PATENCY

A multi-center randomized study comparing the effects of the No-touch vein harvesting technique versus the conventional approach in coronary artery bypass grafting surgery

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Abstract

Vein graft failure is a crucial challenge in coronary artery bypass graft (CABG) surgery. Previous studies have suggested a patency benefit of the No-touch vein harvesting technique, but only with small sample sizes.

The multi-center randomized study comparing the effects of the No-touch vein harvesting technique versus the conventional approach in coronary artery bypass grafting surgery study (PATENCY) is a prospective, multicenter randomized clinical trial with a large sample size, aiming to investigate the efficacy of the No-Touch technique compared with the conventional approach. All patients requiring isolated CABG with left internal mammary artery plus at least one saphenous vein graft will be considered for entry into the study. 2000 cases (1000 in each arm) will be enrolled over 1 to 2 years in 7 hospitals in China. Participants will be randomized in equal proportions between two surgical strategies: the No-touch or conventional technique. The primary endpoint is graft vessel occlusion at 3 months after CABG surgery by CT coronary angiography. Secondary outcomes are major adverse cardiac or cerebrovascular events at 3- and 12-months post-operation and graft vessel occlusion at 1 year. All participants will be followed up yearly for 10 years to assess the long-term graft occlusion and clinical outcomes.

This study will define the role of the No-touch vein harvesting technique in CABG surgery and provide strong evidence to answer whether this technique could reduce vein graft occlusion.

Introduction

Vein graft occlusion is one of the most crucial challenges in coronary artery bypass graft (CABG) surgery; it substantially increases recurrence of angina and may require repeat revascularization.[1-7] Since CABG was introduced in 1968,[8] surgical technique and perioperative management have evolved, therefore hospital morbidity and mortality have been reduced despite the increasing age and comorbidities of patients.[9] Saphenous vein grafts are used in almost 80% of CABG cases to complete revascularization.[10] At one year after CABG, about 10% of SVG are occluded,[6, 11] with the occlusion rate increasing 1% to 2% annually in the next 1 to 6 years, and increasing 4% annually during 6 to 10 years postoperatively. 10 years after surgery, up to approximately 50% of vein grafts are occluded.[6, 12, 13] Although dual antiplatelet therapy can reduce the risk of vein graft occlusion, the risk of occlusion is still high. A randomized clinical trial shows that 14.3% of vein grafts became occluded 3-month after CABG in patients receiving only aspirin as antiplatelet therapy, and 8.4% in those taking aspirin plus clopidogrel.[14]

Damage to the vein during harvesting is a potential reason for occlusion. Adventitia of saphenous veins are stripped off and forced distention by syringe is usually performed, which are believed to be the major causes of damage.[15] The No-Touch technique was introduced by Dr. Souza in 1996, which features saphenous vein adventitia preservation and avoidance of manual distension after removal from the leg.[16] Theoretically, vessel wall integrity of the vein graft can be well protected and spasm may be avoided. After 16-year follow-up, 17% of saphenous vein grafts harvested by No-Touch technique were occlusive, comparing to 36% by conventional approach. However, this study is limited by its small sample size from a single center.[1] Therefore, it is still uncertain whether No-Touch harvesting technique can reduce rates of vein graft occlusion.

Objectives

Accordingly, we are conducting a multicenter randomized controlled trial to assess whether the No-Touch vein harvesting technique during CABG can reduce vein graft occlusion compared to the conventional vein harvesting technique.

Study design

This is a prospective, multicenter, open-label, randomized controlled trial. We aim to randomize 2600 patients undergoing isolated CABG who had at least one vein graft from 7 hospitals in China. We consecutively screen patients during the study enrollment period and seek informed consent from all eligible patients. Patients who give informed consent are randomly assigned to undergo No-Touch vein harvesting or conventional vein harvesting by a central randomization system. We will follow-up participants via face-to-face interview until at least 1 year after the operation. Each participating hospital records all patients who are screened, their screening status, and reasons for non-enrollment. Flowchart of enrollment and follow-up is shown in Figure 1. To reduce the variation among participating hospitals, we only include hospitals in which annual in-hospital mortality of CABG are lower than 5% from year 2012 to 2016. To reduce the variation among surgeons, we require that both CABG and vein graft harvesting are performed by qualified surgeons. The ethics committees at all 7 participating hospitals approved this Study. The study was registered at http://www.clinicaltrials.gov (NCT03126409).

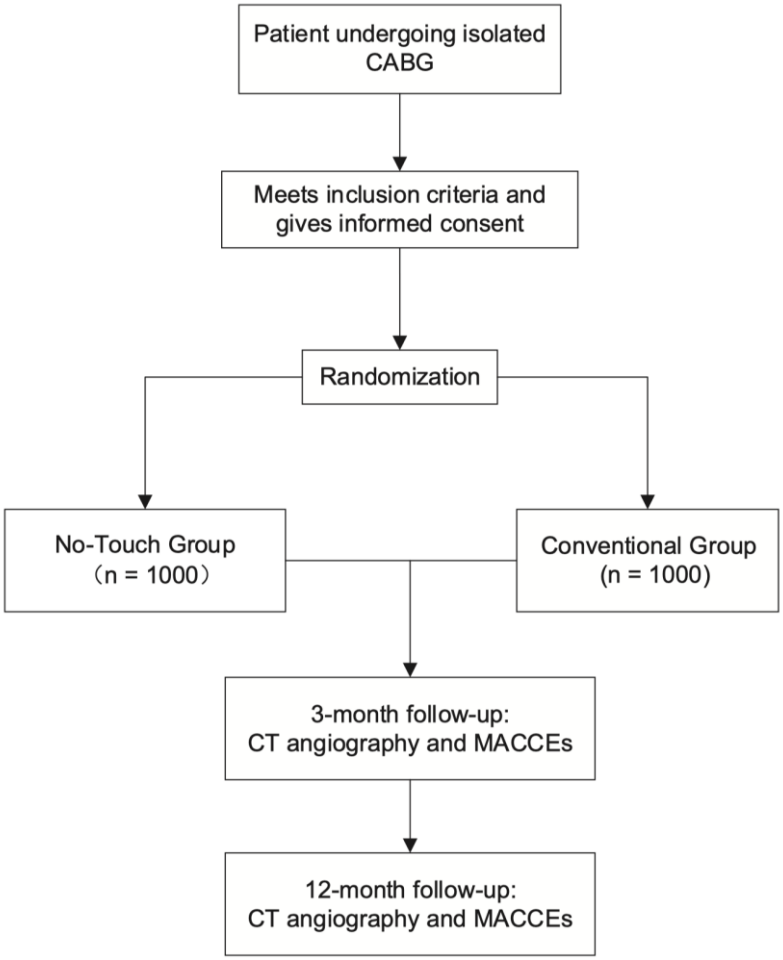

Figure 1. Flowchart of the study.

Patient Population

This study includes patients aged 18 or older who undergo primary isolated open-chest CABG with at least one graft from saphenous vein, with or without cardiopulmonary bypass. Patients who fulfill any of the following criteria are ineligible.

- Concomitant cardiac or vascular surgeries (i.e. valve repair or replacement, Maze surgery)
- Redo CABG
- Emergent CABG
- Use of vascular stapler for anastomosis
- Endarterectomy of coronary artery during surgery
- Left ventricular repair due to ventricular aneurysm
- Malignant tumor or other severe systemic diseases
- Severe renal insufficiency (i.e. creatinine >200 μmol/L)
- Contraindications for dual antiplatelet therapy, such as active gastroduodenal ulcer
- Participant of other ongoing clinical trials

Randomization

A web-based central randomization system incorporated in the registration system is used for allocation (http://ccsr.cvs-

china.com/). The randomization code with fixed block size is generated by SAS. Randomization is stratified by investigation center. When an eligible patient gives informed consent, the investigator logs in to the randomization webpage and obtain the random number along with treatment group (No-Touch or Conventional group) automatically distributed by the system after the basic patient information be confirmed. The statistician responsible for the randomization code and the staff who develops the Interactive Web-based Response (IWR) system are independent of each other.

Intervention

Surgical Procedure

Anesthetic technique and method of myocardial protection are left to individual hospitals to decide. All patients undergo either off-pump or on-pump CABG at the surgeon's discretion based on anatomic and clinical findings.

For the No-Touch vein harvesting technique in our institutions, a longitudinal incision is made on bilateral lower legs (unilateral lower leg, thigh or small saphenous vein will be chosen if great saphenous vein quality is judged before the operation or after the skin incision to be too poor for CABG). As previous reported,[16, 17] the adventitia and perivascular tissue are carefully kept intact to avoid damage. Then a margin of about 5 mm from both sides of the vein is created to include the fat pedicle using electrocautery, and all visible side branches are ligated with 4-0 silk or by metal clipping (branches are divided at the pedicle margin rather than the vein trunk). The saphenous vein is then separated from its bed using scissors and electrocautery, together with surrounding tissue. The vein is left in situ and covered with a saline-moistened gauze until systemic heparin is administered and graft anastomosis is ready. After removal, a small adaptor is inserted into the open distal end and secured with a ligature. The pedicled vein is stored in saline solution to which heparin (2500U) and papaverine (30mg) have been added. We use the same storage solution for patients of the No-Touch group and the conventional technique group. Storing the vein grafts in heparinized saline results in similar vein graft occlusion rates compared with storage in heparinized blood.[18] Since heparinized blood cannot be easily obtained during off-pump CABG, we used heparinized saline with papaverine rather than heparinized blood to store vein grafts for patients undergoing either off-pump CABG or on-pump CABG. Forced distension or flushing using a syringe is strictly prohibited. Before each anastomosis, side braches of the vein are checked by the operator and re-clipped. After proximal anastomosis is completed, each graft is re-checked for leakage due to undiscovered branches or invalid clipping and re-clipped if necessary.(Detailed procedure shown in Figure 2)

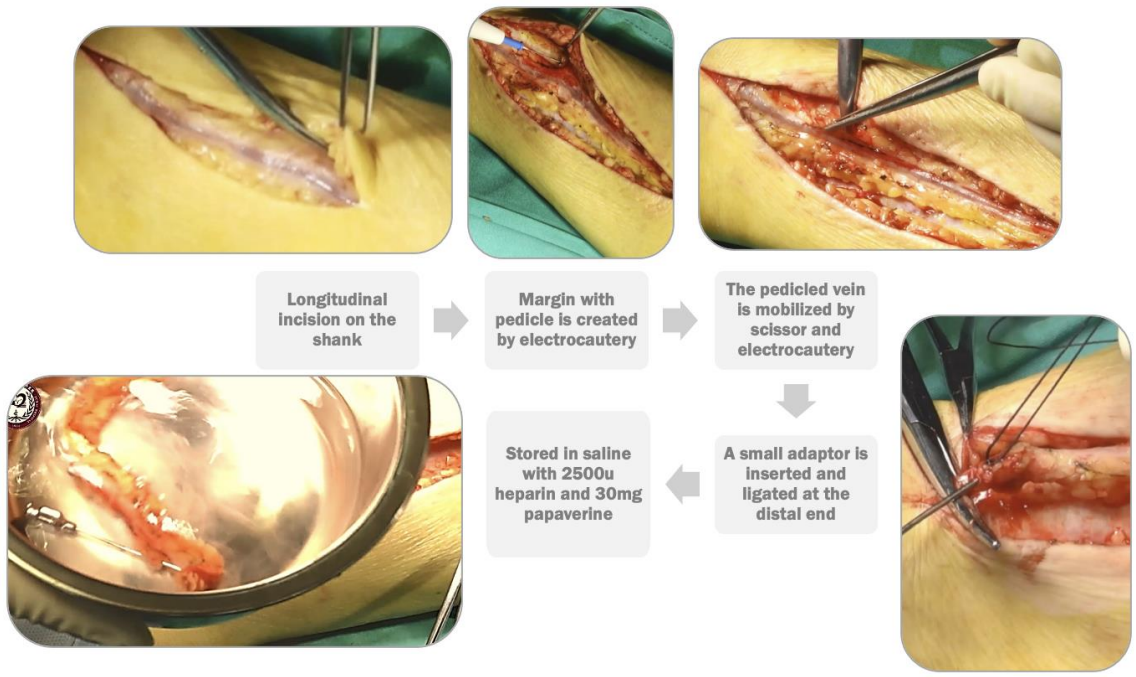

Figure 2. Surgical technique of No-touch saphenous vein harvesting.

For the conventional vein harvesting technique, the incision is the same as in the No-Touch technique. After exposure, the vein is stripped off its adventitia by blunt dissection with scissors. All visible side branches are ligated or clipped. After reaching the needed length, the vein is removed from the distal length, and then a small adaptor is inserted into the open distal end and secured with a ligature. The vein is gently distended by syringe with the storing solution. Remaining unsecured branches are ligated or clipped, and 7-0 polypropylene sutures are made to secure the avulsed branches if necessary.

Leg incisions are closed with continuous suture for both two groups. Remaining coronary bypassing techniques are same in both groups according to clinical practice of the hospital and preference of the operator. Before chest closure, mean flow values and pulsatile index are obtained with transit-time flow measurement (Medi-stim Butterfly flowmeter, Medi-stim AS, Oslo, Norway). If mean flow value is less than 10 ml/min, or pulsatile index greater than 5.0, or any possible graft kinking or compression detected, the anastomosis is redone.

An intraoperative paper questionnaire is answered by the operator after completion of surgery to evaluate the quality of each vein graft. Vein quality is classified as good, moderate, or poor, according to whether there is varicose or aneurysmal dilatation, inflammatory wall thickness, focally thinned wall, or too-small diameter. Although discouraged, exclusion of patients for any other reason is also recorded.

All surgical procedures will be completed by qualified surgeons who have performed at least 100 CABGs. Vein harvesting is performed by qualified senior residents. We identify senior residents who have performed at least 100 cases of vein harvesting in CABG and gave them standard training of No-Touch vein harvesting. When they perform at least 50 cases of No-Touch vein harvesting, they are evaluated by two independent training surgeons to be qualified for vein harvesting. Although ultrasonic mapping is reported to be helpful in preventing unnecessary incision and large skin flaps,[1, 19] it is not widely used in clinical practice in China. According to our experience, well-trained surgeons with sufficient qualifications can harvest the veins with No-Touch technique without ultrasonic mapping. Ultrasonic mapping is not adopted in this study.

Medication

All participants are prescribed dual antiplatelet therapy with aspirin 100mg plus clopidogrel 75mg daily from the first day post-CABG until 3 months post-operation. Prescription of other concomitant medications such as β-blockers, nitrates, statins, and antihypertensive agents is determined by local surgeons according to ACC/AHA guidelines.[9]

Outcome Measurement

Primary outcome

Graft vessel occlusion at 3 months after CABG.

Graft occlusion is detected by multislice computed tomography angiography (MSCTA). Graft assessment is conducted according to the FitzGibbon criteria.[20] Each graft is graded as A (excellent), B (fair), or O (occluded). Contrast filling of the grafts, anastomoses, and coronary arteries beyond the graft are considered in each assessment. Grade A indicates that the graft is patent with ≤50% stenosis. Grade B indicates that graft stenosis is >50% but not occluded. When a conduit does not fill with contrast at all, it is considered Grade O and included with string sign found in any segment (including proximal anastomotic site, distal anastomotic site, and main trunk). Both latter findings are considered together and referred to as occlusion in the analysis.

Secondary outcomes

1. Graft vessel occlusion at 1 year after the CABG (determined by MSCTA).
2. Major adverse cardiac or cerebrovascular events (MACCE, including all-cause death, non-fatal myocardial infarction, stroke and target vessel revascularization) at 3 months and 1 year after the CABG.
3. Individual MACCE, including all-cause death, cardiovascular death, non-fatal myocardial infarction, stroke and target vessel revascularization at 3 months and 1 year after surgery.
4. Recurrence of angina

Safety outcomes

Leg wound complication during the 3-month and 12-month follow-up.

All clinical events including myocardial infarction, stroke, target lesion revascularization, and death will undergo central adjudication by an independent clinical events committee (CEC) according to pre-specified criteria (Appendix 1). All participants will be followed up yearly for 10 years to assess the long-term graft occlusion and clinical outcomes.

Participant timeline

	STUDY PERIOD					
	Enrolment	**Allocation**	**Post-allocation**			**Close-out**
TIMEPOINT**	***1 day pre-operatively***	**0**	***6 days after surgery***	***3 months after surgery***	***12 months after surgery***	***01 September 2020***
ENROLMENT:						
Eligibility screen	X					
Informed consent	X					
Allocation		X				
INTERVENTIONS:						
No-touch Group			♦———	———	———♦	

Conventional Group			◆———	———	———◆	
ASSESSMENTS:						
Basic information, risk factors, presentation of CAD diseases, laboratory tests before and after surgery, angiographic findings, general information of surgery, in-hospital outcomes, pre-operative medications	X	X				
Leg wound condition 6 days after surgery			X			X
CT Graft occlusion Clinical events Leg wound condition 3 months after surgery 3-month and 12-month			X	X	X	X

Figure 3. Participant timeline of the study

Data collection

A web-based and paperless data submission system (http://ccsr.cvs-china.com) for the No-Touch study has been established. A total of 7 hospitals are participating in the study and each has been granted access to the data submission system. For web-data transmission, a high level secure socket layer is adopted. For in-hospital data collection, 12 modules have been set (preoperative saphenous vein screening, patient basic information, preoperative risk factors, cardiovascular presentation, tests and examinations, general information of operation, record of CABG, post-operative complications, preoperative medications, medication prescriptions at discharge, 3-month follow-up results and 12-month follow-up results) with over 300 items. We collect relevant anatomical characteristics, e.g., sites of proximal and distal anastomosis, graft type and quality, proximal lesion stenosis rate, graft flow and pulsation index, application of sequential anastomosis. As to sequential anastomosis, one failure of distal anastomosis will be considered occlusion of the sequential graft. Particularly, as we routinely harvest saphenous veins from bilateral lower legs, there is a concern that risk of surgical-site infection will increase due to larger skin flaps caused by this technique.[21] Therefore, another postoperative questionnaire regarding leg wound condition is filled before patient discharge and during follow-up visit. Content of the data collection is given in Table 1. Visual Analogue Scale[22] is employed for evaluation of leg pain, and any wound healing disturbances including both non-infectious leg wound complications and infection are recorded.[23] Coordinators and investigators are required to submit complete in-hospital data within 14 days of discharge. The No-Touch study adheres to a rigorous standard for medical record transmission and data abstraction, similar to the previously published China Patient-Centered Evaluative Assessment of Cardiac Events (China PEACE)-Retrospective Acute Myocardial Infarction Study and the Percutaneous Coronary Intervention Study.[24, 25]

Table 1. Data collection content

Dataset	Major Content

General in-hospital Data	Basic information, risk factors, presentation of CAD diseases, laboratory tests before and after surgery, angiographic findings, general information of surgery, in-hospital outcomes, pre-operative medications, and prescriptions at discharge
Surgery record	Number of distal and proximal anastomosis; (For each graft) original lesion site, original proximal stenosis, position of proximal anastomosis, graft type, position of distal anastomosis, whether sequential anastomosis, distal runoff, transient time flow, pulsatile index
Intraoperative Graft Quality Assessment	Quality of each graft material assessed by surgeon
Postoperative Leg Wound Healing Assessment	Leg wound condition before discharge
3-month and 12-month Follow-up data	CT angiographic assessment of each graft MACCEs *Survival status (date and cause of death), re-hospitalization, non-fetal myocardial infarction, stroke, revascularization* Recurrence of angina Medication since last visit Leg wound healing status *Persistent pain and scale, lower limb numbness, requiring re-suture* Other events of clinical significance

All participants will be followed-up by clinic visits. The follow-up schedule is shown in Table 2 . Study coordinators will telephone participants to remind them of the scheduled date of return to the hospital. The 2000 randomized patients will undergo predefined clinical follow-up at 3 months and 12 months post-procedure. MSCTA are to be performed, and image discs from all participating hospitals are collected and assessed by a central Core Laboratory. The results of MSCTA are independently reviewed by 2 radiologists blinded to patients' randomized allocation. Discrepancies in occlusion judgement are reviewed by a third radiologist and resolved by consensus. According to our procedural preference, the saphenous veins will be harvested from both shanks if more than one SVG is required. As randomization is per patient, harvesting technique must be consistent for all SVGs of the same patient. Outcomes will be determined both at patient-level and per-graft level. At each follow-up visit, all current medications and events since the last visit are recorded and compared between the two groups. We collect the information of both surgeons of CABG and vein harvesting residents. Surgeon-specific and site-specific outcomes will be considered in exploratory analyses. In order to assess the long-term efficacy of the No-Touch technique, we will continue to follow-up these patients at 5 years and 10 years postoperatively.

Table 2. Follow-up schedule

	Pre-op	**Intra-op**	**6th day Post-op**	**3-month clinic visit (+1m)**	**12-month clinic visit (+3m)**

Baseline characteristics	√					
Clinical history	√					
Physical exam	√				√	√
Medications	√			√	√	√
Operation details		√				
Graft quality assessment		√				
CT angiography					√	√
Clinical events					√	√
Leg wound assessment				√	√	√

Sample size and statistical analysis plan

According to our published work, the vein graft occlusion rate is 8.4% in the conventional harvesting group.[14] A previous trial showed that No-Touch would reduce vein graft occlusion rate by 58.6%.[1] We assume a more conservative effect of 43% relative risk reduction. A trial of 2,600 participants would have 90% power at 2P<0.05 to detect a 43% relative risk reduction with 1% drop-out rate. The allocation rate is 1:1. The study originally planned to enroll 1500 on-pump CABG patients from 7 hospitals. Considering that both on-pump and off-pump CABG are widely used in clinical practice, the study group decided to include patients undergoing both off-pump and on-pump procedures to achieve better generalizability of the results. And the sample size was increased to 2000 so that the study is sufficiently powered to detect a more conservative effect of reducing occlusion. This sample size amendment was under the blinding manner and had no effect on type I error of the study.

The trial data will be analyzed on an intention-to-treat basis with patients included in the groups assigned at randomization, irrespective of future management and events. Subgroup analysis will also be performed according to the actual harvesting technique a patient receives, (e.g., crossover from No-Touch to conventional approach). Demographic and clinical variables will be summarized as means (SDs) for continuous and counts (percentages) for categorical variables. Comparisons across the groups will be performed using a 2-tailed unpaired t test for continuous variables and the Pearson's chi-squared test for categorical variables. Cochran Mantel-Haenszel chi-squared test will be used for the primary endpoint. A generalized linear model with the general estimate equation will be used to estimate treatment effects for the graft level analysis in order to account for the cluster effect of grafts from same patient. Patient-level analysis will also be performed to compare in-hospital death, postoperative complications, follow-up death and MACCE. A P value of less than 0.05 will be considered as statistically significant for all analyses.

According to our practice experience and previous literature, we estimate the cross-over rate to range from 1% to 5%, mainly from the No-Touch group to the conventional group. Thus, we consider the effect of cross-over to be minor. Given variations in the quality of vein grafts, an intraoperative questionnaire for evaluation of the graft quality is required to be answered by the operator immediately after completion of the surgery. Graft quality is stratified as good, moderate, or poor, according to the presence of side branch tears, inflammatory wall thickness, or signs of varicosity.[26] Subgroup analysis will be performed regarding different graft qualities and target vessel runoffs. Use of extracorporeal circulation will also be analyzed as subgroups, using tests for interactions. A variation in graft occlusion differences between the on/off pump subgroups is not expected. Postoperative and follow-up leg wound healing disturbance will also be compared between the two harvesting approaches according to records collected by the questionnaire mentioned above.

Data Monitoring and Interim Analysis

An independent data safety monitoring board (DSMB) (Table 3) is established before the start of recruitment. Only one interim analysis will be carried out (when 50% of subject finish their scheduled follow-up) according to the DSMB

charter. The DSMB review will focus on safety issues. There is no pre-specified stopping rule regarding the primary efficacy endpoint, so there is no need to adjust the type I error rate. The DSMB members will suggest whether the study should be stopped due to unexpected risk for patients. If the safety signal is acceptable, the study will continue to the planned recruitment number and data analysis will be based on the entire population.

Table 3. Data Safety Monitoring Board membership

Name	Role	Title	Affiliation
Professor Hansong Sun	Chairman	Professor of cardiovascular surgery	Fuwai Hospital
Professor Jing Li	Vice-chairman	Director of Clinical Trial Center	Fuwai Hospital
Professor Jian Zhang	Vice-chairman	Consultant Cardiologist	Fuwai Hospital
Professor Wei Li	Statistician	Director of Medical Research & Biometrics Center	Fuwai Hospital

Clinical Events Committee

All clinical events including myocardial infarction, stroke, target lesion revascularization, and death will undergo central adjudication by an independent clinical events committee (CEC) according to pre-specified criteria (Appendix 1).

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Appendix 1. Definitions for clinical outcomes used in adjudication

1. Non-fatal myocardial infraction

Documented non-fetal myocardial infraction is defined according to Diagnostic criteria for myocardial infarction with CABG of the Third Universal Definition of Myocardial Infarction, which is an elevation of cardiac troponin values with at least one value above the 99th percentile upper reference limit, plus evidence of myocardial necrosis:

> *cTn values>10 x 99th percentile URL during the first 48 h following CABG, occurring from a normal baseline cTn value (>99th percentile URL). In addition, either (i) new pathological Q waves or new left bundle branch block, or (ii) angiographically documented new graft or new native coronary artery occlusion, or (iii) imaging evidence of new loss of viable myocardium or new regional wall motion abnormality, should be considered as diagnostic.*

2. Angina

Events that fulfill the following definition are to be coded as Angina:

i. ischemic chest pain or equivalent (e.g. arm, neck or jaw pain or discomfort thought to be related to cardiac ischemia); and
ii. no evidence of MI; and
iii. no clear alternative (non-cardiac) explanation (e.g. anemia, arrhythmia)

3. Revascularization

i. Coronary revascularization includes coronary artery grafting or angioplasty (with or without endovascular stenting), as well as other percutaneous coronary interventions designed to treat coronary artery lesions (e.g. atherectomy, embolectomy).
ii. Non-coronary revascularization includes percutaneous arterial interventions, surgical revascularization procedures, and amputation for presumed vascular disease.

4. Stroke

Stroke is defined as an acute symptomatic episode of focal or global neurological dysfunction caused by brain, spinal, or retinal vascular injury as a result of hemorrhage or infarction.

Appendix 2. Study investigators

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