

## Complete Revascularization with Multivessel PCI for Myocardial Infarction

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### ABSTRACT

#### BACKGROUND

In patients with ST-segment elevation myocardial infarction (STEMI), percutaneous coronary intervention (PCI) of the culprit lesion reduces the risk of cardiovascular death or myocardial infarction. Whether PCI of nonculprit lesions further reduces the risk of such events is unclear.

#### METHODS

We randomly assigned patients with STEMI and multivessel coronary artery disease who had undergone successful culprit-lesion PCI to a strategy of either complete revascularization with PCI of angiographically significant nonculprit lesions or no further revascularization. Randomization was stratified according to the intended timing of nonculprit-lesion PCI (either during or after the index hospitalization). The first coprimary outcome was the composite of cardiovascular death or myocardial infarction; the second coprimary outcome was the composite of cardiovascular death, myocardial infarction, or ischemia-driven revascularization.

#### RESULTS

At a median follow-up of 3 years, the first coprimary outcome had occurred in 158 of the 2016 patients (7.8%) in the complete-revascularization group as compared with 213 of the 2025 patients (10.5%) in the culprit-lesion-only PCI group (hazard ratio, 0.74; 95% confidence interval [CI], 0.60 to 0.91;  $P=0.004$ ). The second coprimary outcome had occurred in 179 patients (8.9%) in the complete-revascularization group as compared with 339 patients (16.7%) in the culprit-lesion-only PCI group (hazard ratio, 0.51; 95% CI, 0.43 to 0.61;  $P<0.001$ ). For both coprimary outcomes, the benefit of complete revascularization was consistently observed regardless of the intended timing of nonculprit-lesion PCI ( $P=0.62$  and  $P=0.27$  for interaction for the first and second coprimary outcomes, respectively).

#### CONCLUSIONS

Among patients with STEMI and multivessel coronary artery disease, complete revascularization was superior to culprit-lesion-only PCI in reducing the risk of cardiovascular death or myocardial infarction, as well as the risk of cardiovascular death, myocardial infarction, or ischemia-driven revascularization. (Funded by the Canadian Institutes of Health Research and others; COMPLETE ClinicalTrials.gov number, NCT01740479.)

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\*A complete list of the COMPLETE trial steering committee members and investigators is provided in the Supplementary Appendix, available at [NEJM.org](http://NEJM.org).

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**P** RIMARY PERCUTANEOUS CORONARY INTERVENTION (PCI) is the preferred method of reperfusion for patients with ST-segment elevation myocardial infarction (STEMI).<sup>1-4</sup> These patients often have multivessel coronary artery disease, with additional angiographically significant lesions in locations separate from that of the culprit lesion that caused the acute event.<sup>5</sup> Whether to routinely revascularize these nonculprit lesions or to manage them conservatively with guideline-based medical therapy alone is a common dilemma.<sup>6-8</sup> Nonculprit lesions, which are usually discovered incidentally at the time of primary PCI, may represent stable coronary artery plaques, for which additional revascularization may not offer additional benefit.<sup>9</sup> However, if nonculprit lesions have morphologic features consistent with unstable plaques, which confer an increased risk of future cardiovascular events, there may be a benefit of routine nonculprit-lesion PCI.<sup>10,11</sup>

Although observational studies have suggested a possible reduction in clinical events with staged nonculprit-lesion PCI,<sup>12,13</sup> these studies are limited by selection bias and confounding. Randomized trials have shown reductions in the risk of composite outcomes with nonculprit-lesion PCI, with results driven predominantly by the decreased risk of subsequent revascularization with that strategy.<sup>14-17</sup> Meta-analyses suggest a reduction in the risk of death from cardiovascular causes or myocardial infarction with nonculprit-lesion PCI,<sup>18-20</sup> but previous individual trials have not had the power to examine this clinically important outcome. The Complete versus Culprit-Only Revascularization Strategies to Treat Multivessel Disease after Early PCI for STEMI (COMPLETE) trial was designed to address this evidence gap.

## METHODS

### TRIAL DESIGN AND OVERSIGHT

The COMPLETE trial was a multinational, randomized trial that evaluated a strategy of complete revascularization (consisting of PCI of all suitable nonculprit lesions) as compared with a strategy of no further revascularization in patients with STEMI and multivessel coronary artery disease who had undergone successful culprit-lesion PCI.<sup>21</sup> The executive committee designed the protocol, which is available with the full text of this article at [NEJM.org](https://www.nejm.org), and was responsible for the conduct and oversight of the trial. The

trial was coordinated and sponsored by the Population Health Research Institute of Hamilton Health Sciences and McMaster University. The trial was funded by the Canadian Institutes of Health Research. AstraZeneca and Boston Scientific provided additional funding. These companies had no role in the trial design; collection, analysis, or interpretation of the data; or writing of the manuscript. The protocol was approved by institutional review boards at all trial centers. The authors vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol.

### ELIGIBILITY

Patients who presented to the hospital with STEMI were considered for inclusion in the trial if they could undergo randomization within 72 hours after successful culprit-lesion PCI. Eligible patients were required to have multivessel coronary artery disease, defined as the presence of at least one angiographically significant non-infarct-related (nonculprit) lesion that was amenable to successful treatment with PCI and was located in a vessel with a diameter of at least 2.5 mm that was not stented as part of the index culprit-lesion PCI. Nonculprit lesions were deemed angiographically significant if they were associated with at least 70% stenosis of the vessel diameter on visual estimation or with 50 to 69% stenosis accompanied by a fractional flow reserve (FFR) measurement of 0.80 or less. The main exclusion criteria were an intention before randomization to revascularize a nonculprit lesion, a planned surgical revascularization, or previous coronary-artery bypass grafting surgery. Details regarding inclusion and exclusion criteria are provided in Table S1 in the Supplementary Appendix, available at [NEJM.org](https://www.nejm.org). Written informed consent was obtained from all the patients.

### RANDOMIZATION AND TRIAL TREATMENTS

Eligible patients were randomly assigned to undergo either complete revascularization or culprit-lesion-only revascularization according to a computer-generated randomization list with the use of randomly permuted blocks and with blinding to trial center. Randomization was stratified according to center and the intended timing of nonculprit-lesion PCI (if the patient were to be assigned to the complete-revascularization group). Randomization was performed as soon as possible (no later than 72 hours) after the index PCI.

Patients who were randomly assigned to the complete-revascularization strategy were to have routine staged PCI (i.e., PCI during a procedure separate from the index PCI procedure for STEMI) of all suitable nonculprit lesions, regardless of whether there were clinical symptoms or there was evidence of ischemia. Investigators specified before randomization whether they intended to perform nonculprit-lesion PCI during the index hospitalization or after hospital discharge (no later than 45 days after randomization). Everolimus-eluting stents were strongly recommended for all PCI procedures. It was recommended that PCI of chronic total occlusions be attempted only by operators who had experience in treating chronic total occlusions and only when there was a high likelihood of successful PCI.

Patients who were randomly assigned to the culprit-lesion-only PCI strategy received guideline-based medical therapy with no further revascularization, regardless of whether there was evidence of ischemia on noninvasive testing. Protocol-specified criteria for crossover to the complete-revascularization strategy are provided in the Supplementary Appendix.

All coronary angiograms obtained during the trial were forwarded to an angiographic core laboratory located at the Population Health Research Institute for detailed assessment.<sup>21</sup> After initial hospital discharge, routine follow-up occurred at 6 weeks, 6 months, 1 year, and yearly thereafter up to the final follow-up visit.

#### RECOMMENDED MEDICAL THERAPY

Guideline-based medical therapy was recommended in both treatment groups. Dual antiplatelet therapy with aspirin and ticagrelor for at least 1 year was recommended.<sup>22</sup> Beyond 1 year, aspirin was recommended for all patients, and ticagrelor (60 mg twice daily) was recommended for patients who were not at high risk for bleeding.<sup>23</sup> High-dose statin therapy, angiotensin-converting-enzyme inhibitors or angiotensin-receptor blockers, mineralocorticoid-receptor antagonists, and beta-blockers were recommended.<sup>21</sup>

#### OUTCOMES

The first coprimary outcome was the composite of death from cardiovascular causes or new myocardial infarction; the second coprimary outcome was the composite of death from cardiovascular causes, new myocardial infarction, or ischemia-driven revascularization. Safety outcomes includ-

ed major bleeding and contrast-associated acute kidney injury. Secondary outcomes are described in the Supplementary Appendix; detailed definitions of all outcomes are provided in Table S2 in the Supplementary Appendix. Myocardial infarction was defined according to the third universal definition and was subclassified according to type.<sup>24</sup> An event-adjudication committee, which consisted of clinicians who were unaware of the treatment assignments, adjudicated primary, secondary, and safety outcome events.

#### STATISTICAL ANALYSIS

We estimated that a sample of 4000 patients would give the trial 80% power to detect a 22% lower risk of the composite of cardiovascular death or myocardial infarction in the complete-revascularization group than in the culprit-lesion-only PCI group, assuming an event rate of 5% per year in the culprit-lesion-only PCI group. To preserve the overall type I error rate of 5% for the testing of both coprimary outcomes, the first coprimary outcome was tested at a P value of 0.045 and the second at a P value of 0.0119.<sup>21</sup> One interim analysis was performed. Because a very conservative monitoring boundary was used for this analysis, no adjustment of the type I error threshold was applied. Details regarding these analyses are provided in the Supplementary Appendix.

All patients who underwent randomization were included in the analysis according to the treatment group to which they were assigned, regardless of the treatment they actually received (intention-to-treat principle). The coprimary outcomes were analyzed with the use of a time-to-first-event approach. Estimates of the hazard ratios and 95% confidence intervals were calculated with the use of Cox proportional-hazards models, with treatment group as an independent variable and with stratification according to the intended timing of nonculprit-lesion PCI. Confidence intervals for secondary and exploratory efficacy outcomes have not been adjusted for multiple comparisons, and therefore inferences drawn from these intervals may not be reproducible. The two treatment groups were compared with the use of the stratified log-rank test. Cumulative incidence was estimated with the Kaplan-Meier method. A sensitivity analysis was performed with a Fine-Gray model to account for the competing risk of death from noncardiovascular causes.<sup>25</sup>

**Table 1. Characteristics of the Patients at Baseline.\***

| Characteristic  | Complete Revascularization (N=2016) | Culprit-Lesion-Only PCI (N=2025) |
|---|-------------------------------------|----------------------------------|
| Age — yr  | 61.6±10.7                           | 62.4±10.7                        |
| Male sex — no. (%)  | 1623 (80.5)                         | 1602 (79.1)                      |
| Diabetes — no. (%)  | 385 (19.1)                          | 402 (19.9)                       |
| Chronic renal insufficiency — no./total no. (%)                         | 37/1884 (2.0)                       | 44/1903 (2.3)                    |
| Previous myocardial infarction — no. (%)                                | 148 (7.3)                           | 154 (7.6)                        |
| Current smoker — no. (%)  | 819 (40.6)                          | 787 (38.9)                       |
| Hypertension — no. (%)  | 982 (48.7)                          | 1027 (50.7)                      |
| Dyslipidemia — no. (%)  | 764 (37.9)                          | 797 (39.4)                       |
| Previous PCI — no. (%)  | 142 (7.0)                           | 141 (7.0)                        |
| Previous stroke — no. (%)   | 64 (3.2)                            | 62 (3.1)                         |
| Time from symptom onset to index PCI — no./total no. (%)                |                                     |                                  |
| <6 hr   | 1383/1994 (69.4)                    | 1341/2000 (67.0)                 |
| 6 to 12 hr  | 322/1994 (16.1)                     | 354/2000 (17.7)                  |
| >12 hr  | 289/1994 (14.5)                     | 305/2000 (15.2)                  |
| Killip class ≥II — no./total no. (%)                                    | 212/1995 (10.6)                     | 218/1996 (10.9)                  |
| Glycated hemoglobin — %   | 6.3±1.6                             | 6.3±1.6                          |
| Low-density lipoprotein cholesterol — mmol/liter                        | 3.1±1.2                             | 3.1±1.2                          |
| Peak creatinine — μmol/liter  | 84.7±30.8                           | 85.2±26.8                        |
| Medications at discharge — no. (%)                                      |                                     |                                  |
| Aspirin   | 2011 (99.8)                         | 2015 (99.5)                      |
| P2Y <sub>12</sub> inhibitor   |                                     |                                  |
| Any   | 2003 (99.4)                         | 2018 (99.7)                      |
| Ticagrelor  | 1298 (64.4)                         | 1281 (63.3)                      |
| Prasugrel   | 193 (9.6)                           | 169 (8.3)                        |
| Clopidogrel   | 516 (25.6)                          | 572 (28.2)                       |
| Beta-blocker  | 1776 (88.1)                         | 1804 (89.1)                      |
| Angiotensin-converting-enzyme inhibitor or angiotensin-receptor blocker | 1723 (85.5)                         | 1714 (84.6)                      |
| Statin  | 1980 (98.2)                         | 1968 (97.2)                      |

\* Plus–minus values are means ±SD. To convert the values for low-density lipoprotein cholesterol to milligrams per deciliter, divide by 0.02586. To convert the values for creatinine to milligrams per deciliter, divide by 88.4. PCI denotes percutaneous coronary intervention.

## RESULTS

### PATIENTS, TREATMENT, AND FOLLOW-UP

From February 1, 2013, through March 6, 2017, a total of 4041 patients from 140 centers in 31 countries underwent randomization: 2016 were assigned to the complete-revascularization group and 2025 to the culprit-lesion-only PCI group. Baseline and procedural characteristics are shown in Tables 1 and 2, respectively. Details are pro-

vided in Table S3 and Figure S1 in the Supplementary Appendix.

Among the patients who underwent complete revascularization, the median time from randomization to nonculprit-lesion PCI was 1 day (interquartile range, 1 to 3) among the 1285 patients for whom the intended timing of nonculprit-lesion PCI was during the index hospitalization and 23 days (interquartile range, 12.5 to 33.5) among the 596 patients for whom the in-

**Table 2. Procedural Characteristics.\***

| Characteristic  | Complete Revascularization (N=2016) | Culprit-Lesion-Only PCI (N=2025) |
|---|-------------------------------------|----------------------------------|
| Index procedure for STEMI — no. (%)   |                                     |                                  |
| Primary PCI   | 1853 (91.9)                         | 1885 (93.1)                      |
| Pharmacoinvasive PCI  | 64 (3.2)                            | 61 (3.0)                         |
| Rescue PCI  | 99 (4.9)                            | 79 (3.9)                         |
| Radial access — no. (%)   |                                     |                                  |
|   | 1629 (80.8)                         | 1634 (80.7)                      |
| Thrombus aspiration — no./total no. (%)   |                                     |                                  |
|   | 451/1864 (24.2)                     | 481/1875 (25.7)                  |
| SYNTAX score†‡  |                                     |                                  |
| Culprit lesion-specific score   | 8.8±5.3                             | 8.6±5.3                          |
| Nonculprit lesion-specific score  | 4.6±2.8                             | 4.6±2.7                          |
| Baseline score, including culprit lesion  | 16.3±6.8                            | 16.0±6.6                         |
| Residual score, after index PCI   | 7.2±4.9                             | 7.0±4.7                          |
| Location of culprit lesion — no./total no. (%)†                                       |                                     |                                  |
| Left main coronary artery   | 3/1918 (0.2)                        | 4/1940 (0.2)                     |
| Left anterior descending artery   | 660/1918 (34.4)                     | 657/1940 (33.9)                  |
| Circumflex artery   | 346/1918 (18.0)                     | 307/1940 (15.8)                  |
| Right coronary artery   | 909/1918 (47.4)                     | 972/1940 (50.1)                  |
| No. of residual diseased vessels — no./total no. (%)†                                 |                                     |                                  |
| 1   | 1458/1917 (76.1)                    | 1492/1934 (77.1)                 |
| ≥2  | 459/1917 (23.9)                     | 442/1934 (22.9)                  |
| Location of nonculprit lesions — no./total no. of lesions (%)†                        |                                     |                                  |
| Left main coronary artery   | 10/2731 (0.4)                       | 3/2624 (0.1)                     |
| Left anterior descending artery   | 1037/2731 (38.0)                    | 1080/2624 (41.2)                 |
| Proximal  | 267/2731 (9.8)                      | 274/2624 (10.4)                  |
| Middle  | 592/2731 (21.7)                     | 621/2624 (23.7)                  |
| Circumflex artery   | 993/2731 (36.4)                     | 933/2624 (35.6)                  |
| Proximal left circumflex artery, obtuse marginal branch, and ramus intermedius artery | 744/2731 (27.2)                     | 697/2624 (26.6)                  |
| Distal left circumflex artery and posterior left ventricular branch                   | 249/2731 (9.1)                      | 236/2624 (9.0)                   |
| Right coronary artery   | 691/2731 (25.3)                     | 608/2624 (23.2)                  |
| Diameter of vessel with nonculprit lesion — mm†                                       |                                     |                                  |
|   | 2.8±0.5                             | 2.9±0.6                          |
| Nonculprit-lesion stenosis on visual estimation                                       |                                     |                                  |
| %   | 79.3±8.1                            | 78.7±7.9                         |
| No./total no. of lesions (%)  |                                     |                                  |
| 50–69%, with fractional flow reserve <0.80  | 21/2612 (0.8)                       | 16/2576 (0.6)                    |
| 70–79%  | 1078/2612 (41.3)                    | 1162/2576 (45.1)                 |
| 80–89%  | 875/2612 (33.5)                     | 839/2576 (32.6)                  |
| 90–99%  | 583/2612 (22.3)                     | 508/2576 (19.7)                  |
| 100%  | 55/2612 (2.1)                       | 51/2576 (2.0)                    |

\* Plus-minus values are means ±SD. Percentages may not total 100 because of rounding. STEMI denotes ST-segment elevation myocardial infarction.

† Data were obtained at the angiographic core laboratory.

‡ The SYNTAX (Synergy between PCI with Taxus and Cardiac Surgery) score is used to describe the degree of angiographic complexity; a score of 0 indicates no angiographically significant disease, and higher scores indicate more extensive and complex coronary artery disease.

tended timing of nonculprit-lesion PCI was after hospital discharge. Within the first 45 days, crossover from the culprit-lesion-only PCI group to the complete-revascularization group occurred in 96 patients (4.7%), and crossover from the complete-revascularization group to the culprit-lesion-only PCI group occurred in 78 patients (3.9%). After nonculprit-lesion PCI, 90.1% of the patients in the complete-revascularization group had a SYNTAX (Synergy between PCI with Taxus and Cardiac Surgery) score of 0, indicating no angiographically significant disease (i.e., complete revascularization).

Outcome events were assessed up to the date of each patient's final follow-up visit, which ranged from September 1, 2018, to June 7, 2019, when the database was locked. The mean follow-up time was 36.2 months, and the median follow-up time was 35.8 months (interquartile range, 27.6 to 44.3). Data on vital status were complete for 99.1% and 99.3% of the patients in the complete-revascularization and culprit-lesion-only PCI groups, respectively. Data on concomitant medication use at hospital discharge and throughout follow-up are provided in Table S4 in the Supplementary Appendix.

#### PRIMARY AND SECONDARY OUTCOMES

At a median follow-up of 3 years, death from cardiovascular causes or new myocardial infarction (the first coprimary composite outcome) had occurred in 158 patients (7.8%) in the complete-revascularization group as compared with 213 patients (10.5%) in the culprit-lesion-only PCI group (hazard ratio, 0.74; 95% confidence interval [CI], 0.60 to 0.91;  $P=0.004$ ) (Table 3 and Fig. 1A). This result was driven by the lower incidence of new myocardial infarction in the complete-revascularization group than in the culprit-lesion-only PCI group (5.4% vs. 7.9%; hazard ratio, 0.68; 95% CI, 0.53 to 0.86); the incidence of death from cardiovascular causes was 2.9% and 3.2%, respectively (hazard ratio, 0.93; 95% CI, 0.65 to 1.32). Specifically, the following types of myocardial infarction occurred less frequently in the complete-revascularization group than in the culprit-lesion-only PCI group: non-STEMI (66 events vs. 105 events), new STEMI (43 vs. 53), and predominantly, myocardial infarction type 1 (63 vs. 128) (Table S5 in the Supplementary Appendix).

Death from cardiovascular causes, new myocardial infarction, or ischemia-driven revascular-

ization (the second coprimary composite outcome) occurred in 179 patients (8.9%) in the complete-revascularization group as compared with 339 patients (16.7%) in the culprit-lesion-only PCI group (hazard ratio, 0.51; 95% CI, 0.43 to 0.61;  $P<0.001$ ) (Table 3 and Fig. 1B). The results of competing-risk analyses with respect to the two coprimary outcomes were consistent with the results of the primary analyses (Table S6 in the Supplementary Appendix).

Death from cardiovascular causes, new myocardial infarction, ischemia-driven revascularization, unstable angina, or New York Heart Association class IV heart failure (the key secondary outcome) occurred in 272 patients (13.5%) in the complete-revascularization group as compared with 426 patients (21.0%) in the culprit-lesion-only PCI group (hazard ratio, 0.62; 95% CI, 0.53 to 0.72). Results for other secondary outcomes are shown in Table 3.

#### SUBGROUP ANALYSES AND TIMING OF NONCULPRIT-LESION PCI

For the coprimary outcomes, there was no differential treatment effect in prespecified subgroups (Fig. 2). The benefit of complete revascularization was consistently observed among patients for whom the intended timing of nonculprit-lesion PCI was during the index hospitalization and those for whom the intended timing was after hospital discharge ( $P=0.62$  and  $P=0.27$  for interaction for the first and second coprimary outcomes, respectively). In 87.1% of the patients in the complete-revascularization group, the actual timing of nonculprit-lesion PCI corresponded to the intended timing specified by the investigator before randomization. The hazard ratio for the first coprimary outcome with a complete-revascularization strategy as compared with a culprit-lesion-only PCI strategy was 0.77 (95% CI, 0.59 to 1.00) in the subgroup for which in-hospital nonculprit-lesion PCI was intended and 0.69 (95% CI, 0.49 to 0.97) in the subgroup for which postdischarge nonculprit-lesion PCI was intended.

#### SAFETY AND OTHER OUTCOMES

There was no significant difference between the two treatment groups in the risk of major bleeding, stroke, or stent thrombosis (Table 3). Results for specific types of stent thrombosis are shown in Table S7 in the Supplementary Appendix. Contrast-associated acute kidney injury oc-

**Table 3. Efficacy and Safety Outcomes.\***

| Outcome   | Complete Revascularization (N=2016) |                 | Culprit-Lesion-Only PCI (N=2025) |                 | Hazard Ratio (95% CI) | P Value |
|---|-------------------------------------|-----------------|----------------------------------|-----------------|-----------------------|---------|
|   | no. (%)                             | % per person-yr | no. (%)                          | % per person-yr |                       |         |
| <b>Coprimary outcomes</b>   |                                     |                 |                                  |                 |                       |         |
| Cardiovascular death or myocardial infarction   | 158 (7.8)                           | 2.7             | 213 (10.5)                       | 3.7             | 0.74 (0.60–0.91)      | 0.004   |
| Cardiovascular death, myocardial infarction, or ischemia-driven revascularization   | 179 (8.9)                           | 3.1             | 339 (16.7)                       | 6.2             | 0.51 (0.43–0.61)      | <0.001  |
| <b>Key secondary outcome</b>  |                                     |                 |                                  |                 |                       |         |
| Cardiovascular death, myocardial infarction, ischemia-driven revascularization, unstable angina, or NYHA class IV heart failure | 272 (13.5)                          | 4.9             | 426 (21.0)                       | 8.1             | 0.62 (0.53–0.72)      |         |
| <b>Other secondary outcomes</b>   |                                     |                 |                                  |                 |                       |         |
| Myocardial infarction   | 109 (5.4)                           | 1.9             | 160 (7.9)                        | 2.8             | 0.68 (0.53–0.86)      |         |
| Ischemia-driven revascularization   | 29 (1.4)                            | 0.5             | 160 (7.9)                        | 2.8             | 0.18 (0.12–0.26)      |         |
| Unstable angina   | 70 (3.5)                            | 1.2             | 130 (6.4)                        | 2.2             | 0.53 (0.40–0.71)      |         |
| Death from cardiovascular causes  | 59 (2.9)                            | 1.0             | 64 (3.2)                         | 1.0             | 0.93 (0.65–1.32)      |         |
| Death from any cause  | 96 (4.8)                            | 1.6             | 106 (5.2)                        | 1.7             | 0.91 (0.69–1.20)      |         |
| <b>Other outcomes</b>   |                                     |                 |                                  |                 |                       |         |
| Stroke  | 38 (1.9)                            | 0.6             | 29 (1.4)                         | 0.5             | 1.31 (0.81–2.13)      |         |
| NYHA class IV heart failure   | 58 (2.9)                            | 1.0             | 56 (2.8)                         | 0.9             | 1.04 (0.72–1.50)      |         |
| Stent thrombosis  | 26 (1.3)                            | 0.4             | 19 (0.9)                         | 0.3             | 1.38 (0.76–2.49)      |         |
| <b>Safety outcomes</b>  |                                     |                 |                                  |                 |                       |         |
| Major bleeding  | 58 (2.9)                            | 1.0             | 44 (2.2)                         | 0.7             | 1.33 (0.90–1.97)      | 0.15    |
| Contrast-associated acute kidney injury†  | 30 (1.5)                            | —               | 19 (0.9)                         | —               | 1.59 (0.89–2.84)      | 0.11    |

\* P values were calculated with the use of the stratified log-rank test. Confidence intervals for secondary and exploratory efficacy outcomes have not been adjusted for multiple comparisons, and therefore inferences drawn from these intervals may not be reproducible. NYHA denotes New York Heart Association.

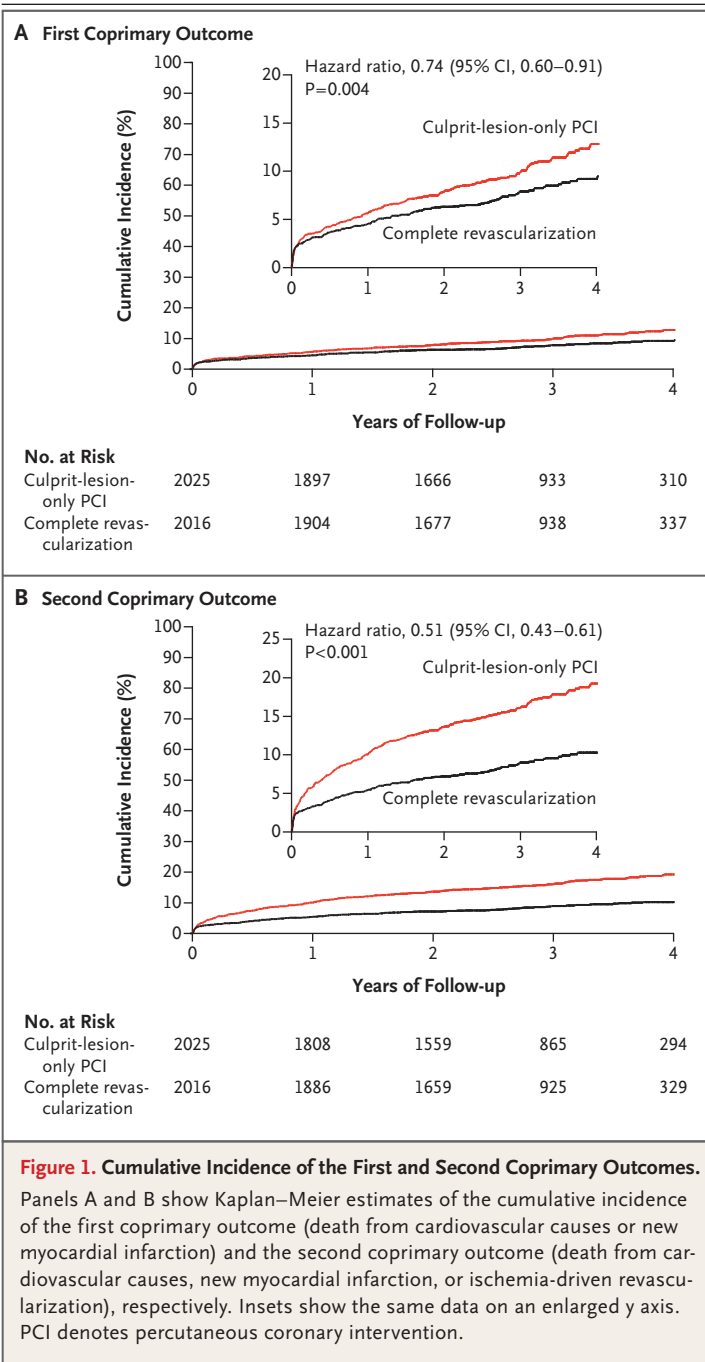
† Contrast-associated acute kidney injury was treated as a binary outcome. Shown are an odds ratio (instead of a hazard ratio), 95% confidence interval, and P value that were calculated with stratified logistic regression.

occurred in 30 patients in the complete-revascularization group as compared with 19 patients in the culprit-lesion-only PCI group (odds ratio, 1.59; 95% CI, 0.89 to 2.84; P=0.11). This event was attributed to the nonculprit-lesion PCI procedure in 7 patients in the complete-revascularization group as compared with none (in accordance with the protocol) in the culprit-lesion-only PCI group. For those 7 patients, the intended timing of nonculprit-lesion PCI was during the index hospitalization.

## DISCUSSION

The COMPLETE trial showed that, among patients with STEMI and multivessel coronary artery disease, a strategy of staged nonculprit-lesion PCI

with the goal of complete revascularization resulted in a 26% lower risk of a composite of death from cardiovascular causes or new myocardial infarction at a median follow-up of 3 years than did a strategy of culprit-lesion-only PCI. This benefit was driven by the 32% lower risk of new, nonfatal myocardial infarction in the complete-revascularization group than in the culprit-lesion-only PCI group; the incidence of death from cardiovascular causes was similar in the two groups. For the second coprimary outcome, which included ischemia-driven revascularization in addition to the other two events, the risk with a complete-revascularization strategy was approximately half the risk with a culprit-lesion-only PCI strategy. There was no significant difference between the two groups in the risk of



**Figure 2 (facing page). Subgroup Analyses of the First and Second Coprimary Outcomes.**

P values for interaction have not been adjusted for multiple comparisons. The SYNTAX (Synergy between PCI with Taxus and Cardiac Surgery) score is used to describe the degree of angiographic complexity; a score of 0 indicates no angiographically significant disease, and higher scores indicate more extensive and complex coronary artery disease.

larization strategy would lead to a meaningful reduction in the risk of the clinically important outcome of cardiovascular death or new myocardial infarction. Previous trials that evaluated a complete-revascularization strategy in patients with STEMI were smaller and included revascularization as part of the composite primary outcome.<sup>14-17</sup> In the absence of a reduction in irreversible events such as cardiovascular death or new myocardial infarction, the clinical relevance of performing early nonculprit-lesion PCI in all patients with multivessel coronary artery disease to prevent later PCI in a smaller number of those patients is debatable. We have now found that routine nonculprit-lesion PCI with the goal of complete revascularization confers a reduction in the long-term risk of cardiovascular death or myocardial infarction. Over a period of 3 years, the number needed to treat to prevent cardiovascular death or myocardial infarction from occurring in 1 patient is 37 patients, and the number needed to treat to prevent cardiovascular death, myocardial infarction, or ischemia-driven revascularization from occurring in 1 patient is 13 patients.

At least 70% stenosis in coronary arteries on visual estimation is routinely reported to be a standard criterion used in coronary angiography to establish the presence of angiographically significant coronary artery disease. Evidence of ischemia in the form of an FFR measurement of 0.80 or less was required only in patients with moderate stenosis (50 to 69%), and only a small number of such patients were enrolled in the trial. Although it is possible that an FFR-based approach to guide nonculprit-lesion PCI could have reduced the number of PCI procedures among the patients included in the complete-revascularization group, it is unclear how this strategy might have influenced the effect on hard clinical outcomes. It is possible that angiographically significant lesions associated with an FFR measurement

major bleeding or stroke. The benefit of complete revascularization was consistently observed regardless of whether nonculprit-lesion PCI was to be performed during the index hospitalization or several weeks after discharge from the hospital.

We designed the trial to have sufficient power to determine whether a complete-revascu-



| Subgroup  | First Coprimary Outcome  |   |                       |                         | Second Coprimary Outcome   |   |                       |                         |
|---|--|---|-----------------------|-------------------------|--|---|-----------------------|-------------------------|
|   | Complete revascularization no. of events/total no. of patients (% per person-yr) | Culprit-lesion-only PCI no. of events/total no. of patients (% per person-yr) | Hazard ratio (95% CI) | P value for interaction | Complete revascularization no. of events/total no. of patients (% per person-yr) | Culprit-lesion-only PCI no. of events/total no. of patients (% per person-yr) | Hazard ratio (95% CI) | P value for interaction |
| Overall   | 158/2016 (2.7)   | 213/2025 (3.7)  | 0.74 (0.60–0.91)      | 0.62                    | 179/2016 (3.1)   | 339/2025 (6.2)  | 0.51 (0.43–0.61)      | 0.27                    |
| Intended timing of nonculprit-lesion PCI  |  |   |                       |                         |  |   |                       |                         |
| During index hospitalization  | 101/1353 (2.7)   | 130/1349 (3.5)  | 0.77 (0.59–1.00)      | 0.62                    | 113/1353 (3.0)   | 227/1349 (6.6)  | 0.47 (0.38–0.59)      | 0.27                    |
| After hospital discharge  | 57/663 (2.7)   | 83/676 (3.9)  | 0.69 (0.49–0.97)      | 0.2                     | 66/663 (3.1)   | 112/676 (5.4)   | 0.59 (0.43–0.79)      | 0.82                    |
| Nonculprit lesion involving proximal or middle left anterior descending artery                |  |   |                       |                         |  |   |                       |                         |
| Presence  | 64/820 (2.7)   | 78/849 (3.1)  | 0.86 (0.62–1.20)      | 0.03                    | 71/820 (3.0)   | 141/849 (6.0)   | 0.50 (0.38–0.67)      | 0.01                    |
| Absence   | 87/1097 (2.7)  | 129/1085 (4.2)  | 0.65 (0.49–0.85)      | 0.32                    | 97/1097 (3.0)  | 190/1085 (6.5)  | 0.48 (0.38–0.61)      | 0.98                    |
| Nonculprit lesion with stenosis of ≥80% on visual estimation or ≥60% on laboratory assessment |  |   |                       |                         |  |   |                       |                         |
| Presence  | 127/1668 (2.6)   | 183/1631 (3.9)  | 0.67 (0.53–0.84)      | 0.08                    | 143/1668 (3.0)   | 291/1631 (6.6)  | 0.46 (0.37–0.56)      | 0.37                    |
| Absence   | 31/346 (3.2)   | 29/392 (2.6)  | 1.23 (0.74–2.04)      | 0.74                    | 36/346 (3.8)   | 47/392 (4.4)  | 0.87 (0.56–1.34)      | 0.92                    |
| Residual SYNTAX score   |  |   |                       |                         |  |   |                       |                         |
| ≤6, lower than median score   | 60/885 (2.3)   | 90/870 (3.6)  | 0.65 (0.47–0.90)      | 0.13                    | 69/885 (2.7)   | 133/870 (5.5)   | 0.49 (0.37–0.66)      | 0.27                    |
| >6, median score or higher  | 91/1033 (3.0)  | 117/1070 (3.8)  | 0.80 (0.61–1.05)      | 0.35                    | 99/1033 (3.3)  | 198/1070 (6.9)  | 0.49 (0.39–0.63)      | 0.68                    |
| Sex   |  |   |                       |                         |  |   |                       |                         |
| Male  | 118/1623 (2.5)   | 171/1602 (3.7)  | 0.67 (0.53–0.85)      | 0.18                    | 136/1623 (2.9)   | 274/1602 (6.3)  | 0.47 (0.38–0.57)      | 0.07                    |
| Female  | 40/393 (3.6)   | 42/423 (3.5)  | 1.05 (0.68–1.61)      | 0.68                    | 43/393 (3.9)   | 65/423 (5.7)  | 0.70 (0.48–1.03)      | 0.78                    |
| Age   |  |   |                       |                         |  |   |                       |                         |
| <65 yr  | 82/1233 (2.2)  | 109/1195 (3.1)  | 0.72 (0.54–0.96)      | 0.23                    | 97/1233 (2.7)  | 189/1195 (5.7)  | 0.48 (0.37–0.61)      | 0.79                    |
| ≥65 yr  | 76/783 (3.5)   | 104/830 (4.5)   | 0.77 (0.58–1.04)      | 0.62                    | 82/783 (3.8)   | 150/830 (6.8)   | 0.56 (0.43–0.74)      | 0.07                    |
| Left ventricular ejection fraction  |  |   |                       |                         |  |   |                       |                         |
| <45%  | 33/396 (2.7)   | 65/398 (5.6)  | 0.49 (0.32–0.74)      | 0.13                    | 38/396 (3.2)   | 84/398 (7.7)  | 0.42 (0.29–0.62)      | 0.27                    |
| ≥45%  | 62/945 (2.2)   | 82/929 (3.0)  | 0.74 (0.53–1.03)      | 0.35                    | 69/945 (2.5)   | 151/929 (5.9)   | 0.43 (0.32–0.57)      | 0.68                    |
| Diabetes  |  |   |                       |                         |  |   |                       |                         |
| Yes   | 46/385 (4.4)   | 57/402 (5.0)  | 0.87 (0.59–1.29)      | 0.62                    | 49/385 (4.8)   | 84/402 (7.9)  | 0.61 (0.43–0.87)      | 0.07                    |
| No  | 112/1631 (2.3)   | 156/1623 (3.3)  | 0.70 (0.55–0.89)      | 0.68                    | 130/1631 (2.7)   | 255/1623 (5.7)  | 0.48 (0.39–0.60)      | 0.78                    |
| Type of P2Y <sub>12</sub> inhibitor   |  |   |                       |                         |  |   |                       |                         |
| Ticagrelor  | 90/1298 (2.3)  | 125/1281 (3.3)  | 0.70 (0.54–0.92)      | 0.18                    | 99/1298 (2.6)  | 196/1281 (5.5)  | 0.48 (0.38–0.61)      | 0.07                    |
| Prasugrel   | 13/192 (2.6)   | 11/169 (2.4)  | 1.07 (0.48–2.39)      | 0.68                    | 18/192 (3.7)   | 25/169 (5.9)  | 0.63 (0.34–1.15)      | 0.79                    |
| Clopidogrel   | 53/513 (3.6)   | 76/568 (4.8)  | 0.75 (0.53–1.07)      | 0.23                    | 60/513 (4.1)   | 117/568 (7.9)   | 0.53 (0.39–0.73)      | 0.07                    |
| Type of PCI   |  |   |                       |                         |  |   |                       |                         |
| Primary PCI   | 148/1853 (2.7)   | 195/1885 (3.6)  | 0.77 (0.62–0.95)      | 0.68                    | 168/1853 (3.2)   | 309/1885 (6.0)  | 0.53 (0.44–0.64)      | 0.78                    |
| Pharmacoinvasive or rescue PCI  | 10/163 (2.1)   | 18/140 (4.7)  | 0.45 (0.21–0.97)      | 0.23                    | 11/163 (2.3)   | 30/140 (8.5)  | 0.28 (0.14–0.56)      | 0.79                    |
| Killip class  |  |   |                       |                         |  |   |                       |                         |
| I   | 140/1855 (2.6)   | 186/1861 (3.5)  | 0.75 (0.60–0.93)      | 0.68                    | 160/1855 (3.0)   | 302/1861 (6.0)  | 0.51 (0.42–0.62)      | 0.79                    |
| ≥II   | 16/141 (4.0)   | 23/136 (6.3)  | 0.65 (0.34–1.23)      | 0.23                    | 17/141 (4.3)   | 32/136 (9.4)  | 0.47 (0.26–0.84)      | 0.79                    |
| Type of stent   |  |   |                       |                         |  |   |                       |                         |
| Polymer-free or biodegradable-polymer drug-eluting stent                                      | 8/136 (2.4)  | 14/145 (3.8)  | 0.62 (0.26–1.49)      | 0.68                    | 10/136 (3.1)   | 21/145 (6.0)  | 0.50 (0.24–1.06)      | 0.79                    |
| Durable-polymer drug-eluting stent  | 120/1568 (2.6)   | 146/1562 (3.2)  | 0.81 (0.64–1.03)      | 0.68                    | 132/1568 (2.9)   | 241/1562 (5.6)  | 0.52 (0.42–0.65)      | 0.79                    |
| Bare-metal stent  | 24/276 (2.7)   | 45/272 (5.5)  | 0.51 (0.31–0.84)      | 0.68                    | 31/276 (3.6)   | 65/272 (8.4)  | 0.44 (0.29–0.68)      | 0.79                    |

of more than 0.80 may still contain morphologic features consistent with unstable plaques, which confer an increased risk of recurrent events. At least two trials involving patients with STEMI and multivessel coronary artery disease that evaluated an FFR-based approach to guide nonculprit-lesion PCI did not show a reduction in the risk of cardiovascular death or myocardial infarction, although neither trial was powered for this outcome.<sup>16,17</sup>

In the COMPLETE trial, randomization was stratified according to the intended timing of nonculprit-lesion PCI. Investigators had to specify before randomization whether they intended to perform nonculprit-lesion PCI during the index hospitalization or after hospital discharge (within 45 days) if the patient were to be assigned to the complete-revascularization group. We found a consistent benefit of complete revascularization regardless of whether nonculprit-lesion PCI was performed earlier, during the index hospitalization, or later, several weeks after discharge. During the early period after STEMI, events related to the index infarction and culprit-lesion PCI probably accounted for a substantial proportion of the events that occurred in both treatment groups. The benefit of complete revascularization seems to have emerged over the long term, with continued divergence of the Kaplan-Meier curves for several years.

Limitations of our trial should be considered. We did not evaluate nonculprit-lesion PCI that was performed during the same procedure as that for the index culprit-lesion PCI for STEMI. Although cardiogenic shock was not an exclusion criterion, no patients with cardiogenic shock were enrolled in the trial and the results should not be extrapolated to such patients. Complete revascularization was attained in more than 90% of the patients in the complete-revascularization group, and crossover to the nonculprit-lesion PCI strategy occurred in only 4.7% of the patients in the culprit-lesion-only PCI group. It is unclear whether the trial results would have been similar if complete revascularization had been observed in fewer patients or if the crossover criteria in the culprit-lesion-only PCI group had been more liberal.

In conclusion, the COMPLETE trial showed that, among patients with STEMI and multivessel coronary artery disease, a strategy of routine

nonculprit-lesion PCI with the goal of complete revascularization, performed either during the index hospitalization or soon after discharge, was superior to a strategy of culprit-lesion-only PCI in reducing the risk of death from cardiovascular causes or new myocardial infarction, as well as the risk of death from cardiovascular causes, new myocardial infarction, or ischemia-driven revascularization, at a median follow-up of 3 years.

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## APPENDIX

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