Design and rationale of the COMPLETE trial: A randomized, comparative effectiveness study of complete versus culprit-only percutaneous coronary intervention to treat multivessel coronary artery disease in patients presenting with ST-segment elevation myocardial infarction

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Introduction A significant proportion of patients with ST-segment elevation myocardial infarction (STEMI) have multivessel coronary artery disease (CAD). Following successful culprit lesion percutaneous coronary intervention (PCI) for STEMI, the question of whether to routinely revascularize non-culprit lesions or manage them conservatively with optimal medical therapy (OMT) alone is a common dilemma facing clinicians.

Methods COMPLETE is a prospective, randomized, international, multicenter, parallel group, open-label trial with blinded evaluation of outcomes. Following successful PCI (contemporary drug eluting stents recommended) of the culprit lesion for STEMI, a total of 4041 patients from 140 centers in 31 countries were randomized to receive either complete revascularization, consisting of staged PCI of all suitable non-culprit lesions plus optimal medical therapy (OMT), or to culprit lesion-only PCI, consisting of OMT alone. OMT comprises evidence-based therapy for STEMI, including and dual antiplatelet therapy with ticagrelor, HTN and lipid management. All coronary angiograms in the trial are being evaluated in a central angiographic core lab to assess quality and completeness of revascularization. The co-primary outcomes are (1): the composite of CV death or new non-fatal MI and (2 the composite of CV death, new non-fatal MI or ischemia-driven revascularization at a median follow-up of 3 years.

Conclusions The COMPLETE trial is an international multicenter randomized trial that will help determine whether complete revascularization involving staged PCI of non-culprit lesions improves outcomes in patients with STEMI and multivessel CAD. (clinicaltrials.gov NCT01740479). (Am Heart J 2019;215:157-66.)

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Approximately one-third to one-half of patients presenting with ST-segment elevation myocardial infarction (STEMI) have multivessel coronary artery disease (CAD), defined as a significant stenosis in 1 or more major non-culprit vessels, in addition to the vessel containing the culprit lesion.[1] Whether to routinely revascularize non-culprit lesions or to manage them conservatively with optimal medical therapy (OMT) alone is a common dilemma.[2-4]

Observational studies have suggested a reduction in long-term mortality with non-culprit lesion percutaneous coronary intervention (PCI),[5,6] however they are limited by selection bias and residual confounding. Nine randomized trials have compared routine non-culprit lesion PCI with OMT alone in patients with multivessel disease

undergoing primary PCI for STEMI.[7-15] In the 4 largest trials,[7-10] with systematic non-culprit lesion PCI, there was a lower rate of revascularization and/or refractory angina, regardless of whether non-culprit lesion PCI was performed during the same procedure for the index STEMI [7,8] or as a staged procedure, [9] and whether or not fractional flow reserve (FFR) was used to identify non-culprit lesions suitable for PCI.[10] However, none of the trials were adequately powered to detect even moderate reductions in the harder outcome of cardiovascular (CV) death or non-fatal MI.[16] A recent meta-analysis of these 9 trials involving 2633 people suggested (with wide confidence intervals), a possible benefit of routine non-culprit lesion PCI for death or non-fatal coronary events.[17] On the other hand, a recent trial in patients with STEMI and multivessel disease presenting with cardiogenic shock demonstrated that the primary outcome of death or renal-replacement therapy was less frequent in the culprit-lesion-only group compared with the multivessel PCI group (45.9% vs 55.4% relative risk, 0.83, $P = .01$) as was death alone (RR 0.84; $P = .03$).[18] It remains unclear whether routine non-culprit lesion PCI is of benefit in patients with STEMI who have multivessel CAD.[19,20] Further, if revascularization is considered, there is conflicting data from prior trials on the optimal timing of non-culprit lesion revascularization.[21,22]

The COMPLETE trial (clinicaltrials.gov NCT01740479) was designed to address this evidence gap. It randomized patients with multivessel disease presenting with STEMI, who have had successful PCI (with a current generation drug-eluting stent) of the culprit lesion, to either staged PCI of all feasible non-culprit lesions in addition to OMT or to OMT alone. OMT includes the use of dual antiplatelet therapy with aspirin and ticagrelor in a high proportion of patients.[23,24] Randomization was stratified according to the timing of intended non-culprit lesion PCI.

Methods

Design and oversight

COMPLETE is a prospective, randomized, international, multicenter, parallel group, open-label trial with blinded evaluation of outcomes. A total of 4041 patients from 140 centers in 31 countries were recruited between February 1, 2013 and March 6, 2017. A flowchart depicting the trial design is shown in Fig. 1. The Executive Committee designed the protocol and is responsible for the conduct and oversight of the study. The trial is coordinated by the Population Health Research Institute, Hamilton Health Sciences and McMaster University, Hamilton, Canada. The trial was funded by the Canadian Institutes of Health Research, with additional support in the form of unrestricted, investigator-initiated research grants from AstraZeneca and Boston Scientific. The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the paper and its final contents. The protocol was approved by institutional review boards in all participating centers. Written informed consent was obtained from all participants.

Study objectives

The primary objective of COMPLETE is to determine if, in patients with multivessel disease who have undergone early successful culprit lesion PCI for STEMI, a strategy of further revascularization involving PCI of all suitable non-culprit lesions plus optimal medical therapy is superior to a strategy of optimal medical therapy alone in reducing (1): the composite outcome of cardiovascular (CV) death or new non-fatal myocardial infarction (MI), or (2) the composite of CV death, new non-fatal MI or ischemia-driven revascularization (IDR). There are also a number of secondary objectives evaluating additional CV outcomes as well as all-cause mortality.

Eligibility criteria

Eligibility criteria are shown in Table I. Women or men presenting to hospital with STEMI were eligible if they were within 72 hours after successful early PCI of the culprit lesion. Early PCI for STEMI could be primary PCI, rescue PCI for failed fibrinolysis, or a pharmacoinvasive strategy where PCI is performed routinely 3–24 hours after initiation of fibrinolysis. Eligible patients had multivessel CAD defined as at least 1 additional non-infarct-related coronary artery lesion that was (1): in a vessel with diameter of at least 2.5 mm that was not stented as part of the index PCI (2); at least 70% diameter stenosis by visual estimation or, alternatively, 50–69% diameter stenosis by visual estimation and accompanied by a FFR measurement of less than or equal to 0.80; and (3) amenable to successful treatment with PCI. Patients were excluded if there was a pre-randomization intent to revascularize a non-culprit lesion, a planned surgical revascularization, prior coronary artery bypass graft (CABG) surgery, a non-CV co-morbidity reducing life expectancy to <5 years, or any other medical, geographic, or social factor making study participation impractical or precluding long-term yearly follow-up.

Outcomes

The co-primary outcomes are (1): the composite of CV death or new non-fatal MI and (2) the composite of CV death, new non-fatal MI or ischemia-driven revascularization (IDR). The key secondary outcome is the composite of CV death, new non-fatal MI, IDR, or unstable angina or new or worsening New York Heart Association (NYHA) class IV heart failure. Other secondary outcomes include each component of this outcome taken separately and all-cause mortality taken separately. Additional outcomes include stroke and stent thrombosis. Furthermore, a health economic study, including health resource utilization, costs and cost-effectiveness will be performed concurrent with the main trial. Health-related quality of life based on the EQ-5D Quality of Life Scale from baseline to 6 months and final visit was performed, as well as

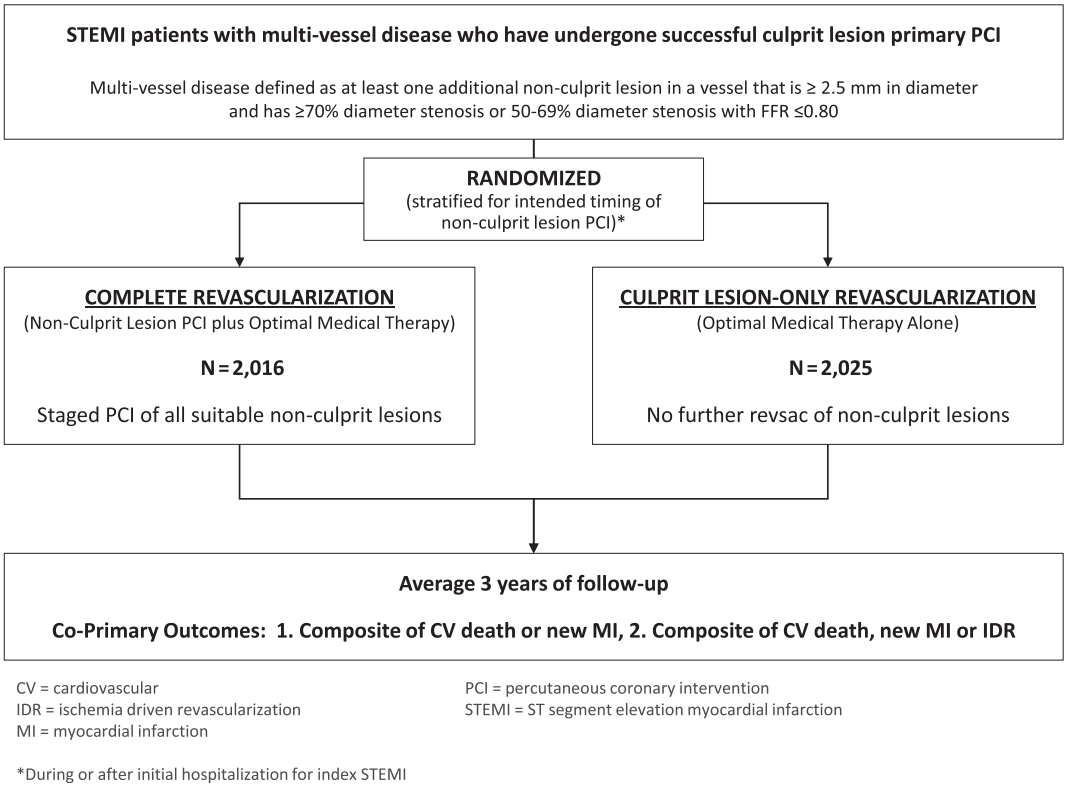

Fig. 1

eStudy design and overview of the COMPLETE trial.

Table I. Eligibility criteria for the COMPLETE trial

Inclusion criteria
1. Men and women within 72 hours after successful early PCI to the culprit lesion for STEMI. Early PCI for STEMI can be either primary PCI or rescue PCI for failed fibrinolysis or a pharmacoinvasive strategy where PCI is performed routinely 3–24 hours after initiation of fibrinolysis.
2. Multivessel disease defined as at least 1 additional non-infarct-related coronary artery lesion that is:
   a) in a vessel that is at least 2.5 mm in diameter that has not been stented as part of the index PCI
   and
   b) is amenable to successful treatment with PCI
   and
   c) at least 70% diameter stenosis by visual estimation (or 50–69% diameter stenosis by visual estimation plus FFR ≤ 0.80)

Exclusion criteria
1. Intent to revascularize non-culprit lesion(s) irrespective of randomized allocation
2. Planned surgical revascularization
3. Non-CV co-morbidity reducing life expectancy to <5 years
4. Any other medical, geographic, or social factor making study participation impractical or precluding 5 year follow-up
5. Prior coronary artery bypass graft surgery

anginal status as per the Seattle Angina Questionnaire. Safety outcomes include major bleeding and contrast induced nephropathy following initial and staged PCIs.

Screening and randomization

All patients undergoing early PCI for STEMI (i.e., primary, rescue or pharmacoinvasive) were routinely screened for eligibility. Sites were requested to keep a screening log for all potentially eligible patients. After eligibility was confirmed, written informed consent was obtained prior to randomization.

Coronary angiograms, including those for the initial qualifying culprit lesion PCI, the index non-culprit lesion PCI and any unplanned PCIs or coronary angiograms were collected and forwarded to a central angiographic core lab for detailed assessment.

Randomization was performed as soon as possible (and no later than 72 hours) after culprit lesion index PCI. Randomization was performed using a concealed central computerized randomization system accessed via a secure website. Treatment allocation was assigned according to a computer-generated randomization list stratified by center using permuted random block sizes blinded to centers and by pre-randomization intended timing of revascularization (during the initial hospitalization or after initial hospital discharge) should the patient be randomized to the complete revascularization arm of the trial.

All consenting patients who were randomized were deemed irrevocably enrolled in the study, whether or not they were subsequently found to be ineligible, or actually received the allocated treatment.

Study procedures

Complete revascularization group. All patients randomized to complete revascularization were to have staged PCI of all suitable non-culprit lesions with ≥70% stenosis diameter or 50–69% diameter with FFR ≤0.80 as soon as possible after randomization and preferably during initial hospitalization (but no later than 45 days after randomization) and irrespective of whether there were clinical symptoms or other evidence of ischemia. All patients, regardless of treatment allocation, were to be treated with low-dose aspirin and ticagrelor (clopidogrel and prasugrel were allowed if there was a contraindication to ticagrelor). The use of a glycoprotein IIb/IIIa inhibitor and anticoagulation regimen (heparin, bivalirudin or low-molecular-weight heparin) was left to the discretion of the investigator. Either a radial or a femoral artery approach could be used. Drug-eluting stents were mandated unless there were contraindications. In general, it was recommended that PCI of chronic total occlusions (CTO) be attempted only by experienced CTO operators, and only if there was a high likelihood of PCI success.

Culprit-lesion-only group. Patients who were randomized to the culprit-lesion-only strategy received optimal medical therapy, including low-dose aspirin and ticagrelor, with no further revascularization, regardless of whether there was evidence of ischemia on non-invasive testing. It was recommended that residual angina be treated medically, with addition (or increased doses) of nitrates, β-blockers, calcium-channel blockers or ranolazine. Revascularization of non-culprit lesions was permitted only if one of the following criteria was met (1): recurrent MI (STEMI or NSTEMI), (2) hemodynamic instability, (3) refractory ischemic heart failure (defined as Killip class ≥3) or (4) intractable angina (Canadian Cardiovascular Society (CCS) Class 3 or 4 symptoms) despite optimal medical therapy *and* objective, proven and documented evidence of ischemia in the territory of one or more non-culprit vessels. In the absence of all of these criteria within the first 45 days, revascularization of a non-culprit lesion was deemed a protocol violation. Routine stress testing and repeat angiography were discouraged in patients with stable symptoms.

Optimal medical therapy

Recommended optimal medical therapy for secondary prevention, to be used in both randomized groups, included aspirin, ticagrelor, ACE inhibitors, β-blockers and statins. Recommendations were also specified for

Table II. Recommendations for optimal medical therapy and lifestyle modification

1. Aspirin	75–100 mg po daily
2. Ticagrelor	180 mg loading dose then 90 mg po BID*†‡ 60 mg po BID beyond 1 year should be considered in patients who are not at high risk of bleeding
3. β-Blocker	To target a resting heart rate of 60-70 beat/min
4. ACE inhibitor or ARB	Appropriately titrated to target a blood pressure of <130/85. If the patient continues to experience hypertension with BP> 130/85, additional blood pressure lowering treatments should be added: either a thiazide diuretic or dihydropyridine calcium-channel blocker. The goal of antihypertensive therapy is to achieve and maintain a target blood pressure (BP) of <130/85 mm Hg.
5. Statin	Atorvastatin 40–80 mg daily or rosuvastatin 20–40 mg daily or simvastatin 40 mg daily. If, at any time during follow-up, the LDL cholesterol is above the target of 2.0 mmol/L, the statin dose should be maximized (if not already attempted). If this still does not result in the desired effect, then ezetimibe or a PCSK-9 inhibitor can be added. If a patient has a statin related side effect, then, either a lower dose of the same statin or use of a different statin with or without the addition of ezetimibe can be considered.
6. Diabetes management	The goal is to maintain fasting blood glucose levels between 4.4–7.5 mmol/L and hemoglobin A1c levels <7.0%, in accordance with published recommendations of the American Diabetes Association and the DCCT Consensus Report. If these criteria are not met on oral hypoglycemic therapy, then insulin should be strongly considered.
7. Management of LV dysfunction	If the patient has significant LV dysfunction, consideration should be given to administration of an aldosterone antagonist.
8. Optimal risk factor and lifestyle modification	Other recommendations for optimal risk factor and lifestyle modification as per the 2012 ACCF/AHA/ACP/AATS/PCNA/SCAI/STS Guideline for the Diagnosis and Management of Patients With Stable Ischemic Heart Disease

†For patients who received a fibrinolytic, ticagrelor 180 mg loading dose should be administered 24 hours after the thrombolytic has been administered.
‡Patients having standard primary PCI should receive standard ticagrelor dose pre- or post-randomization irrespective of prior clopidogrel use.
*Clopidogrel or prasugrel may be used if there is a contra-indication to ticagrelor or where ticagrelor is not available. This must be documented on the case record forms.

management of diabetes and LV dysfunction (as applicable) as well as lifestyle modification (Table II).

Angiographic core laboratory

All angiograms including the index PCI for STEMI, study PCI or any unplanned PCIs or coronary angiograms were anonymized and sent to the central angiographic core laboratory located at McMaster University and Hamilton Health Sciences. The objectives of the core laboratory analysis are to describe and quantitate the extent of CAD (before and after primary PCI), and the completeness and complexity of revascularization in patients randomized to PCI and to determine whether the completeness of revascularization is related to outcome. Quantitative coronary angiography was performed and the SYNTAX score (or residual SYNTAX score) was determined for all identified culprit and non-culprit lesions. Angiographic and procedural complications were evaluated for all procedures. For chronic total occlusions, the J-CTO score was determined. The completeness of revascularization was defined as the proportion of non-culprit lesions in a vessel ≥2.5 mm in diameter with at least 70% diameter stenosis or 50–69% diameter stenosis with FFR ≤0.80 that underwent successful PCI.

Follow-up

After initial hospital discharge, routine clinic follow-up occurred at 6 weeks, 6 months, 1 year and yearly thereafter up to the final follow-up visit, which was to occur on or after September 1, 2018. Under exceptional circumstances where a clinic visit was not possible, visits could be conducted by telephone. At each visit, clinical outcomes, compliance with medical therapy and smoking cessation were assessed. Levels of low-density lipoprotein cholesterol (LDL), blood pressure and glycemic targets were assessed at the 6-month and final follow-up visits. The Seattle Angina Questionnaire and the EQ-5D questionnaire were used to measure quality of life. In addition, costs were collected during the course of the study, including those for medical and resource utilization (including medication and cardiac procedures), re-hospitalizations and emergency room visits.

Definitions of study outcomes

Study outcomes are defined in Table III.

Event adjudication

An Event Adjudication Committee, comprising clinicians who were masked to treatment allocation, adjudicated primary and secondary efficacy outcomes as well as bleeding events. The following events were adjudicated: death (CV versus non-CV), MI, IDR, unstable angina, new or worsening NYHA class IV heart failure, stroke, stent thrombosis and major bleeding.

Interim analyses

A Data Monitoring Committee (DMC) conducted 2 formal interim analyses of efficacy, the first when the total of unrefuted primary outcomes had reached approximately 50% of the anticipated total events expected by the completion of follow-up and the second when 75% of these events had occurred. Convincing evidence of benefit required a difference in the rates of the primary outcomes of ≥4 standard deviations (SD) at the first interim analysis or ≥ 3 SD at the second. There was a requirement that the boundary be crossed on 2 successive analyses at least 1 month apart for the DMC to recommend early stopping for efficacy. Given this conservative monitoring boundary applied in a superiority setting and the limited number of interim analyses, the type-I error level adjustment for the final analysis was negligible. A recommendation by the DMC to stop the trial was to be based on the pattern of treatment effect across all outcomes, as well as the benefit/risk ratio.

Statistical considerations

Sample size and study power. The Steering Committee reviewed the overall (combined group) blinded event rates every 6 months. On November 2, 2016 (when 3607 patients had been randomized), the original primary outcome event rate (composite of CV death or new non-fatal MI) was 5.6% per year, which was lower than the originally estimated event rate in the initial protocol of 6% per year, and the original key secondary outcome event rate (composite of CV death, new non-fatal MI or IDR) was 8.9% per year. The temporal pattern of annualized combined event rates over time for the composite of CV death or new non-fatal MI indicated a steady decline, such that by trial end it was projected that the study would be underpowered. Therefore, the Steering Committee made 3 changes to the study protocol. First, the sample size was modestly increased from 3900 to 4000 patients (a greater increase was unfeasible). Second, in order to accrue more events, allowance was made for the duration of follow-up to be extended beyond 5 years to a common study end date in patients enrolled early on in the trial. Finally, co-primary outcomes were adopted. The original primary outcome of the composite of CV death or new non-fatal MI was considered of great clinical importance and was retained as the new first co-primary outcome. The original key secondary outcome of the composite of CV death, new non-fatal MI, or IDR was adopted as the new second co-primary outcome. The overall type 1 error probability for the two co-primary outcomes was retained at 5% (0.05) and was partitioned between the two co-primary outcomes, taking into consideration the overlap between these outcomes (i.e., CV death or MI is a subset of CV death, MI or IDR). Using simulation, the fraction of overlap between the two co-primary outcomes was calculated to be 0.642 (based on November 24, 2016 combined group, overall blinded data). Assuming this overlap and a pre-specified alpha of 0.045 for the first co-primary outcome (CV death or new non-fatal MI), the

Table III. Outcome definitions

Outcome	Definition
Cardiovascular death	Deaths will be classified as CV or non-CV. All deaths with a clear CV or unknown cause, will be classified as CV. However, within CV deaths, hemorrhagic deaths will be clearly identified. Only deaths due to a documented non-CV cause (e.g., cancer) will be classified as non-CV.
Myocardial infarction	Any one of the following criteria meets the diagnosis for myocardial infarction: 1. a) For individuals with normal (or presumed normal) cardiac troponin values (cTn), detection of a rise and/or fall of cardiac troponin values with at least one value above the 99th percentile upper reference limit (URL) and with at least one of the following: (i) New symptoms suggestive of myocardial ischemia (i.e., significant, sustained ischemic symptoms lasting at least 20 minutes) or (ii) New or presumed new significant ST–T wave changes or new left bundle branch block (LBBB) (iii) Development of pathological Q waves on the ECG (iv) Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality (v) Identification of an intracoronary thrombus by angiography or autopsy b) For individuals whose cardiac troponin values are already elevated or were recently elevated (i.e., suspected new MI occurs within 1 week of the last troponin measurement), new ischemic symptoms of at least 20 minutes and either new ST-segment elevation of at least 1 mm in 2 adjacent limb leads or 2 mm in 2 adjacent precordial leads are required. These ECG changes must be distinct from the original MI and not due to the usual ECG evolution of this event. 2. Cardiac death with symptoms suggestive of myocardial ischemia and presumed new ischemic ECG changes or new LBBB, but death occurred before the cardiac troponin measurements were obtained, or before cardiac troponin values would be increased. 3. Possible MI in conjunction with PCI: a) For individuals with normal or presumed normal cardiac troponin prior to percutaneous coronary intervention (PCI), a PCI-related MI within 24 hours following PCI is defined by elevation of cardiac troponin values (35× 99th percentile URL or CK-MB >5×URL) and with at least one of the following: (i) New symptoms suggestive of myocardial ischemia (i.e., significant, sustained ischemic symptoms lasting at least 20 minutes) or (ii) New or presumed new significant ST–T wave changes or new left bundle branch block (LBBB) or (iii) Angiographic findings consistent with a major procedural complication (e.g., abrupt closure, no reflow, new angiographic thrombus, distal embolization, major side branch occlusion or dissection with reduced flow) or (iv) Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality is required. b) For individuals whose cardiac troponin values are already elevated or were recently elevated (i.e., suspected new MI occurs within 1 week of the last troponin measurement), new ischemic symptoms of at least 20 minutes and either new ST-segment elevation of at least 1 mm in 2 adjacent limb leads or 2 mm in 2 adjacent precordial leads are required. These ECG changes must be distinct from the original MI and not due to the usual ECG evolution of this event. 4. Stent thrombosis associated with MI when detected by coronary angiography or autopsy in the setting of myocardial ischemia and with a rise and/or fall of cardiac troponin values with at least one value above the 99th percentile URL. Note: The incidental angiographic documentation of stent occlusion in the absence of clinical signs or symptoms is not considered a confirmed stent thrombosis related MI (silent occlusion). 5. CABG-related MI is defined by elevation of cardiac troponin values (>70 X 99th percentile URL) in patients with normal baseline troponin values (>99th percentile URL or CK-MB> 10× URL) within 24 h of CABG) and with at least one of the following: 1. New pathological Q waves or new LBBB, or 2. Angiographic documented new graft or new native coronary artery occlusion, or 3. Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality

Table III (*continued*)

Outcome	Definition
Ischemia-driven revascularization	Requires all of the following criteria: 1. Ischemic symptoms consistent with CCS class ≥2 angina despite optimal medical therapy, and 2. PCI or CABG of either the culprit lesion (within 5 mm of the stented segment) associated with the index PCI or a non-culprit lesion that led to enrollment into the trial, and 3. At least ONE of the following: (i) Positive functional study (exercise or persantine myocardial perfusion imaging or stress or dobutamine echo or other imaging) demonstrating clear evidence of reversible ischemia corresponding to a stenosis (ii) New Ischemic ECG changes at rest or with exertion in a distribution consistent with a stenosis (iii) FFR ≤0.80
Unstable angina	Requires hospital admission for unstable angina and is characterized by prolonged ischemic symptoms at rest (usually ≥10 minutes in duration) or accelerating pattern of ischemic symptoms (more frequent) that occurs with a lower activity threshold (it takes less activity to trigger angina symptoms), and no evidence of acute MI.
New or worsening NYHA Class IV heart failure	New or worsening NYHA Class IV heart failure is defined as a physician decision to treat HF with IV diuretic, inotropic agent or vasodilator plus at least one of the following: 1) presence of pulmonary edema or pulmonary vascular congestion on chest radiograph thought to be due to HF; 2) râles reaching above the lower 1/3 of the lung fields thought to be due to HF; or 3) PCWP or LVEDP ≥18 mm Hg. In the case of NYHA Class IV heart failure occurring as an outpatient, re-admission to an acute care facility is required in addition to the above criteria. Worsening HF is defined as requiring assisted ventilation (CPAP) or cardiogenic shock for those patients that already have HF.

alpha for the second co-primary outcome (CV death, new non-fatal MI or IDR) was calculated to be 0.0119. With a sample size of 4000 patients (2000 patients per group), for co-primary outcome 1, the power to detect a 20% to 22% hazard ratio reduction (HRR) with an alpha of 0.045 and a 5% per year event rate in the culprit-lesion-only group would range from 71% to 80%, respectively. For co-primary outcome 2, the power to detect a 20% to 22% HRR with an alpha of 0.0119 and a 9% per year event rate in the culprit-lesion-only group would range from 80% to 89%, respectively.

Analysis of co-primary outcomes. All patients who were randomized will be included in the analysis according to the treatment group to which they were assigned, regardless of the treatment they actually received (i.e., intention-to-treat principle). The co-primary efficacy outcomes will be analyzed using a time-to-event approach, counting the first occurrence of any component of the composite outcome. Censoring will occur if the patient is lost to follow-up or reaches the end of the follow-up period without experiencing the primary outcome. Patients who prematurely discontinue their follow-up prior to the development of a primary composite outcome will be censored as of their last completed follow-up visit. Plots of the cumulative incidence curves by treatment group will be provided using the product limit estimation method. Estimates of the hazard rate ratios and 95% confidence intervals (CI) will be calculated using a Cox proportional hazards model with treatment group as an independent variable. Stratification will be by study site and by intended timing of revascularization.

Censoring will be assumed to be independent of the randomized group assignment. The proportionality assumption of the Cox regression model will be assessed graphically and also with the use of Schoenfeld residuals, and by including a time-treatment interaction term in the Cox model (log transformed time). The number and incidence of each component of the composite primary co-outcomes will be summarized in each treatment group. To gain insight into the optimal timing of non-culprit lesion PCI, subgroup analysis will be performed according to the intended timing of revascularization, which is the main pre-randomization stratification factor in the trial. The hazard ratio and 95% confidence intervals in each stratum (intended timing of revascularization during the initial hospitalization or after the initial hospitalization) will be calculated, along with a treatment by stratum interaction term.

Co-primary outcome 1 (composite of CV death or non-fatal MI) will be tested at a 4.5% level of significance, whereas co-primary outcome 2 (composite of CV death, non-fatal MI or IDR) will be tested at a level of 1.19%. A positive result from the comparison of complete revascularization strategy with the OMT alone strategy will be declared if either one of the two co-primary outcomes is significant.

Analyses of the co-primary outcomes will also be performed in on-treatment and per-protocol populations.

The on-treatment population will consist of those patients, regardless of treatment group, receiving non-culprit lesion PCI or not receiving non-culprit lesion PCI within 45 days of randomization. The per-protocol population will consist of those randomized patients who actually received the assigned treatment, as per the protocol.

Main pre-specified subgroups include: intent to perform non-culprit lesion PCI during vs after initial hospitalization (stratification variable), presence or absence of proximal/mid LAD non-culprit stenosis, presence or absence of non-culprit lesion stenosis severity ≥80% (visual) or≥ 60% by core laboratory analysis (not including chronic total occlusion), above or below the median/mean residual SYNTAX score. Subgroup by treatment interaction terms will be evaluated. Additional exploratory pre-specified subgroup analyses include: left ventricular ejection fraction <45% vs ≥45%, male vs female, age <65 vs ≥65, diabetes vs no diabetes, timing of non-culprit lesion PCI relative to index PCI, type of $P2Y_{12}$ inhibitor during initial hospitalization and at discharge, double vs triple vessel disease before index PCI, glomerular filtration rate (GFR) <60 cc/min vs ≥60 cc/min, prior MI vs no prior MI, primary vs pharmacoinvasive/rescue PCI, Killip class 1 vs ≥2, type of stent used, contrast-induced kidney injury after index PCI, current smokers vs non-smokers, North American site vs rest of world, radial vs femoral artery access for index and non-culprit lesion PCI, non-culprit lesion 50–69% stenosis with FFR ≤0.80 vs non-culprit lesion ≥70% visual stenosis.

Discussion

The COMPLETE trial will evaluate whether staged non-culprit lesion PCI is beneficial in patients with multivessel disease who present with STEMI. Prior trials have evaluated non-culprit lesion PCI in STEMI with different designs. The PRAMI randomized 465 patients with multivessel STEMI undergoing primary culprit lesion PCI to immediate non-culprit lesion PCI (>50% visual stenosis) or no further PCI. There was a reduction in cardiac death, MI, or refractory angina (9.0% vs 22.9%, $P < .001$) at a mean follow-up of 23 months. The CvLPRIT randomized 296 patients to either culprit vessel-only PCI or multivessel PCI (immediate or staged) and found a reduction in the composite primary outcome of death, MI, heart failure and IDR within 12 months with non-culprit lesion PCI. The DANAMI-3-PRIMULTI randomized 627 multivessel STEMI patients presenting with visual stenosis >50% in one or more non-infarct-related vessels to either staged FFR-guided complete revascularization or no further invasive treatment. Complete revascularization reduced the primary composite outcome of all-cause death, MI or IDR (13% vs 22%, $P = .004$). The reduction in the primary outcome was driven mainly by the IDR component, with similar rates of death and MI. The COMPARE-ACUTE trial randomized 885 patients with STEMI and multivessel disease to FFR-guided complete revascularization or to no revascularization of non-culprit lesions. There was a reduction in the primary endpoint of death, MI, revascularization and cerebrovascular events at 12 months (8% vs 21%, HR 0.35, $P < .001$), driven mainly by a reduction in revascularization, with no significant reduction in hard endpoints.[10]

The COMPLETE trial will complement these trials in several ways. First, it is larger in size and thus will have greater statistical power to detect moderate reductions in hard outcomes, including death or MI. Second, average follow-up is approximately 3 years, allowing longer-term evaluation and durability of a complete revascularization strategy. Third, COMPLETE utilizes an angiographic core laboratory, where lesion complexity and completeness and quality of revascularization (including PCI-related complications) can be described in a consistent fashion. Fourth, COMPLETE may offer important insights into optimal timing of non-culprit lesion intervention because randomization is stratified for the intended timing of revascularization: early, during the initial hospitalization or after discharge from hospital. Fifth, COMPLETE recommends the use of ticagrelor, a $P2Y_{12}$ inhibitor that is superior to clopidogrel for prevention of major cardiovascular events in patients with ACS (including STEMI).[23] Finally, the trial is global in scope and includes centers in North America, Europe and Asia, allowing broad generalizability.

It is still not resolved whether future death or MI is more closely related to plaque composition (thin fibrous cap, large lipid core and inflammation) or to lesions that cause ischemia.[25] Plaques that are angiographically more severe are also more likely to be unstable, regardless of whether or not they cause ischemia.[25] This is the rationale for intervening on angiographically severe non-culprit lesions in the COMPLETE trial. The Fractional Flow Reserve versus Angiography for Multivessel Evaluation (FAME) 2 trial demonstrated a reduction in revascularization, but not in death or MI with an FFR-guided PCI strategy versus medical therapy alone.[26] It is still not resolved whether routine ischemia testing with FFR or with other modalities results in fewer hard outcomes. The ISCHEMIA trial will help determine whether intervening on lesions that cause moderate to severe ischemia in the context of stable ischemic heart disease improves hard outcomes.[27] The FULL REVASC trial is evaluating whether FFR-guided PCI of non-culprit lesions during index hospital admission is superior to an initial conservative management strategy following acute PCI of the culprit lesion in preventing death or MI (clinicaltrials.gov NCT02862119).

In summary, the COMPLETE trial will help determine the role of a complete revascularization strategy comprising staged non-culprit lesion PCI plus optimal medical therapy versus optimal medical therapy in patients presenting with STEMI and multivessel CAD who have undergone successful culprit lesion PCI.

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Appendix. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ahj.2019.06.006.

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