consulting fees and advisory board fees from Corindus and Boston Scientific; and

institutional research grants from Boston Scientific and Asahi. Dr Kirtane has received institutional funding to Columbia University and/or the Cardiovascular Research Foundation (including fees paid to Columbia University and/or Cardiovascular Research Foundation for consulting and/or speaking engagements in which Dr Kirtane controlled the content) from Medtronic, Boston Scientific, Abbott Vascular, Abiomed, CSI, Siemens, Philips, ReCor Medical, and Neurotronic; has served as a consultant for Interventional Medical Device Solutions; and has received travel expenses/meals from Medtronic, Boston Scientific, Abbott Vascular, Abiomed, CSI, Siemens, Philips, ReCor Medical, Chiesi, OpSens, Zoll, and Regeneron. Dr Karmpaliotis has received honoraria from Abbott Vascular and Boston Scientific; and owns equity interest in Nanowear, Soundbite, Traverse Vascular, and Saranas. Dr Ali has received institutional research/grant support from Abbott Vascular, Boston Scientific, Philips Volcano, Cardiovascular Systems, Medtronic, ACIST Medical, and Opsens; received personal consulting honoraria from Amgen, AstraZeneca, and Boston Scientific; and owns equity in Shockwave Medical. Dr Kandzari has received institutional research/grant support from Abbott Vascular, Biotronik, Boston Scientific, Cardiovascular Systems, Medtronic, Orbus Neich, and Teleflex; and personal consulting honoraria from Biotronik, Cardiovascular Systems, and Medtronic. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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PERSPECTIVES

WHAT IS KNOWN? A growing number of patients with left main and multivessel CAD are noted to be at prohibitive risk for bypass surgery, but few studies have described these patients, their clinical outcomes, or their symptom burden.

WHAT IS NEW? In a 22-center prospective study, we described the characteristics of patients deemed surgically ineligible and their short-term outcomes after treatment with GDMT + PCI. Patients experienced high mortality with observed 30-day mortality similar to predicted risk using surgical risk scores, were profoundly symptomatic at baseline, and experienced large health status improvement in follow-up.

WHAT IS NEXT? These findings inform decision making a high-risk and largely unstudied patient population and underscore the importance of developing tools to augment decision making by incorporating predictions of health status in follow-up after treatment with GDMT + PCI.

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KEY WORDS coronary artery disease, health status, multivessel coronary disease, patient-reported outcomes, percutaneous coronary intervention, quality of life

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