Percutaneous coronary intervention of native coronary artery versus saphenous vein graft in patients with prior coronary artery bypass graft surgery: Rationale and design of the multicenter, randomized PROCTOR trial

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Background Patients with prior coronary artery bypass grafting (CABG) frequently require repeat percutaneous revascularization due to advanced age, progressive coronary artery disease and bypass graft failure. Percutaneous coronary intervention (PCI) of either the bypass graft or the native coronary artery may be performed. Randomized trials comparing native vessel PCI with bypass graft PCI are lacking and long-term outcomes have not been reported.

Methods PROCTOR (NCT03805048) is a prospective, multicenter, randomized controlled trial, that will include 584 patients presenting with saphenous vein graft (SVG) failure and a clinical indication for revascularization, as determined by the local Heart Team. The trial is designed to compare the clinical and angiographic outcomes in patients randomly allocated in a 1:1 fashion to either a strategy of native vessel PCI or SVG PCI. The primary study endpoint is a 3-year composite of major adverse cardiac events (MACE: all-cause mortality, non-fatal target coronary territory myocardial infarction [MI], or clinically driven target coronary territory revascularization). At 3-years, after evaluation of the primary endpoint, follow-up invasive coronary angiography will be performed. Secondary endpoints comprise individual components of MACE at 1, 3 and 5 years follow-up, PCI-related MI, MI >48 hours after index PCI, target vessel failure, target lesion revascularization, renal failure requiring renal-replacement therapy, angiographic outcomes at 3-years and quality of life (delta Seattle Angina Questionnaire, Canadian Cardiovascular Society Grading Scale and Rose Dyspnea Scale).

Conclusion PROCTOR is the first randomized trial comparing an invasive strategy of native coronary artery PCI with SVG PCI in post-CABG patients presenting with SVG failure. (Am Heart J 2023;257:20–29.)

Coronary artery bypass grafting (CABG) remains the recommended revascularization strategy in patients with complex multivessel and/or left main disease.[1,2] Bypass surgery effectively alleviates angina symptoms and may improve prognosis, particularly in patients with diabetes and left ventricular dysfunction.[1,2] However, long-term efficacy is impeded by bypass graft failure and progression of native coronary artery disease.[3] Numerous studies demonstrated lasting arterial graft patency, whereas vein graft failure is reported in up to 50% of patients within 10 years after CABG.[4-7] However, despite advances in surgical techniques, saphe-

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Abbreviations: CABG, coronary artery bypass grafting; CCS, Canadian cardiovascular society grading scale; CCTA, coronary computed tomography angiography; CTO, chronic total occlusion; DSMB, data safety monitoring board; ECG, electrocardiogram; EPD, embolic protection device; ICA, invasive coronary angiography; MACE, major adverse cardiac events; PCI, percutaneous coronary intervention; RDS, rose dyspnea scale; SAQ, Seattle angina questionnaire; SVG, saphenous vein graft.

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nous vein grafts (SVG) remain the most commonly used conduit in contemporary bypass surgery.[8-10] Graft failure has been associated with recurrent angina symptoms, myocardial ischemia and a higher risk of adverse patient outcome.[3,4,11] Indeed, patients with prior CABG often require repeat revascularization therapy.[12-14] Redo CABG is associated with high risk of periprocedural mortality, hence percutaneous coronary intervention (PCI) of either the bypass graft or the native coronary artery is the preferred revascularization strategy, specifically in patients with a patent internal mammary artery graft to the left anterior descending coronary artery.[1,2] Native vessel PCI in post-CABG patients is challenging due to complex atherosclerotic lesion morphology, extensive coronary calcification and a high incidence of chronic total coronary occlusions (CTOs), which are observed in >50% of patients.[15-17]. On the other hand, vein graft PCI is limited by a substantial procedural risk of distal embolization and subsequent no-reflow, possibly related to friable atheromatous plaques.[17] Moreover, SVGs are prone to accelerated atherosclerosis and in-stent restenosis, and as such, recurrent graft failure following SVG PCI is frequently observed.[10] Large patient-cohort studies reported worse short- and long-term outcomes with bypass graft PCI compared to native vessel PCI.[12,13,18] Based on this observational work, the guidelines on myocardial revascularization advocate PCI of the bypassed native vessel over bypass graft PCI (Class 2a, Level of evidence C).[1,2] To date, randomized clinical trials comparing a strategy of native vessel PCI with SVG PCI have not been conducted.

Methods

Objectives

The aim of the PROCTOR (PeRcutaneous cOronary intervention of native Coronary arTery versus saphenous vein graft in patients with prior cORonary artery bypass graft surgery) trial is to compare the clinical and angiographic outcomes of a strategy of native vessel PCI with SVG PCI in patients with prior CABG presenting with SVG failure and a clinical indication for repeat revascularization, as determined by the local Heart Team. The present study is designed to test the hypothesis that a strategy of native vessel PCI is superior to SVG PCI in a randomized setting.

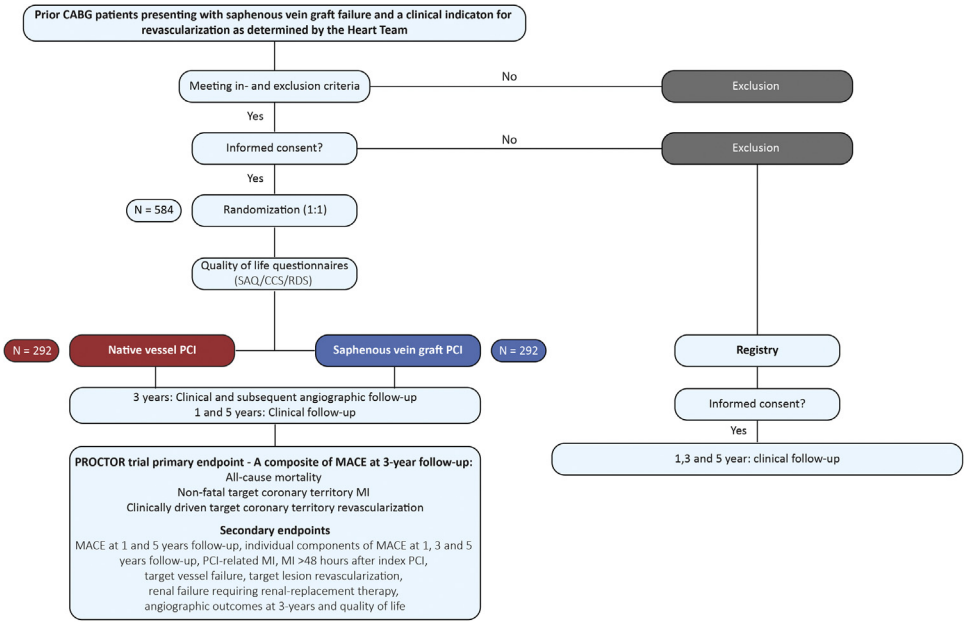
Study design and population

PROCTOR (www.clinicaltrials.gov identifier: NCT03805048) is a prospective, international, multicenter, randomized clinical trial. The study design chart is shown in Figure 1. Consecutive patients presenting with a significant stenosis in a SVG (>50% diameter stenosis on invasive coronary angiography [ICA]) who are discussed in the local Heart Team for revascularization will be screened for potential inclusion in the study. Patients will be eligible for inclusion if revascularization is deemed clinically indicated by the Heart Team and the patient is referred for PCI. The indication for revascularization will be based on symptoms, documented ischemia and evidence of viability in the target vessel territory. Both the native coronary artery lesion(s) and the SVG lesion(s) must be deemed technically feasible for PCI by the Heart Team. The PROCTOR randomization strategy is depicted in Figure 2. After eligibility is verified according to the in- and exclusion criteria for study enrollment (Table I), patients will be approached for study participation. Patients who do meet these criteria but decline to participate in the randomized study will be approached for inclusion in the PROCTOR registry. The objective of the registry is to investigate the clinical outcomes in patients with SVG failure and a clinical indication for revascularization who were not included in the randomized study.

Study procedures

After written informed consent is obtained, participants will be randomly assigned 1:1 to either a strategy of native coronary artery PCI or SVG PCI, using an interactive Web-based randomization platform in OpenClinica (OpenClinica, LCC, Massachusetts, United States) provided by Sealed Envelope Ltd. Both SVG PCI and native vessel PCI will be performed according to the current standard of care. In current revascularization guidelines, the use of an embolic protection device (EPD) during SVG PCI is recommended in selected patients when technically feasible (Class 2a, Level of evidence B), with the aim to reduce the risk of distal embolization and subsequent no-reflow.[1,2] In the PROCTOR trial, EPD utilization for bypass graft PCI will be left at the discretion of the operator to reflect clinical practice. However, operators are encouraged to use EPDs according to contemporary guidelines. When the native coronary artery lesion is a CTO, the hybrid approach will be applied, which is a percutaneous treatment algorithm focusing on revascularization of a CTO in the most safe, effective and efficient manner.[19] This approach uses angiographic characteristics to guide strategical planning of the PCI using complementary antegrade and retrograde crossing techniques: antegrade wire escalation, antegrade dissection re-entry, retrograde wire escalation and retrograde dissection re-entry. Successful PCI is defined as <30% residual stenosis and Thrombolysis In Myocardial Infarction (TIMI) flow III to the distal vascular bed of the bypassed native vessel. A staged procedure may be performed for revascularization of the target vessel territory. If the PCI procedure fails, a second attempt can be performed within 1 month. If successful PCI of the native vessel cannot be accomplished, PCI of the SVG is allowed to restore myocardial blood flow to the target myocardial territory. Vice-versa, in case SVG PCI fails, the native coronary artery may be treated. Only commercially avail-

Figure 1



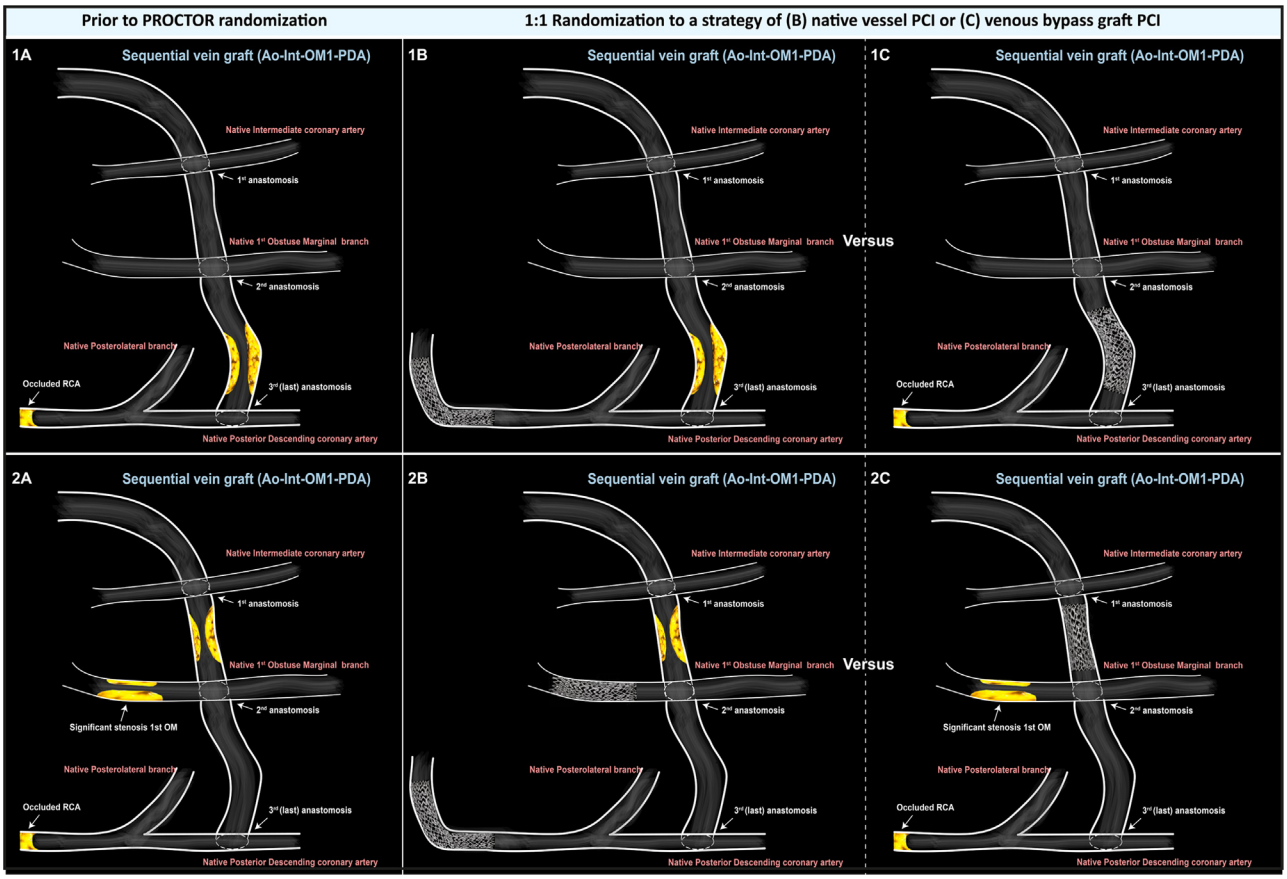
PROCTOR study design chart. Study design chart of the PROCTOR trial, a prospective, multicenter, randomized controlled trial, that will include 584 patients presenting with saphenous vein graft failure and a clinical indication for revascularization, as determined by the local Heart Team.
CABG, coronary artery bypass graft; CCS, Canadian cardiovascular society; MACE, major adverse cardiovascular events; MI, myocardial infarction; PCI, percutaneous coronary intervention; RDS, rose dyspnea scale; SAQ, Seattle angina questionnaire.

Table I. PROCTOR trial inclusion and exclusion criteria.

Inclusion criteria
1. A significant diameter stenosis (>50% on angiography) in a saphenous vein graft
2. Clinical indication for revascularization as determined by the local Heart Team (based on symptoms, documented ischemia, and viability)
3. Both the native coronary artery lesion(s) and the saphenous vein graft lesion(s) must be deemed technically feasible for PCI by the Heart Team
Exclusion criteria
1. < 18 years of age
2. Cardiogenic Shock
3. STEMI at presentation
4. NSTEMI patients with ongoing ischemia (characterized by 1 or more of the following components: recurrent or ongoing chest pain, marked ST-segment depression on 12-lead ECG, heart failure, and hemodynamic or electrical instability)[26]
5. Pregnancy
6. CABG performed < 1 year prior to inclusion
7. Estimated life expectancy < 3 year
8. Target vessel diameter < 2.5 mm
9. Graft diameter > 5.5 mm
10. Aneurysm formation in the bypass graft
11. Heavy burden of thrombus in the bypass graft (>50% of the bypass graft lumen in ≥2 out of 3 of the proximal, middle or distal third of the bypass graft)
12. Failure to provide informed consent

Abbreviations; CABG: coronary artery bypass graft, ECG: electrocardiogram, NSTEMI: non-ST-segment elevation myocardial infarction, PCI: percutaneous coronary intervention, STEMI: ST-segment elevation myocardial infarction

Figure 2



PROCTOR randomization strategy. Patients are eligible for inclusion in the PROCTOR trial when they have a significant diameter stenosis (>50% on angiography) in a SVG and a clinical indication for percutaneous revascularization as determined by the local Heart Team. Figure 2.1 schematically illustrates: **(1A)** a significant lesion in a sequential SVG (Aorta – Intermediate branch – 1st OM branch – right PDA) distally to the second-to-last anastomosis with the OM1 branch. The native RCA is occluded. **(1B)** The patient was randomized to native vessel PCI and the native RCA was successfully treated. **(1C)** The patient was randomized to SVG PCI and the vein graft lesion was successfully treated. A similar strategy would be anticipated in patients with a significant lesion in a SVG with a single anastomosis. Figure 2.2 schematically illustrates: **(2A)** the same sequential SVG (Aorta – Intermediate branch – 1st OM branch – right PDA) with a more proximal lesion located between the anastomosis with the intermediate branch and the 1st OM branch. The native RCA is occluded, whereas the OM branch shows a significant stenosis. **(2B)** The patient was randomized to native vessel PCI and both the native RCA and the 1st OM branch were successfully revascularized. **(2C)** The patient was randomized to SVG PCI and the vein graft lesion was successfully treated.
OM branch, obtuse marginal branch; PDA, posterior descending artery; RCA, right coronary artery; SVG, saphenous vein graft; other abbreviations as in Figure 1.

able second generation drug-eluting stents will be used during index PCI. In PROCTOR, the preferred stent will be everolimus-eluting coronary stent system (XIENCE Sierra™, Abbott Vascular, Santa Clara, California, USA). Patients will receive dual antiplatelet or triple antithrombotic therapy following the procedure according to the current coronary artery revascularization guidelines.[1,2] The Seattle Angina Questionnaire (SAQ), Canadian Cardiovascular Society (CCS) Grading Scale, and Rose Dyspnea Scale (RDS) will be used to assess baseline quality of life scores. After the index PCI, all patients will be hospitalized for a minimum of 6-8 hours. Blood samples to measure renal function and cardiac biomarkers, including CK, CK-MB and cardiac troponin, will be collected routinely at the beginning of the procedure and 3-6 hours after PCI to assess contrast-induced kidney injury and PCI-related myocardial damage. If cardiac biomarkers are elevated (according to the local upper limit of normal) or significantly increased compared to the values at the beginning of the procedure, serial

measurements must be taken to document a rise and fall. Electrocardiograms (ECGs) will be performed prior to and following index PCI.

Clinical and angiographic follow-up

Follow-up is scheduled at 1, 3 and 5 years (± 3 months) after the index procedure. The 1 and 5 year follow-up will be performed using national registry databases, electronic medical patient records and standardized telephone interviews to collect information on endpoints, adverse events and quality of life scores through the CCS and RDS questionnaires. The 3-year follow-up visit will consist of the evaluation of endpoints and adverse events, and quality of life assessment using the SAQ, CCS and RDS questionnaires. Subsequently, a control invasive coronary angiogram will be performed. The occurrence of the primary endpoint and patient quality of life scores will be evaluated before patients undergo the per-protocol angiographic follow-up. ECGs will be performed before and after ICA. Any clinically indicated angiogram performed between 2 and 3 years after the index procedure may apply as the scheduled 3-year follow-up angiogram if all target lesions are visualized. Follow-up for patients included in the PROCTOR registry will be performed by telephone at 1, 3, and 5 years. In addition, national registry databases and electronic medical patient records will be used to collect data on endpoints and adverse events in these patients.

PROCTOR trial endpoints

A list of study and endpoint definitions is provided in Table II. The primary study endpoint consists of a composite of major adverse cardiac events (MACE) adapted to fit the PROCTOR study participants (all-cause mortality, non-fatal target coronary territory myocardial infarction [MI], or clinically driven target coronary territory revascularization) at 3-year follow-up. Clinically driven target coronary territory revascularization will be defined as a revascularization in the entire coronary vessel proximal and distal of the target lesion, including revascularization in side branches, as well as revascularization of the supplying bypass graft to the native target vascular territory. Repeat revascularization during follow-up will be clinically driven if stenosis of the treated lesion is ≥50% of the luminal diameter on the basis of quantitative coronary angiography in the presence of ischemic signs and/or symptoms or if there is a diameter stenosis ≥70% irrespective of the presence or absence of angina symptoms. Repeat revascularization of the target coronary territory (instead of target coronary artery) will be defined as a component of the primary endpoint because patients that initially underwent PCI of the SVG during the study index procedure may undergo revascularization of the bypassed native coronary artery during follow-up, and vice-versa (Figure 3). Secondary endpoints include MACE at 1 and 5 years follow-up, the individual components of MACE at 1, 3 and 5 years follow-up, PCI-related MI, MI >48 hours after index PCI, target vessel failure, target lesion revascularization, renal failure requiring renal-replacement therapy, angiographic outcomes at 3-years and quality of life assessed using the SAQ, CCS, and RDS questionnaires. Contemporary PCI-related MI definitions include thresholds for cardiac biomarker elevation, ECG changes following the procedure and evidence of new onset myocardial ischemia on cardiac imaging. Currently, 3 definitions for clinically relevant MI following coronary revascularization are widely accepted in clinical trials: the fourth Universal Definition of Myocardial Infarction, the Society for Cardiovascular Angiography and Interventions (SCAI) definition and the Academic Research Consortium (ARC)-2 criteria based definition.[20-22] Patients with previous CABG, as included in the current PROCTOR trial, generally have a greater extent of complex, heavily calcified atherosclerotic lesions and a higher prevalence of CTOs compared to CABG-naïve patients.[15,17] Given the higher procedural complexity during native vessel PCI, commonly involving CTO crossing techniques, in conjunction with the substantial risk of distal embolization and no-reflow following PCI of a degenerated vein graft in these patients, a PCI related MI in the PROCTOR trial will be defined using the SCAI definition.[20] The occurrence of MI >48 hours after the index procedure will be adjudicated according to the fourth Universal Definition of Myocardial Infarction.[21] Target vessel failure will comprise a composite of cardiac death, MI attributable to the target vessel, clinically driven target coronary territory revascularization, and binary angiographic in-stent restenosis or reocclusion. Target lesion revascularization will be defined as a revascularization due to a stenosis within a 5-mm border proximal or distal to the stent(s) implanted in the target vessel during index PCI. Baseline and follow-up angiographic images (clinically indicated or per-protocol at 3-year follow-up) will be centrally evaluated by an independent core laboratory blinded to the initial randomization strategy and index procedure. Core lab analysis will entail standardized assessment of anatomical complexity (e.g. the Japanese CTO score, the extent of collateralization and lesion location) and lesion dimensions (e.g. lesion length, minimal luminal diameter and % diameter stenosis) in both the native coronary artery and the bypass graft.[23] Quantitative Coronary Analysis will be used to calculate reference vessel diameters, minimal luminal dimensions and diameter stenosis percentages. Secondary angiographic endpoints comprise late lumen loss, in-stent binary restenosis (≥50%), in-stent reocclusion and delta in-stent diameter stenosis.

Statistical considerations

Sample size calculation

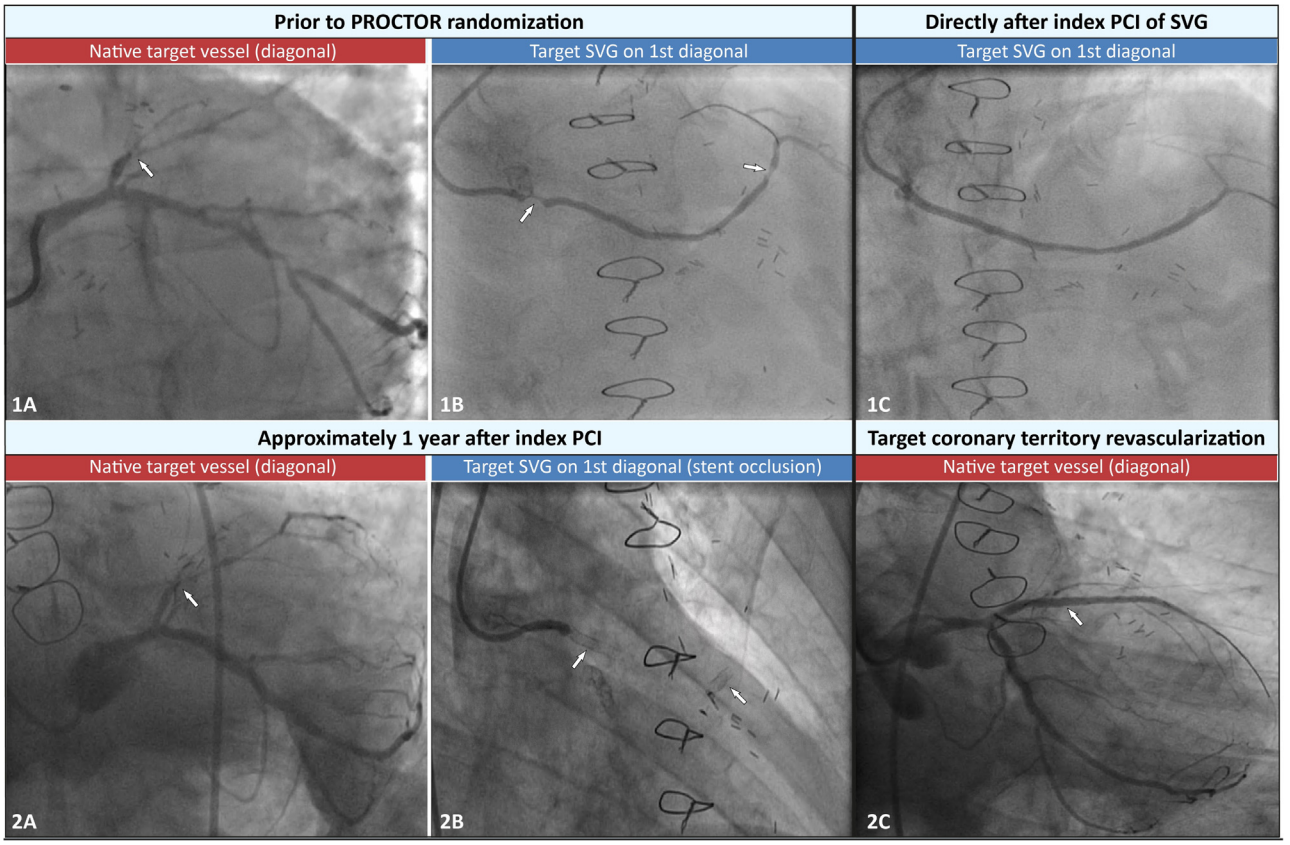
In a large post-CABG patient cohort study, Brilakis et al. reported a 3-year MACE-rate of 47% after bypass graft

Table II. PROCTOR study definitions.

Definitions
Saphenous vein graft failure: Saphenous vein graft failure will be defined as a saphenous vein graft with a significant diameter stenosis (≥50% on coronary angiography) and a clinical indication for revascularization as determined by the local Heart Team (based on symptoms, documented ischemia and viability). MACE: all-cause mortality, non-fatal target coronary territory MI, or clinically driven target coronary territory revascularization. Non-fatal myocardial infarction: a PCI-related MI, or MI during follow-up >48 hours after index PCI (in case the MI is clearly related to a coronary territory which was not revascularized during index PCI, this will not be adjudicated as a primary endpoint). PCI-related myocardial infarction: PCI-related MI will be defined based on the SCAI definition.[20] 1. In patients with normal baseline CK-MB: a. The peak CK-MB measured within 48 hours of the procedure rises to ≥10 x the local laboratory ULN, or to ≥5 x ULN with new pathologic Q-waves in ≥2 contiguous leads or new persistent LBBB, OR in the absence of CK-MB measurements and a normal baseline cTn, a cTn (I or T) level measured within 48 hours of the PCI rises to ≥70 x the local laboratory ULN, or ≥35 x ULN with new pathologic Q-waves in ≥2 contiguous leads or new persistent LBBB. 2. In patients with elevated baseline CK-MB (or cTn) in whom the biomarker levels are stable or falling: a. The CK-MB (or cTn) rises by an absolute increment equal to those levels recommended above from the most recent pre-procedure levels. 3. In patients with elevated CK-MB (or cTn) in whom the biomarker levels have not been shown to be stable or falling: a. The CK-MB (or cTn) rises by an absolute increment equal to those levels recommended above plus new ST-segment elevation or depression plus signs consistent with a clinically relevant MI, such as new onset or worsening heart failure or sustained hypotension. Myocardial infarction ≥48 hours after index PCI: Myocardial infarction >48 hours after index PCI will be defined according to the fourth universal definition of myocardial infarction.[21] 1. Detection of a rise and/or fall of cardiac biomarker values (preferably cTn) with at least 1 value >99th percentile of the URL. 2. At least 1 of the following: a. Symptoms of acute myocardial ischemia. b. New ischemic ECG changes. c. Development of pathological Q waves. d. Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischemic etiology. e. Identification of a coronary thrombus by angiography including intracoronary imaging or by autopsy. Clinically driven repeat revascularization after the index PCI: Revascularization will be clinically driven if stenosis of the treated lesion is ≥50% of the luminal diameter on the basis of quantitative coronary angiography in the presence of ischemic signs and/or symptoms or if there is a diameter stenosis ≥70% irrespective of the presence or absence of ischemic signs or symptoms. Target coronary territory revascularization: Revascularization in the entire coronary vessel proximal and distal of the target lesion, including revascularization in side branches, as well as revascularization of the supplying bypass to the native target vascular territory. Target vessel failure: Composite of cardiac death, myocardial infarction attributable to the target vessel, clinically driven target coronary territory revascularization, and binary angiographic in-stent restenosis or reocclusion. Cardiac death: death due to any of the following: 1. Acute MI. 2. Cardiac perforation/pericardial tamponade. 3. Arrhythmia or conduction abnormality. 4. Stroke through hospital discharge or stroke suspected of being related to the procedure. 5. Death due to complication of the procedure, including bleeding, vascular repair, transfusion reaction, or bypass surgery. 6. Any death in which a cardiac cause cannot be excluded. Target lesion revascularization: Revascularization due to a stenosis within a 5-mm border proximal or distal to the stent. Diameter stenosis: Diameter stenosis will be measured by means of QCA and will be defined as the difference between reference vessel diameter and MLD / reference diameter x 100. Late lumen loss: Late lumen loss will be defined as difference between reference vessel diameter and MLD / reference diameter x 100. In-stent binary stenosis: Binary in-stent restenosis will be defined as ≥50% diameter stenosis within the stent as measured by QCA. In-stent reocclusion: In-stent reocclusion will be defined as recurrent total occlusion at the previously stented site.

CK, creatine kinase; cTn, cardiac troponin; LBBB, left bundle branch block; MACE, major adverse cardiac events; MI, myocardial infarction; MLD, minimal luminal diameter; QCA, quantitative coronary analysis; SCAI, the Society for Cardiovascular Angiography and Interventions; ULN, upper limit of normal; URL, upper reference limit; other abbreviations as in Table I.

Figure 3



Target coronary territory revascularization. A patient with stable recurrent angina symptoms after CABG (LIMA-LAD, Aorta-D1) was referred for ICA which showed **(1A)** a significant lesion in the first diagonal branch and **(1B)** degenerative vein graft disease in the single SVG supplying the D1. The LIMA graft to the LAD was patent. The patient was discussed in the local Heart Team and referred for percutaneous revascularization of the myocardial territory supplied by the vein graft on the D1 (either a strategy of native vessel PCI or a strategy of SVG PCI). **(1C)** After written informed consent was obtained for participation in the PROCTOR trial, the patient was randomized to SVG PCI and 3 drug eluting stents were implanted. Approximately 1 year later, the patient again presented with stable angina symptoms. ICA showed **(2A)** the same lesion in the first diagonal branch and **(2B)** in-stent reocclusion in the SVG to the D1 that was treated during the index PCI. **(2C)** Subsequently, the patient underwent PCI of the native D1. This is an example of target coronary territory revascularization, which is one of the components of MACE in the PROCTOR trial.

D1, 1st diagonal branch; ICA, invasive coronary angiography; LAD, left anterior descending coronary artery; LIMA, left internal mammary artery; other abbreviations as in Figure 1 and 2.

PCI, whereas the event-rate of native vessel PCI in these patients was 33%.[13] However, the presence of CTO lesions in this cohort was relatively low (4.5%). Based on a study conducted by Toma et al, the 3-year event rate of CTO PCI in post-CABG patients is approximately 36%.[24] The MACE-rate of native vessel PCI (both non-CTO and CTO) in patients with previous CABG is predicted to be 35%. Assuming an event rate of 47% in the bypass graft PCI group versus 35% in the native vessel PCI group, with a 2-sided alpha of 5% and a drop-out rate of 10%, 584 patients should be included to achieve 80% power and allow for the assessment of superiority of native vessel PCI.

Statistical plan and data analysis

Categorical variables will be summarized as numbers with percentages, whereas continuous variables will be displayed as mean ± standard deviation (SD) and median (interquartile range) where appropriate. The primary analysis will be conducted by comparing proportions of patients experiencing MACE at 3-years follow-up

for the 2 treatment strategy groups (native vessel PCI vs. SVG PCI) using a univariable logistic regression analysis. The analysis will include outcome measures for all randomized patients and will be conducted in accordance with the intention-to-treat principle. We will use similar logistic regression analyses for comparison of the binary secondary endpoints (i.e. MACE at 1 and 5 years follow-up, the individual components of MACE, PCI-related MI, MI >48 hours after index PCI, target vessel failure, target lesion revascularization and renal failure requiring renal-replacement therapy) between treatment arms. In addition, Kaplan-Meier curves with log-rank testing will be computed to compare event-free survival between both treatment groups for MACE, the individual components of MACE, target vessel failure and target lesion revascularization to take into account the time-to-event distribution. Multivariable Cox proportional hazard regression analyses will be performed to calculate hazard ratios between treatment groups. Longitudinal mixed-model analysis of covariance will be used to compare the overall intervention effect of the treatment strategy over time for continuous outcomes, i.e. the quality of life scores (SAQ/CCS/RDS), providing regression coefficients and their 95% confidence intervals. The mixed model analysis will be adjusted for the baseline value of the outcome variable and adjustment for the dependency of repeated measurements within the same patient will be performed by adding a random intercept to the model. In addition, time (treated as a categorical variable and represented by dummy variables) and an interaction between the intervention and time will be included in the model to assess the treatment effect at the different time-points during follow-up. All analyses will be evaluated using a 2-sided significance level of 0.05. Statistical data analyses will be performed using SPSS software (IBM SPSS Statistics, Armonk, New-York).

Ethical considerations

This study is conducted in full accordance with the principles of the "Declaration of Helsinki" (Fortaleza, Brazil, October 2013), the ICH-Good Clinical Practice (ICH-GCP) guidelines, and the Medicinal scientific Research Involving Human Subjects act (WMO). In all participating countries, study execution will be performed in accordance with national/local laws and regulations. It is the responsibility of the investigators to obtain written informed consent. The information is intended to give each participant a thorough understanding of the purpose and the nature of the trial, the cooperation required, anticipated benefits, and potential hazards of the study. The investigator also explains that the patient is free to refuse or to withdraw from the trial at any moment and that if the patient decides to do so, standard treatment with the same degree of care will be provided. After being informed, patients will have at least 24 hours to consider participation. A consent form (in the native language) will be made available.

PROCTOR coronary computed tomography angiography substudy

Contemporary coronary computed tomography angiography (CCTA) can be used for the assessment of plaque morphology.[25] No-reflow and distal embolization are considered important mechanisms for clinical events in patients undergoing bypass graft PCI and knowledge of SVG plaque morphology might aid in the selection of patients eligible for this kind of treatment. However, to date, the prognostic value of CCTA-derived plaque characteristics in patients undergoing bypass graft PCI has not been studied. The PROCTOR CCTA substudy is an exploratory, single-center experience (Amsterdam University Medical Centers) in which patients included in the PROCTOR trial will undergo CCTA after randomization to either a strategy of native vessel PCI or SVG PCI. Additional written informed consent is required. CCTA scans will only be performed at the sponsor site and not be used for revascularization strategy selection. The objective of this substudy is to assess CCTA-derived plaque characteristics in diseased SVGs with the aim to predict adverse outcome in patients undergoing repeat revascularization after CABG. We hypothesize that adverse plaque characteristics may be associated with the occurrence of MACE at 3-year follow-up after bypass graft PCI. CCTA will be performed using a standard scanning protocol with a ≥64 slice CT device, with 128 × 0.625 mm section collimation, 420-ms gantry rotation time, 120-kV tube voltage and a tube current of 200 mAs (for CCTA), and 100 mAs (for calcium scoring) depending on patients body size. Conventional CCTA reading and plaque quantification will be performed with commercially available software. In addition to the calcium score, plaque morphology will be studied on the following parameters: maximal cross-sectional plaque area, maximal plaque burden (plaque area divided by vessel area 100%), remodeling index, volumetric measurements of the plaque, mean attenuation of the entire plaque in Hounsfield units and composition (percentage calcified and noncalcified morphology). Furthermore, the following adverse plaque characteristics will be studied: positive remodeling (remodeling index >1.1), low attenuation plaque (<30 HU), absent or spotty calcification, and napkin ring sign. CCTA images will be evaluated by an independent core laboratory in a blinded fashion.

Study funding, responsibilities and organization

PROCTOR is an investigator-initiated clinical trial funded by a research grant from Abbott Vascular International BVBA (Diegem, Belgium). The trial will be performed under direct supervision of the Steering Committee. The study sponsor, in collaboration with the Contract Research Organization (KCRI, Kraków, Poland)

committed to the trial, are responsible for operational oversight, review of the study protocol and amendments, and trial progression. An independent clinical events committee (CEC) consisting of 3 experienced Interventional Cardiologists will review study adverse events and adjudicate clinical primary and secondary endpoints. Members of the CEC are not involved as investigators in the trial. The CEC will provide regular event adjudication reports to the sponsor investigators and the independent data safety monitoring board (DSMB). The DSMB will consider the consistency of primary and secondary endpoints, provide ongoing safety surveillance and perform interim analyses on the safety data. All members will have no conflict of interest with the sponsor of the study. The DSMB will oversee trial conduct and continuously evaluate the progress of the trial to subsequently give advice about continuation, modification or early termination of the study, as per the DSMB charter. 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.

Current study status

Patient enrollment started in January 2019. At the time of submission of this paper, 176 patients have been included in the trial. In addition, the first patients successfully underwent the 3-year follow-up ICA. Currently, 14 sites in the Netherlands, the United Kingdom, Belgium, and Poland are actively recruiting patients, whereas several additional centers are currently going through the steps of the initiation process in order to enhance patient enrollment. Inclusion is anticipated to conclude at the end of 2024. Final results are expected in 2027 after the completion of the 3-year follow-up.

Conclusions

PROCTOR is a prospective, multicenter, randomized controlled trial conducted to compare the clinical and angiographic outcomes of a strategy of native vessel PCI with a strategy of SVG PCI in patients with SVG failure and a clinical indication for revascularization, as determined by the Heart Team. According to contemporary repeat revascularization guidelines based on observational work, PCI of the bypassed native coronary artery is advocated over PCI of the diseased bypass graft. PROCTOR is designed to test the hypothesis that native vessel PCI is superior to SVG PCI in a randomized setting. Results of the PROCTOR trial will impact the repeat revascularization guidelines in patients with a history of CABG presenting with degenerated vein graft disease.

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Disclosures

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