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One-month DAPT with ticagrelor and aspirin for patients undergoing coronary artery bypass grafting: rationale and design of the randomised, multicentre, double-blind, placebo-controlled ODIN trial

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ABSTRACT

The optimal antiplatelet strategy after coronary artery bypass graft (CABG) surgery in patients with chronic coronary syndromes (CCS) is unclear. Adding the $P2Y_{12}$ inhibitor, ticagrelor, to low-dose aspirin for 1 year is associated with a reduction in graft failure, particularly saphenous vein grafts, at the expense of an increased risk of clinically important bleeding. As the risk of thrombotic graft failure and ischaemic events is highest early after CABG surgery, a better risk-to-benefit profile may be attained with short-term dual antiplatelet therapy followed by single antiplatelet therapy. The One Month Dual Antiplatelet Therapy With Ticagrelor in Coronary Artery Bypass Graft Patients (ODIN) trial is a prospective, randomised, double-blind, placebo-controlled, international, multicentre study of 700 subjects that will evaluate the effect of short-term dual antiplatelet therapy with ticagrelor plus low-dose aspirin after CABG in patients with CCS. Patients will be randomised 1:1 to ticagrelor 90 mg twice daily or matching placebo, in addition to aspirin 75-150 mg once daily for 1 month; after the first month, antiplatelet therapy will be continued with aspirin alone. The primary endpoint is a hierarchical composite of all-cause death, stroke, myocardial infarction, revascularisation and graft failure at 1 year. The key secondary endpoint is a hierarchical composite of all-cause death, stroke, myocardial infarction, Bleeding Academic Research Consortium (BARC) type 3 bleeding, revascularisation and graft failure at 1 year (net clinical benefit). ODIN will report whether the addition of ticagrelor to low-dose aspirin for 1 month after CABG reduces ischaemic events and provides a net clinical benefit in patients with CCS. (ClinicalTrials.gov: NCT05997693)

KEYWORDS: adjunctive pharmacotherapy; multiple vessel disease; stable angina

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The majority of patients undergoing coronary artery bypass graft (CABG) surgery present with chronic coronary syndromes (CCS)[1]. Saphenous vein grafts (SVG) are used in approximately 90% of CABG procedures[2]. Aspirin (acetyl salicylic acid [ASA]) is the standard of care after CABG to reduce SVG occlusion and adverse cardiovascular events. Although dual antiplatelet therapy (DAPT) with a $P2Y_{12}$ inhibitor in addition to ASA is recommended in patients undergoing CABG for acute coronary syndromes (ACS)[3], the role of DAPT in patients with CCS undergoing CABG is unclear.

In an individual patient-data meta-analysis of all randomised clinical trials (RCTs) comparing ticagrelor DAPT with ASA after CABG, ticagrelor DAPT – with a median treatment duration of 12 months – was associated with a significantly lower incidence of SVG failure (11.2% vs 20%; odds ratio [OR] 0.51, 95% confidence interval [CI]: 0.35-0.74; p<0.001), a finding that was consistent across subgroups, including patients with CCS[4]. Ticagrelor DAPT was also associated with a significant reduction of the composite of SVG failure or cardiovascular death (13.9% vs 23.4%, OR 0.52, 95% CI: 0.36-0.76; p<0.001). However, these benefits were accompanied by a significantly increased risk of clinically important bleeding events (defined as Bleeding Academic Research Consortium[5] [BARC] type 2, 3, or 5): 22.1% for ticagrelor DAPT versus 8.7% for ASA (OR 2.98, 95% CI: 1.99-4.47; p<0.001). These findings underscore the need for post-CABG antiplatelet regimens that reduce bleeding risk while preserving efficacy against ischaemic events.

Thrombosis is the predominant mechanism of early SVG failure and typically occurs during the first month after surgery[6,7]. Graft thrombosis is driven by platelet activation and aggregation[8]. The pathophysiology of SVG failure provides a biological rationale for intensified antiplatelet therapy in the first month after CABG. In fact, despite the use of ASA, approximately 10-15% of SVG fail early after surgery[7], and graft failure is associated with adverse cardiac events and death[9,10]. Data from contemporary CABG trials show that the rate of ischaemic events is highest in the first month after CABG and decreases markedly thereafter, remaining at a constantly lower rate for up to 5 years after surgery[11-15]. A short-term intensified antiplatelet regimen therefore seems biologically and clinically justified.

In the PEGASUS and THEMIS trials which tested ticagrelor DAPT versus aspirin alone in patients with CCS and high-risk coronary artery disease, bleeding events accrued at a near-constant rate during follow-up, and the excess bleeding risk with ticagrelor DAPT remained stable over time with a hazard ratio >2.0[16-18]. This suggests that the increased risk of bleeding with ticagrelor DAPT is related to the duration of treatment, and when DAPT is used for ≥12 months, the excess bleeding risk may partially offset the ischaemic benefit. This further strengthens the rationale for a short-term, intensified antiplatelet regimen to balance the ischaemic benefit with the bleeding risk.

Several recent RCTs have shown the benefit of a shorter duration of DAPT in stable patients after percutaneous coronary intervention (PCI) with drug-eluting stents avoiding exposing patients to long-term bleeding risks[19]. A short-term intensified antiplatelet regimen after CABG is consistent with contemporary PCI practice of limiting the duration of DAPT to the postprocedural period during which endothelialisation of the stent occurs.

Methods

ODIN TRIAL DESIGN

STUDY OBJECTIVES

The primary objective of the One Month Dual Antiplatelet Therapy With Ticagrelor in Coronary Artery Bypass Graft Patients (ODIN) trial is to compare the effects of treatment with ticagrelor versus with placebo, in addition to low-dose ASA for 1 month, on the 1-year incidence of ischaemic events and graft failure among patients with CCS undergoing CABG. The secondary objective is to determine the net clinical benefit of short-term ticagrelor versus placebo, in addition to low-dose ASA.

STUDY DESIGN

The ODIN trial (ClinicalTrials.gov: NCT05997693) is an investigator-initiated, prospective, randomised, double-blind, placebo-controlled, international, multicentre trial of 700 subjects at approximately 20 study centres in 6 countries. Eligible patients will be enrolled before CABG and randomised (1:1) after surgery to receive ticagrelor 90 mg twice daily or placebo, in addition to low-dose ASA for 1 month. Follow-up for all randomised subjects includes the assessment of graft status by coronary computed tomography angiography (CCTA) at 1 year, and follow-up will continue for 5 years with an option for additional follow-up for up to 10 years. The study design is shown in **Figure 1**.

ENROLMENT AND RANDOMISATION

The inclusion and exclusion criteria are shown in **Table 1**. Patients will be screened for inclusion and enrolled before CABG but will be randomised after surgery to ensure that all eligibility criteria are met. Randomisation will be performed within 48 hours of CABG, when – based on the surgeon's evaluation – there is minimal bleeding risk. Randomisation after surgery will increase the likelihood that patients receive the randomised treatment and reduce the risk of protocol violation due to perioperative complications. Randomisation after CABG also allows for assessment of heterogeneity of the treatment effect according to how soon after CABG ticagrelor can be initiated. Eligible patients will be randomised

Abbreviations

ACS	acute coronary syndromes	**CCTA**	coronary computed tomography angiography	**PCI**	percutaneous coronary intervention
ASA	acetyl salicylic acid	**DAPT**	dual antiplatelet therapy	**QoL**	quality of life
BARC	Bleeding Academic Research Consortium	**ITT**	intention-to-treat	**RCT**	randomised clinical trial
CABG	coronary artery bypass graft	**MI**	myocardial infarction	**SVG**	saphenous vein graft
CCS	chronic coronary syndromes				

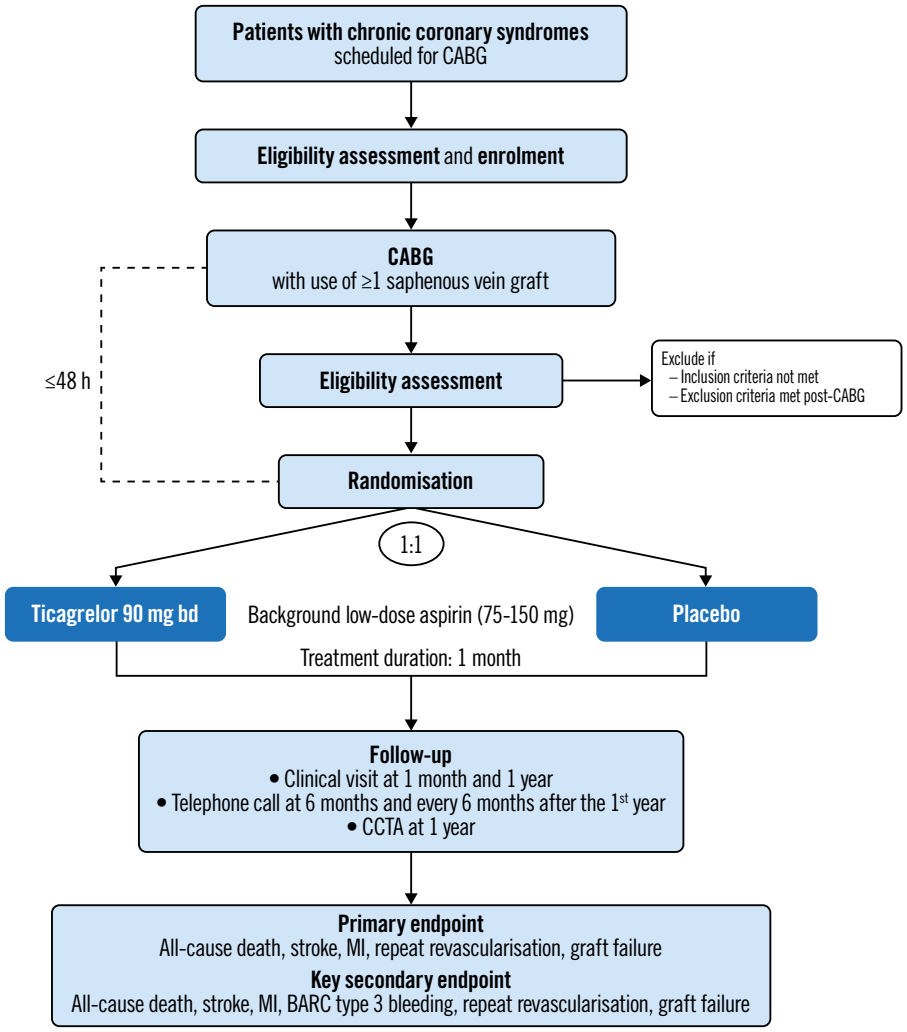

Figure 1. *Study flowchart. BARC: Bleeding Academic Research Consortium; bd: twice daily; CABG: coronary artery bypass grafting; CCTA: coronary computed tomography angiography; MI: myocardial infarction*

(1:1) to ticagrelor or placebo through a centrally controlled, automated web system using permuted block randomisation stratified by study centre and the number of grafts (2 vs ≥3 grafts).

TREATMENT PROTOCOL

The ticagrelor dose (90 mg twice daily) is the dose that has been evaluated in prior RCTs of ticagrelor after CABG[4,11]. The efficacy and safety of the 90 mg twice-daily dose was established in the PLATelet Inhibition and Patient Outcomes (PLATO) Study[20], including the subgroup of patients undergoing CABG[21]. The initial dose will be administered after randomisation, and a loading dose is recommended. Subsequent maintenance doses will consist of one tablet of active ticagrelor or matching placebo twice daily. The duration of treatment with the study medication for an individual patient will be 1 month. Patients will receive a drug diary in which each study drug dose will be recorded to assess compliance.

All patients will take background open-label low-dose (75-150 mg once daily) ASA administered ideally within 6 hours (and no later than 24 hours) after CABG, consistent with guideline recommendations and dosing labels for ticagrelor.

The use of additional antithrombotic therapy, including other $P2Y_{12}$ receptor inhibitors and oral anticoagulants, will not be allowed prior to randomisation or for the duration of treatment with the study medication.

All patients will receive secondary preventive measures, including lifestyle modifications and pharmacotherapy, consistent with guideline recommendations[22,23].

FOLLOW-UP

Randomised patients will return for study visits at 1 month (+14 days) and 1 year (+60 days) **(Figure 1)**. Telephone calls are scheduled at 6 months, and at 6-month intervals after the first year for 5 years. Follow-up may be continued annually for up to 10 years, and patients are preconsented for this option. At each follow-up visit, patients will be assessed for adverse events and potential endpoint events. All patients will undergo CCTA at 1 year for the assessment of graft status by blinded readers, based on Society of Cardiovascular Computed Tomography (SCCT) guidelines[24]. To protect against inflation of revascularisation rates, clinical sites will remain blinded to data. Details of the CCTA analysis are provided in **Supplementary Appendix 1**.

Table 1. Inclusion and exclusion criteria.

Inclusion criteria	Exclusion criteria
1. Age ≥18 years	1. Any indication for dual antiplatelet therapy, including
2. Elective first-time CABG with use of ≥1 saphenous vein graft	• acute/recent (within 1 year) ACS (NSTE-ACS or STEMI)
3. Ability to sign informed consent and comply with all study procedures, including follow-up for at least 5 years	• recent PCI requiring continuation of dual antiplatelet therapy after CABG
	2. Current or anticipated use of oral anticoagulation
	3. Paroxysmal, persistent or permanent atrial fibrillation
	4. Any concomitant cardiac or non-cardiac procedure
	5. Planned cardiac or non-cardiac surgery within 1 year
	6. Preoperative end-organ dysfunction (dialysis, moderate to severe liver failure, respiratory failure), cancer or other non-cardiac comorbidity with a life expectancy <5 years
	7. Inability to use the saphenous vein
	8. Contraindications to the use of aspirin
	9. Contraindications to the use of ticagrelor, including
	• known hypersensitivity to ticagrelor
	• active pathological bleeding (including but not limited to gastrointestinal or intracranial bleeding)
	• history of intracranial haemorrhage
	• concomitant therapy with strong CYP3A4 inhibitors (e.g., ketoconazole, clarithromycin, nefazodone, ritonavir, atazanavir)
	10. Inability to undergo CCTA
	11. Participation in another investigational device or drug study
	12. Women of childbearing potential
	13. Any major perioperative complication occurring between CABG and randomisation, including, but not limited to, stroke, TIA, MI, CABG-related bleeding (BARC type 4), sepsis

ACS: acute coronary syndrome; BARC: Bleeding Academic Research Consortium; CABG: coronary artery bypass graft; CCTA: computed coronary tomography angiography; MI: myocardial infarction; NSTE-ACS: non-ST-elevation acute coronary syndrome; PCI: percutaneous coronary intervention; STEMI: ST-segment elevation myocardial infarction; TIA: transient ischaemic attack

ENDPOINTS

The primary endpoint of the trial is the 1-year hierarchical composite of all-cause death, stroke, myocardial infarction (MI), repeat revascularisation and any graft failure **(Table 2)**. The primary endpoint addresses the question of whether 1-month ticagrelor DAPT reduces the risk of ischaemic events and graft failure in the first year after CABG. The key secondary endpoint is the 1-year hierarchical composite of all-cause death, stroke, MI, BARC type 3 bleeding, repeat revascularisation and any graft failure. The key secondary endpoint includes a safety endpoint (BARC major bleeding) and provides an estimate for the 1-year net clinical benefit of 1-month ticagrelor DAPT **(Table 2)**. The hierarchical nature of the composite endpoints accounts for the different clinical priority of the individual endpoint components. Two powered secondary endpoints are prespecified and will evaluate the 5-year effects of 1-month ticagrelor DAPT on clinically important endpoints, quality of life (QoL), and the 5-year net clinical benefit. Endpoints are listed in **Table 2**. The definitions of the primary and secondary endpoints are shown in **Supplementary Table 1**.

QUALITY OF LIFE AND HEALTH ECONOMICS

QoL will be evaluated using both disease-specific and generic instruments. The 7-item Seattle Angina Questionnaire (SAQ) is a validated disease-specific instrument for assessing the health status of patients with coronary artery disease and is a component of the patient-centric powered 5-year secondary endpoints[25,26]. Generic health status using the Medical Outcomes Study 12-item Short Form (SF-12) will also be assessed over the course of follow-up. These measures will be assessed at baseline (prior to randomisation), 1 month, 6 months, 1 year, and annually thereafter until 5 years after surgery.

An economic analysis will be performed from a US perspective. If the intervention is cost-saving or cost neutral, no additional analysis will be performed[27]. However, if the mean cost per patient in the intervention group exceeds that in the placebo group, a cost-effectiveness analysis will be performed using in-trial survival data and SF-12 scores mapped to EuroQol-5D utility values[28] and expressed as cost per quality-adjusted life years.

STATISTICAL CONSIDERATIONS AND SAMPLE SIZE

The main analysis for the primary and secondary endpoints will be performed in the intention-to-treat (ITT) population, defined as all randomised subjects, irrespective of protocol adherence or the duration of exposure to study treatment. Sensitivity analyses will be performed in the modified ITT

Table 2. Endpoints.

Primary and key secondary endpoints (assessed at 1-year follow-up)
Primary endpoint
• Hierarchical composite of all-cause death, stroke, MI, repeat revascularisation and any graft failure
Key secondary endpoint
• Hierarchical composite of all-cause death, stroke, MI, BARC type 3 bleeding, repeat revascularisation and any graft failure
Secondary endpoints (assessed at 5-year follow-up)
1. Hierarchical composite of all-cause death, stroke, MI, repeat revascularisation, and 5-year time-averaged[a] disease-specific QoL score
2. Hierarchical composite of all-cause death, stroke, MI, BARC type 3 bleeding, repeat revascularisation, and 5-year time-averaged[a] disease-specific QoL score
Exploratory endpoints
Assessed at 1 month:
• BARC ≥type 2 bleeding
• BARC ≥type 3 bleeding
• Generic and disease-specific QoL
Assessed at 1 year:
• Any graft failure (patient and graft level)
• Any vein graft failure (patient and graft level)
• Any arterial graft failure (patient and graft level)
Assessed at 1 year and then annually for 5 years:
• Composite of death, stroke, MI or repeat revascularisation
• Composite of death, stroke, MI, BARC type 3 bleeding or repeat revascularisation
• All-cause death
• Cardiovascular death
• Stroke
• MI
• Repeat revascularisation
• BARC ≥type 2 bleeding
• BARC ≥type 3 bleeding
• Generic and disease-specific QoL

[a] Defined as time-averaged QoL over 5 years (or the shared duration of follow-up if follow-up for either patient is <5 years in a given pairwise comparison), based on QoL assessments at 1, 6, 12, 24, 36, 48, and 60 months. All endpoints are adjudicated by an independent clinical events adjudication committee. BARC: Bleeding Academic Research Consortium; MI: myocardial infarction; QoL: quality of life

population, defined as the subset of the ITT population that received at least one dose of randomly assigned study medication.

The primary, key secondary and 5-year secondary endpoints are hierarchical composite endpoints and will each be compared between groups using the win ratio method[29] and the joint rank test proposed by Finkelstein and Schoenfeld. The prespecified hierarchies for each endpoint are shown in **Supplementary Table 2**. Sequential endpoint testing of the primary, key secondary and 5-year secondary endpoints will be employed to preserve type I error.

The primary and key secondary endpoints will also be analysed using Finkelstein-Schoenfeld statistics in the following prespecified subgroups: age (≥ vs <65 years), sex, diabetes mellitus, left ventricular ejection fraction (< vs ≥50%), SYNTAX score (≥ vs <32), complete versus incomplete revascularisation, number of vein grafts, number of arterial grafts, total number of grafts, off- versus on-pump CABG, SVG harvesting technique (endoscopic vs open), bleeding risk (Academic Research Consortium for High Bleeding Risk criteria[30] and PRECISE-DAPT score), and gender (according to self-identified gender category at randomisation and gender score [≥ vs <median]).

SAMPLE SIZE

Event rate assumptions for endpoint components were based on event rates in contemporary CABG RCTs and an individual patient-data meta-analysis of RCTs investigating the association of ticagrelor DAPT with SVG failure **(Supplementary Table 3)**. With a sample size of 700 patients, the trial has 87.6%, 83.4%, 90.0% and 86.1% power to show superiority of ticagrelor versus placebo for the primary endpoint, key secondary endpoint, and 5-year secondary endpoints, assuming a yearly combined rate of all-cause death, stroke, MI and repeat revascularisation of 7.0% in the placebo group and 5.6% in the ticagrelor group (corresponding to a relative risk reduction [RRR] of 20%); an incidence of graft failure at 1 year of 24.8% in the placebo group and 14.3% in the ticagrelor group (corresponding to an RRR of 42%); 1-month BARC type 3 bleeding rates of 1.2% in the placebo group and 1.5% in the ticagrelor group (corresponding to a relative risk increase of 25%), and a BARC type 3 bleeding rate of 0.7% in both groups between 1 month and 1 year; a difference in the time-averaged SAQ-7 overall summary score of 5 points; loss to follow-up of 2.5% per year; missing data on graft status at 1 year for 7.5% of event-free patients (i.e., patients without death, stroke, MI or repeat revascularisation within 1 year); and a 2-sided significance level of 0.05. A decision on increasing the sample size will be made based on a blinded interim review of aggregate data for the primary endpoint after approximately 80% (n=560) of subjects have been enrolled.

TRIAL ORGANISATION AND FUNDING

The study is coordinated by the principal investigators and the Weill Cornell Medicine Joint Clinical Trials Office. An independent data safety monitoring board will monitor the trial. The ODIN trial will be funded by the Canadian Institutes of Health Research from 2023 to 2030.

REPORTING OF TRIAL RESULTS

The primary and key secondary endpoints, as well as exploratory endpoints at 1 month and 1 year, will be reported in a primary publication. The powered 5-year secondary endpoints, as well as exploratory endpoints up to 5 years, will be reported in a subsequent publication.

Conclusions

ODIN will report whether the addition of ticagrelor to low-dose ASA for 1 month after CABG reduces ischaemic events and provides a net clinical benefit in patients with CCS.

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Conflict of interest statement

D.J. Angiolillo has received consulting fees or honoraria from Abbott, Amgen, AstraZeneca, Bayer, Biosensors, Boehringer Ingelheim, Bristol-Myers Squibb, Chiesi, CSL Behring, Daiichi Sankyo, Eli Lilly, Haemonetics, Janssen, Merck, Novartis, PhaseBio, PLx Pharma, Pfizer, Sanofi, and Vectura; his institution has received research grants from Amgen, AstraZeneca, Bayer, Biosensors, CeloNova (now Alta Biomaterials), CSL Behring, Daiichi Sankyo, Eisai, Eli Lilly, Gilead Sciences, Idorsia, Janssen, Matsutani Chemical Industry Co., Merck, Novartis, and the Scott R. MacKenzie Foundation. D.L. Bhatt has had advisory board roles with ANGIOWave, Bayer, Boehringer Ingelheim, Cardax, CellProthera, Cereno Scientific, Elsevier, High Enroll, Janssen, Level Ex, McKinsey & Company, Medscape Cardiology, Merck, MyoKardia, NirvaMed, Novo Nordisk, PhaseBio, PLx Pharma, Regado Biosciences, and Stasys; he has held board of directors' positions with ANGIOWave (stock options), Boston VA Research Institute, Bristol-Myers Squibb (stock), DRS.LINQ (stock options), High Enroll (stock), Society of Cardiovascular Patient Care, and TobeSoft; he has held Chair roles including inaugural Chair for American Heart Association Quality Oversight Committee; he has held consultant roles with Broadview Ventures, and Hims; and has been on data monitoring committees, including for Acesion Pharma, Assistance Publique-Hôpitaux de Paris, Baim Institute for Clinical Research, Boston Scientific, Cleveland Clinic, Contego Medical, Duke Clinical Research Institute, Mayo Clinic, Mount Sinai School of Medicine, Novartis, Population Health Research Institute, and Rutgers University; and has received honoraria from various organisations; he has also held other roles with Clinical Cardiology, NCDR-ACTION Registry Steering Committee, and VA CART Research and Publications Committee; he has held a patent for Sotagliflozin; he has received research funding from numerous entities, including AstraZeneca; he has received royalties from Elsevier; he has been a site co-investigator for multiple companies; he has been a trustee for the American College of Cardiology; and he has carried out unfunded research with FlowCo and Takeda. S.E. Fremes has received grant support from CIHR, NIH, Medtronic, Boston Scientific, and Amgen. S.V. Rao has received research funding from NHLBI. J.A. Spertus has provided consultancy services to Alnylam, AstraZeneca, Bayer, Merck, Janssen, Bristol-Myers Squibb, Edwards Lifesciences, Kineksia, 4D Medical, Terumo, Cytokinetics, Imbria, and UnitedHealthcare; he has received research grants from Bristol-Myers Squibb, Abbott, and Janssen; he has held ownership of copyrights to the Seattle Angina Questionnaire, Kansas City Cardiomyopathy Questionnaire, and Peripheral Artery Questionnaire; and he has been on the board of directors for Blue Cross Blue Shield of Kansas City. The other authors have no conflicts of interest to declare.

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Supplementary data

Supplementary Appendix 1. Cardiac computed tomography angiography (CCTA) protocol.

Supplementary Table 1. Primary and secondary endpoint definitions.

Supplementary Table 2. Hierarchical order of endpoint analyses.

Supplementary Table 3. Incidence of endpoints in contemporary randomised clinical trials.

The supplementary data are published online at: https://eurointervention.pcronline.com/doi/10.4244/EIJ-D-23-00699

Supplementary data

Supplementary Appendix 1. Cardiac computed tomography angiography (CCTA) protocol.

Each patient will undergo a single cardiac computed tomography angiography (CCTA) at one-year post-surgery. Details of the computed tomography (CT) scanner used, medications used during the CCTA, heart rate, contrast type and dose, radiation dose, electrocardiogram (ECG) gating techniques and any complications due to the CCTA will be recorded. The CCTA produces high-resolution images of the bypass grafts used to characterize the location and severity of luminal obstruction based on changes in luminal diameter (i.e., graft stenosis). Requirements are a ≥64-slice CT scanner, slice thickness (ST) of 0.6-0.75 mm with or without 50% overlap reconstruction increment (RI) depending on scanner type, field of view (FOV) of <25cm, matrix of 512x512, with a medium convoluted kernel, in addition to optimized heart-rate (HR) and nitrates in order to maintain consistency with established CCTA acquisition standards. CCTA scans will be labelled with site-specific subject ID's and have patient identifiers removed by sites in accordance with local data use policies. CCTA scans will be electronically transferred through a secure web-based connection to pre-specified study investigators with dedicated expertise in CCTA who will be responsible for CT analyses for ODIN trial purposes. Readers, blinded to patient identifiers, will perform reads of the CCTAs for image quality and graft patency/stenosis severity using Society of Cardiovascular Computed Tomography (SCCT) guidelines. Evaluation will be performed on a per-segment basis (proximal anastomosis/origin, proximal graft, mid graft, distal graft, distal anastomosis).

Sites will be responsible for reporting of the non-coronary/bypass graft findings as per standard of care by their local institution for safety concerns of the patient if urgent or emergent non-cardiac findings were present. However, to protect against inflation of revascularization rates should graft data be seen by site, all coronary/bypass graft data will remain blinded to the sites.

1. Equipment: CCTA imaging will be performed using ≥64-slice CT scanner technology according to the vendor specific protocol used at participating sites. Since vendor specific differences for cardiac CT scan protocols are variable depending on scanner type, all scan protocols must be approved by the ODIN Core Lab prior to the CT enrollment period by requiring submission and approval of one test bypass graft CCTA case.

2. Image Acquisition: Sites will be allowed to use their own local CABG protocols for CCTA. If institutional standard does not exist, we recommend the below protocols. Image acquisition takes ~15-20 minutes. However, preparation for adequate HR is needed and typically requires oral or intravenous HR-lowering medications (e.g., metoprolol or diltiazem) prior to the exam. Recommended HR-lowering medication protocols are in **Table 1.** Less aggressive HR-lowering is needed (goal HR<70, preferably <65 beats per minute [bpm]) with newer generation dual-source and wide detector volumetric scanners (**Table 1A**), while more aggressive HR-lowering

medication (goal HR<60 bpm) is needed for the single-source 64-slice scanners (**Table 1B**) to optimize image quality and minimize radiation exposure to the patient.

Table 1. Recommended per os (PO)/intravenous (IV) Heart Rate Lowering Medication Chart

A. Dual-source CT & Wide Detector Volumetric 256- or 320-slice CT scanners

Non-asthmatics

1. Upon Check-in, Staging Area: Check BP and HR		
Heart Rate	**Systolic BP (mmHg)**	**HR lowering pre-medication**
-	<100 mmHg	No HR lowering meds.
>70 bpm	100-110 mmHg	Metoprolol 50 mg PO 1 hour prior to CT scan**
>70 bpm	>110 mmHg	Metoprolol 100 mg PO 1 hour prior to CT scan**
65-70 bpm	>100 mmHg	Metoprolol 5 mg IV x 1 on table.
<65 bpm		No HR lowering meds.
2. On CT table: 45 minutes after PO med, check BP and HR. **If HR 65-70 bpm and SBP >100 mmHg: Give rescue Metoprolol 5mg IV x 1 on table.		

Asthmatics or contraindication to beta-blockers

1. Upon Check-in, Staging Area: Check BP and HR		
Heart Rate	**Systolic BP (mmHg)**	**HR lowering pre-medication**
-	<100 mmHg	No HR lowering medication
>70 bpm	100-110 mmHg	Diltiazem 60 mg PO 1 hour prior to CT scan
>70 bpm	>110 mmHg	Diltiazem 120 mg PO 1 hour prior to CT scan
2. On CT table: 45 minutes after PO medication, check BP and HR.		

B. Single-source 64-slice CT scanners

Non-asthmatics

1. Upon Check-in: Check BP and HR		
Heart Rate	**Systolic BP (mmHg)**	**HR lowering pre-medication**
>70 bpm	<100 mmHg	No HR lowering medication
>65 bpm	>110 mmHg	Metoprolol 100 mg PO 1 hour prior to CT scan
>65 bpm	100-110 mmHg	Metoprolol 50 mg PO 1 hour prior to CT scan
60-65 bpm	>100 mmHg	Metoprolol IV as below in staging area.
55-60 bpm	>100 mmHg	Not on home BB, Metoprolol 2.5 mg IV x 1 on table.
2. Staging Area: 45 minutes after PO medication, check BP and HR. If HR not at goal of <60 bpm: Give rescue Metoprolol 5mg IV Q3-5 minutes as needed (up to 25 mg) in **staging area** if SBP>100mmHg.		
3. On CT table: Check BP and HR. If HR not at goal of <60 bpm and SBP>100 mmHg: Continue rescue IV Metoprolol (max 25 mg).		

Asthmatics or contraindication to beta-blockers

1. Upon Check-in: Check BP and HR		
Heart Rate	**Systolic BP (mmHg)**	**HR lowering pre-medication**
>70 bpm	<100 mmHg	No HR lowering medication
>65 bpm	>110 mmHg	Diltiazem 120 mg PO 1 hour prior to CT scan
>65 bpm	90-110 mmHg	Diltiazem 60 mg PO 1 hour prior to CT scan
60-65 bpm	>100 mmHg	Diltiazem IV as below in staging area.

2. Staging Area: 45 minutes after PO medication, check BP and HR. If HR not at goal of <60 bpm: Give rescue Diltiazem 10 mg IV Q15 minutes as needed (up to 50 mg) in **staging area** if SBP>100mmHg. If HR >70 despite Diltiazem: Notify CT attending for potential additional meds.
3. On CT table: Check BP and HR.

BB: beta blocker; BP: blood pressure; Bpm: beats per minute; CT: computed tomography; HR: heart rate; IV: intravenous: PO:per os.

3. Blood pressure management: Check blood pressure (BP) and HR prior to and 45 minutes after PO med. PO dose to be given at check-in. After PO, gown and placement of appropriate IV access for contrast injection rate of 5-7 ml/sec. Right antecubital/forearm IV is preferable to minimize competitive streak artifacts to the left internal mammary artery (LIMA) graft.

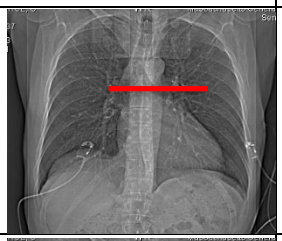
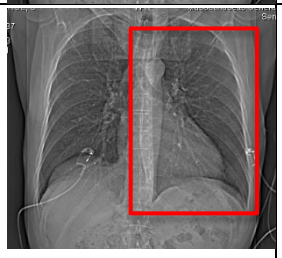
Step 1 - Subject Preparation: Subjects will be instructed and trained in breath holding. ECG electrodes will be mounted on the chest to enable co-registration of image acquisition and ECG signal. All subjects will have their HR optimized per **Table 1.** Appropriate IV access for contrast injection rate of 5-7 ml/sec is required, preferably in the right antecubital/preforearm to minimize competitive streak artifacts to the LIMA graft. Subjects will also receive sublingual nitroglycerine to vasodilate the coronary arteries and bypass grafts (**Table 2)**, unless contraindications exist (phosphodiesterase 5-inhibitor use within 48 hours, severe/critical aortic stenosis, or hypertrophic cardiomyopathy). **Step 2 - Image Acquisition:** All image acquisitions will be performed during a breath hold in inspiration. Cardiac CT imaging will start with a topogram of the chest to localize position of the heart. Either a test bolus or bolus tracking method at the ascending or descending aorta at the level of the right pulmonary artery may be performed to determine timing of scan acquisition. A high iodinated-contrast agent (≥320 mgI/mL) is required at a flow-rate of 5-7 mL/sec, with total contrast volume estimated to be ~90-130 mL, depending on scanner type and body habitus. Image acquisition is recommended to be caudo-cranial to minimize streak artifacts due to high CA concentration along the innominate vein or SVC. Scan coverage should be from the lung apex to the base of the heart. Depending on scanner type and HR, either prospective ECG-gated sequential scan, prospective ECG-gated high-pitch spiral scan, or retrospective ECG gated spirtal scan with tube modulation can be used (see **Table 2**). Delivery of proper iodinated contrast dose (**Table 2 and 3**), HR control for motion-free imaging (**Table 1**), coronary vasodilation (**Table 2**), and topographic-based or body mass index (BMI)-based photons (**Table 4**) are below. If available, use “automatic exposure control” or “automatic tube potential” or a noise index of 15, which are topographic-based. Range of kilovoltage peak (kVp) depending on scanner can be 70 kVp – 140 kVp. **Step 3 - Image Reconstruction:** The following datasets will be reconstructed after scanning and sent to the ODIN Core Lab (**Table 2A and 2B**): multiple diastolic (at 2% or 5% increments) or systolic (at 50 ms increments) datasets (0.6-0.75 mm slice thickness axial images, with or without 50% overlap) from the CTA scan for the evaluation of the bypass grafts (pixel matrix: 512x512, FOV <25 cm). An additional full FOV with 2.0-2.5 mm slice thickness should be reconstructed and sent to the local site’s reading queue for standard of care interpretation of non-cardiac findings. All coronary/bypass graft data/reconstructions will remain blinded to sites and should not be reviewed by the local site.

4. Image Submission: CCTA images must be in Digital Imaging and Communications in Medicine (DICOM) format and submitted to the core lab via the internet using Ambra (Medical Imaging Cloud). Sites will de-identify scans in accordance with local data use policies and assign site-

specific subject identifiers. The submission procedure will be detailed in the core lab Site Operations Manual.

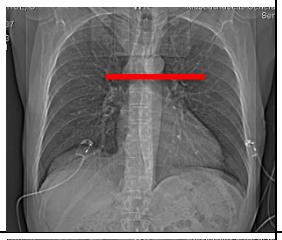
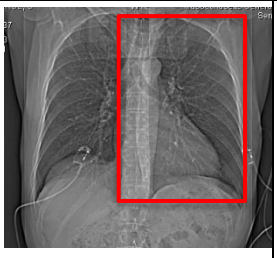
Table 2. Recommended CABG protocols

A. For Wide Detector Volumetric 256- or 320-slice CT scanners

CT scanner type	Wide Detector Volumetric 256- or 320-slice CTscanners
HR meds	PO/IV Heart Rate Lowering Medication Chart
Nitrates	2 SLNG before scout if SBP >110 mmHg, or 1 SLNG if SBP between 100-110 mmHg (if no contraindication to nitrates [e.g., phosphodiesterase in <48 hours, severe/critical aortic stenosis, or hypertrophic cardiomyopathy])
Breath-hold instructions	Inspiratory breath hold.
Contrast + bolus chaser (50-60ml at same @-rate)	320 mg/mL or higher iodinated contrast. Load 150 ml of contrast.
IV	- Right antecubital/pre-forearm is preferrable (to minimize streak artifacts to the proximal LIMA graft). -Power injector compatible IV (18-gauge preferred): BMI<30—5 cc/sec (If weight >160 lbs, 6 cc/s) | 30-35—6 cc/sec | >35—7cc/sec -Non-power injector compatible IV, 18-gauge, use 5 cc/sec flow rate
Scout	PA/lateral
Test bolus -or- bolus tracking 	1 cm below tracheal carena Test bolus: (10-15mL contrast), 40-50mL saline at flow rate above. Scan 6-8 secs after aortic peak. Bolus tracking: trigger at HU>100. Scan at least 8 secs after HU>100.
CTA 	- Topographic-based or BMI-based photons (kVp and mA/mAs) (**Table 4**). -Caudocranial suggested (to minimize competitive streak arteftacs from veins) -Prescribe FOV: CABG extend up to lung apex to get the Left subclavian artery for the LIMA and go to below the diaphragm. -Slice thickness of 0.6-0.75 mm, with or without overlap, depends on scanner (e.g., 0.75 mm slice thickness with 0.4 mm increment, or 0.625 mm slice thickness no overlap). -Contrast volume= (scan delay+ scan time+5 sec) x flow rate, followed by 40-50mL saline chase. Example #1: if test bolus used and scan 8 secs after Ao peak and duration of scan time is 3 secs, then contrast volume= (8 secs+3 secs+5 sec fudge) x flow rate, followed by saline chase Example #2: if bolus tracking is used and scan acquisition starts 9 secs after HU>100 and duration of scan time is 3 secs, then contrast volume= (9 secs+3 sec +5 sec fudge) x flow rate, followed by 40-50mL saline chase -FOV<25cm, medium convoluted kernel. **For wide-detector 256- or 320-slice scanner:** - if HR is regular and < 70, scan prospective 70-80% -Reconstruct 70-80% x 5%.

	-If temporal enhance option available, provide the processed dataset of 75% (e.g. SS-Freeze 75%). - if HR is irregular or ≥70, scan prospective 35-80% -Reconstruct 35-80% x 5%. -If temporal enhance option available, provide the processed dataset of 45% and 75% (e.g. SS-Freeze 45% and 75%).
Reconstructions	-The above reconstructions should remain blinded to the clinical site. -Full field of view (FOV) with 2.0-2.5 mm slice thickness of one phase chest wall-chest wall coverage should be reviewed and reported by the clinical site for noncardiac findings as part of standard of care interpretation. All coronary/bypass graft data/reconstructions will remain blinded to the clinical sites and should not be reviewed by the local site.

B. For Single-Source 64-slice or Dual-Source CT scanners

CT scanner type	Single-Source 64-slice or Dual-Source CT scanners
HR meds	PO/IV Heart Rate Lowering Medication Chart
Nitrates	2 SLNG before scout if SBP >110 mmHg, or 1 SLNG if SBP btwn 100-110 mmHgv (if no contraindication to nitrates [e.g. phosphodiesterase in 48 hrs, severe/critical aortic stenosis, or hypertrophic cardiomyopathy])
Breath hold instructions	Inspiratory breath hold.
Contrast+ bolus chaser….	320 mg/mL or higher iodinated contrast. Load 150 ml of contrast.
IV	- Right antecubital preferred (to minimize streak artifacts to LIMA graft). -Power injector compatible IV (18-gauge preferred, if 20G, max 5.7 cc/sec). BMI<30—5 cc/sec | 30-35—6 cc/sec | >35—7cc/sec -Non-power injector compatible IV, 18-gauge, use 5 cc/sec flow rate **Alternative Weight-based flow rate are provided in **Table 3**.
Scout	PA/lateral
Test bolus -or- bolus tracking 	1 cm below tracheal carena Test bolus: (10-15mL contrast), 40-50mL saline @ flow rate above. Scan 5 secs after Ao peak. Bolus tracking: trigger at HU>100. Scan at least 5-6 secs after HU>100.
CTA 	- Topographic-based or BMI-based photons (kVp and mA/mAs) (**Table 4**). For topographic-based, hone into the heart to get kV. Change the kV to "Semi" and fix the kV to that value. Then extend coverage to the chest so as to avoid overdosing radiation due to density of the clavicle/neck region. -Caudocranial (to minimize streak artefatc from veins) -Prescribe FOV: CABG extend up to lung apex to get the Left subclavian artery for the LIMA and go to below the diaphragm. -Slice thickness of 0.6-0.75 mm, with or without overlap (e.g. 0.75 mm slice thickness with 0.4 mm increment, or 0.625 mm slice thickness no overlap. -Contrast volume= (scan delay + scan time + 4 secs fudge factor) x flow rate, followed by 40 cc saline chase. <u>Example #1</u>: if test bolus used and scan 5 secs after peak Ao and duration of scan time is 10 secs, then contrast volume = (5 secs + 10 secs + 4 secs fudge) x flow rate, followed by saline chase <u>Example #2</u>: if bolus tracking is used and scan acquisition starts 9 secs after HU>100 and duration of scan time is 10 secs, then contrast volume = (9 secs + 10 secs + 4 secs fudge) x flow rate, followed by 40 cc saline chase -FOV<25cm, medium convoluted kernel. **For DSCT:**

	- if HR is regular and <70, scan prospective diastolic from 60-80 -Reconstruct 68, 70, 73% - if HR is irregular or ≥70, scan prospective systolic 250-400 ms -Reconstruct 250-400 ms x 50 ms **For single-source 64-slice scanner:** - if HR is regular and <65, scan prospective 70-80%. -Reconstruct 70-80% x 5% -If temporal enhance option available, provide the processed dataset of 75% (e.g., SS-Freeze 75%). - if HR is regular and ≥65, scan retrospective w/ tube modulation 35-80% -Reconstruct 35-80% x 5%. -If temporal enhance option available, provide the processed dataset of 45% and 75% (e.g., SS-Freeze 45% and 75%). - if HR is irregular, scan retrospective without tube modulation. -Reconstruct 35-80% x 5%. -If temporal enhance option available, provide the processed dataset of 45% and 75% (e.g.; SS-Freeze 45% and 75%).
Reconstructions	-The above reconstructions should remain blinded to the clinical site. -Full FOV with 2.0-2.5 mm slice thickness of one phase (e.g., 75%) chest wall-chest wall coverage should be reviewed and reported by the clinical site for noncardiac findings as part of standard of care interpretation. All coronary/bypass graft data/reconstructions will remain blinded to the clinical sites and should not be reviewed by the local site.

BMI: body mass index; CT: computed tomography; CTA: computed tomography angiogram; FOV: field of view; HR: heart rate; HU: houndsfield unit;; LIMA: left internal mammary artery; PA: poster-anterior; SBP: systolic blood pressure; Secs: seconds; SLNG: sublingual nitroglycerine; SS: single-sliceSVC: superior vena cava

Table 3. **Suggested Weight-based Optimal Cardiac Flow Rate for Contrast (Alternative to BMI-based Flow rate).

Weight	Visipaque 320 (6.4g of Iodine)	Omnipaque 350 (7g of Iodine)	Isovue 370 (7.4g of Iodine)	Iodine Flux
<88 lb	3.9 cc/seconds	3.6 cc/seconds	3.4 cc/seconds	1.3 g/seconds
88-131 lb	4.9 cc/seconds	4.5 cc/seconds	4.2 cc/seconds	1.6 g/seconds
132-163 lb	5.2 cc/seconds	4.8 cc/seconds	4.5 cc/seconds	1.7 g/seconds
164-208 lb	6.2 cc/seconds	5.7 cc/seconds	5.4 cc/seconds	2.0 g/seconds
209-241 lb	7.0 cc/seconds	6.4 cc/seconds	6.0 cc/seconds	2.2 g/seconds
242-276 lb	7.1 cc/seconds	6.5 cc/seconds	6.2 cc/seconds	2.3 g/seconds
>276 lb	7.3 cc/seconds	6.7 cc/seconds	6.3 cc/seconds	2.3 g/seconds

g:grams; lb: pounds

Table 4. Suggested BMI-based kVp and mA/mAs for CT scanner†

Single-Source CT			Dual-Source CT		
BMI	**kV**	**mA**	**BMI**	**kV**	**mAs**
<25	100	500	**<25**	100	250
25.0-28.9	100	600	**25.0-28.9**	100	300
29.0-31.9	120	600	**29.0-31.9**	120	300
32.0-34.9	120	700	**32.0-34.9**	120	350
35.0- 40‡	120	835	**35.0- 40‡**	120	420

† If available, use “automatic exposure control” or “automatic tube potential” or a noise index 15
‡ For BMI>40, using 140 kV and max out the ma/mAs
BMI: body mass index; CT: computed tomography; kV: kilovolts; mA: miliamps

5. Image evaluation (Core Lab): The ODIN Core Lab will receive, store, and perform quality control (QC) checks on all examinations and related documentation received. CT images will be checked for technical sufficiency, completeness, and protocol compliance. Sites will submit the CCTA cases via web-based transfer using HIPAA compliant mechanisms. Once designated ODIN study investigators receive the case, they will provide study tracking, post-processing, QC checks, and archiving of images and documentation that are associated with the study. All received cases will be reviewed by Level II or III CCTA readers. Anonymized cases will be reviewed on an independent, fully functional 4D virtual workstation (e.g., TeraRecon, Inc, North Carolina USA) for analysis and core lab reads. Analysis will additionally include review of rendered images and curved multiplanar reformats of the bypass grafts. Blinded consensus Core lab reads of de-identified bypass graft cases will be performed by two Level II or Level III cardiac CT readers, with disagreement resolved by a third cardiac CT reader. Multiple phase reconstructed data sets will be viewed using multiplanar reformats, maximum intensity projection, multiplanar reformatted and volume-rendered images. The evaluation usually takes approximately one-half hour.

Step 1 – Image Quality Assessment

- Each case will be evaluated on a 5-point scale for image quality (1-Excellent, 2-Good, 3-Fair, 4-Poor, 5-Nondiagnostic).
- Reasons for suboptimal image quality (fair, poor, or nondiagnostic) will be recorded, such as poor contrast opacification, high noise, motion artifact, respiratory artifact, and beam hardening artifact.

Step 2 – Graft Patency and Stenosis Assessment (Figure 1)

- Each case will be evaluated for the number of grafts and their location (e.g., LIMA-x, aortocoronary bypass graft-x, aortocoronary bypass Y-graft-x, whereby x is defined as the distal runoff vessel [Left anterior descending, Diagonal, Left Circumflex/OM, Left circumflex/Posterior Descending artery if left dominant, Right Coronary artery/Posterior Descending artery]).
- For each graft, analysis will be performed on a per-segment basis (proximal anastomosis/origin, proximal graft, mid graft, distal graft, distal anastomosis)
    - Using a modified semi-quantitative stenosis evaluation based on SCCT Grading Score of Stenosis Severity classification to include the presence

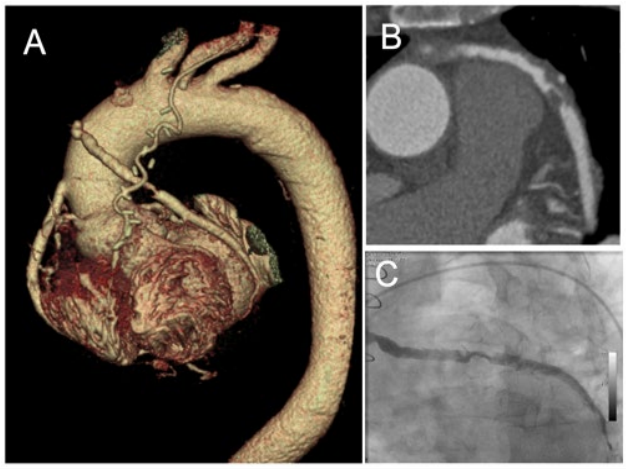


Figure 1. A. Volume-rendered CTA image of a LIMA and 2 aortocoronary bypass grafts. B. Multiplanar-reformat of the graft to the LCx showing noncalcified plaque with severe stenosis. C. Corresponding invasive cardiac angiography confirming severe stenosis.
CTA: computed tomography angiogram, LIMA: left internal mammary artery; Lcx: left circumflex artery

of graft stent. Presence of stent will be categorized with a binary cutoff of >50% stenosis group for statistical analysis: Additional analyses will use an established grading criteria (0-Normal: no luminal stenosis; 1-Minimal: <25% stenosis; 2-Mild: 25-49% stenosis; 3-Moderate: 50-69% stenosis; 4-Severe: 70-99% stenosis; 5-Occluded)

- By plaque morphology (calcified, noncalcified, partially calcified)[3]
- If affected by artifact (yes/no)

Step 3 – Graft Quantitative Stenosis Assessment

- For each graft, a quantitative stenosis assessment (% stenosis) will be performed of the lesion most severely affect.

6. Ancillary Core Lab Practices: CT protocols that reflect specifications of each vendor as well as vendor-independent elements of the imaging procedure (i.e., subject preparation, contrast, post processing and CT image reconstruction), will be developed by the clinical sites in collaboration with vendors and approved by the ODIN core Lab. In addition, the Core Lab will assure adherence to the approved CT protocol during enrollment by checking for appropriate parameters (i.e., slice thickness, field of coverage, contrast rate and amount, radiation dose). The ODIN Core Lab will specifically monitor the application of CT imaging protocols, which are optimized to save radiation exposure. Retraining of the clinical sites is required if 1) there are major deviations from the approved CT imaging protocol in any subject; 2) the image quality is judged to be poor or non-diagnostic in two (2) or more consecutive CT exams.

Supplementary Table 1. Primary and secondary endpoint definitions.

ENDPOINT	DEFINITION
DEATH	The primary and key secondary outcomes include death from any cause. The cause of death will be adjudicated and the cause of death determined. Deaths will be judged to be CV, non-CV, and undetermined as per ARC-2 definition. **CV death** is death resulting from an acute myocardial infarction (MI), sudden cardiac (including unwitnessed) death, death resulting from heart failure, death caused by stroke, death caused by CV procedures, death due to CV hemorrhage, and death due to other CV causes. Examples of deaths due to other CV caused not already mentioned but with a specific, known cause include pulmonary embolism or peripheral arterial disease. **Non-CV death** is defined as any death with a specific cause that is not thought to be CV in nature, as listed above. Deaths should be attributed to a non-CV cause only if clearly related to some other reason. For patients who die after a series of related illnesses which are causally and temporally related to an antecedent cardiac event, for example pneumonia and sepsis after a MI with cardiac arrest, these deaths will be reported as CV. Non-CV death may be death resulting from malignancy, death resulting from pulmonary causes, death caused by infection (includes sepsis), death resulting from gastrointestinal causes, death resulting from accident/trauma, death caused by other non-CV organ failure, death resulting from other non-CV cause. **Undetermined cause of death** refers to a death not attributable to one of the above categories of CV death or to a non-CV cause. This may be due to inadequate information about the death (i.e., only that the patient died without other supporting information surrounding the cause of death). For the purposes of the trial, these deaths will be reported as CV death.
STROKE	Stroke will use the NeuroARC definitions, and all Type 1 strokes will contribute to the primary and key secondary outcomes. Type 1a is defined as sudden onset of neurological signs or symptoms fitting a focal or multifocal territory within the brain, spinal cord or retina that 1: persists for > 24 hours or until death with pathological or neuroimaging that demonstrates either a) CNS infarction in the corresponding territory with or without associated hemorrhage or b) Absence of other causes, including bleeding, even if ischemic changes are absent or 2: Symptoms lasting < 24 hours with pathology or neuroimaging confirmation of CNS infarction in the corresponding vascular territory. (NB: When the CNS infarction does not match the transient symptoms, the event would be classified as a covert stroke (Type 2a) and TIA (Type 3a) and not a Type 1 stroke). It is very strongly recommended, and is standard of care, that a neuro-imaging procedure such as a CT scan or MRI be performed. Types 1.a, 1.aH, and 1.e are classified as ischemic, Types 1b and 1c are defined as hemorrhagic, and Type 1.d as uncertain. Covert strokes will typically not count towards the primary outcome or stroke outcome unless the timing of the event can be ascertained, for example from serial imaging.

MYOCARDIAL INFARCTION	The definition of MI will be assessed using the framework of the 4th Universal Definition, with Types 1-5. Type 5 will not count towards to the primary and key secondary outcomes but will be adjudicated and will be captured in the outcome of any MI. The clinical, ECG and biomarker information (and postmortem findings if available) will be reviewed by the Event Adjudication Committee. Spontaneous MI will be defined for MIs beyond 48 hours of the index procedure and periprocedural for MIs <48 hours of the index procedure. The diagnostic criteria for **Types 1 and 2 MI** include: Detection of rise and/or fall of cardiac biomarkers (preferably cTn) with at least one value above the 99th percentile of the URL together with at least one of the following: 1) Symptoms of acute myocardial ischemia; 2) New ischemic ECG changes; 3) Development of pathological Q waves; 4) Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischemic etiology; 5) Identification of an intracoronary thrombus at angiography or autopsy. For **Type 2**, there is evidence of oxygen supply/demand imbalance likely related to a condition other than acute coronary atherothrombosis. **Type 3 MI** is determined for patients who die with a clinical picture consistent with acute MI but without biomarker sampling or prior to the expected rise in biomarkers. **Type 4 MI:** **Type 4a:** Coronary intervention-related MI is arbitrarily defined by an elevation of cTn values more than five times the 99th percentile URL in patients with normal baseline values. In patients with elevated pre-procedure cTn in whom the cTn level are stable (20% variation) or falling, the post-procedure cTn must rise by >20%. However, the absolute post-procedural value must still be at least five times the 99th percentile URL. In addition, one of the following elements is required: a. New ischemic ECG changes; b. Development of new pathological Q waves† c. Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischemic etiology d. Angiographic findings consistent with a procedural flow-limiting complication such as coronary dissection, occlusion of a major epicardial artery or a side branch occlusion/thrombus, disruption of collateral flow, or distal embolization‡ **Type 4b:** Stent/scaffold thrombosis associated with PCI that meets the criteria for type-1 MI. Events that fulfill the criteria for type 4b MI will also be adjudicated as type 1 MI. **Type 4c:** Restenosis associated with PCI, that meets the criteria for type-1 MI. Events that fulfill the criteria for type 4c MI will also be adjudicated as type 1 MI. **Type 5** (CABG-related) MI is arbitrarily defined as elevation of cTn values>10 times the 99th percentile URL in patients with normal baseline cTn values. In patients with elevated pre-procedure cTn in whom cTn levels are stable (#20% variation) or falling, the post-procedure cTn must rise by>20%. However, the absolute post-procedural value still must be>10 times the 99th percentile URL. In addition, one of the following elements is required: a. Development of new pathological Q waves†;

	b. Angiographic documented new graft occlusion or new native coronary artery occlusion; c. Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischemic etiology
REPEAT REVASCULARIZATION	Repeat Revascularization is defined as any revascularization by either PCI or CABG of a target vessel or a non-target vessel, after the index CABG. **Target vessel**: The target vessel is defined as the entire major intervened coronary vessel, including side branches and bypass grafts. **Target vessel revascularization**: Target vessel revascularization is defined as any repeat PCI or CABG of any segment of the target vessel including any graft for which the target vessel is the target.
GRAFT FAILURE	Any graft stenosis ≥50% or occlusion as assessed by coronary computed tomographic angiography (CCTA) at 12-month follow-up, read by the imaging core lab following Society of Cardiovascular Computed Tomography guidelines classifications; or any graft stenosis ≥50% or occlusion on any unplanned CCTA or invasive coronary angiography imaging, read by the imaging core lab following Society of Cardiovascular Computed Tomography guidelines classifications. Graft failure identified by unplanned imaging within 12 months after randomization will be included in the primary and key secondary endpoints.
QUALITY OF LIFE	Patient reported outcomes will be measured as part of the powered 5-year secondary endpoints of ODIN. The disease-specific quality of life tool will be the 7-item Seattle Angina Questionnaire (SAQ-7). The generic quality of life tool will be the 12-item Short Form Survey (SF-12).
BLEEDING	BLEEDING ACADEMIC RESEARCH CONSORTIUM (BARC) BLEEDING CLASSIFICATION
MAJOR	**Type 3:** **Type 3a:** Overt bleeding plus hemoglobin drop of 3 to < 5g/dL* (provided hemoglobin drop is related to bleed – or – Any transfusion with overt bleeding; **Type 3b:** Overt bleeding plus hemoglobin drop ≥ 5 g/dL* (provided hemoglobin drop is related to bleed) – or – Cardiac tamponade – or – Bleeding requiring surgical intervention for control (excluding dental / nasal / skin / hemorrhoid) – or – Bleeding requiring intravenous vasoactive agents; **Type 3c:** Intracranial hemorrhage (does not include microbleeds or hemorrhagic transformation, does include intraspinal) – or – Subcategories confirmed by autopsy or imaging or lumbar puncture Intraocular – or – Bleed compromising vision

	Type 4: CABG-related bleeding: Perioperative intracranial bleeding within 48 h – or –Reoperation after closure of sternotomy for the purpose of controlling bleeding – or – Transfusion of ≥ 5 U whole blood or packed red blood cells within a 48-h period† – or – Chest tube output ≥ 2L within a 24-h period **Type 5: Fatal bleeding** **Type 5a:** Probable fatal bleeding; no autopsy or imaging confirmation but clinically suspicious **Type 5b:** Definite fatal bleeding; overt bleeding or autopsy or imaging confirmation
NON-MAJOR	**Type 0:** No bleeding **Type 1:** Bleeding that is not actionable and does not cause the patient to seek unscheduled performance of studies, hospitalization, or treatment by a healthcare professional; may include episodes leading to self-discontinuation of medical therapy by the patient without consulting a healthcare professional **Type 2:** Any overt, actionable sign of hemorrhage that does not fit the criteria for type 3, 4, or 5 but does meet at least one of the following criteria: 1. requiring nonsurgical, medical intervention by a healthcare professional 2. leading to hospitalization or increased level of care, or 3. prompting evaluation

Supplementary Table 2. Hierarchical order of endpoint analyses.

	Primary endpoint	**Key secondary endpoint**	**1. Secondary endpoint**	**2. Secondary endpoint**
	Assessed sequentially at 1 year		Assessed sequentially at 5 years	
Tier 1	Time to all-cause death	Time to all-cause death	Time to all-cause death	Time to all-cause death
Tier 2	Time to stroke	Time to stroke	Time to stroke	Time to stroke
Tier 3	Time to MI	Time to MI	Time to MI	Time to MI
Tier 4	Time to repeat revascularization	Time to BARC type 3 bleeding	Time to repeat revascularization	Time to BARC type 3 bleeding
Tier 5	Any graft failure	Time to repeat revascularization	Time-averaged disease-specific QoL score	Time to repeat revascularization
Tier 6		Any graft failure		Time-averaged disease-specific QoL score

Supplementary Table 3. Incidence of endpoints in contemporary randomised clinical trials.

Source	1-year rate of all-cause death, stroke or MI (control group), %	1-year rate of BARC type 3 bleeding (control group), %	Graft failure (Control vs treatment group), %
ART	6.4	NR	NR
TICAB	8.6	0.8	NR
CORONARY	12.7	NR	NR
REGROUP	7.5	NR	NR
EXCEL	14.1	NR	NR
CASCADE	7.1	5.3[a]	NR
PLATO	11.7	NR	NR
CRYSSA	6.6	1.3[a]	27.0 vs 15.2
DACAB	5.4	7.8	28.3 vs 23.5 vs 15.6
Sandner et al. [b]	5.5	1.8	24.8 vs 14.3

[a] CURE bleeding definition

[b] Follow-up imaging was performed in 92.9% of event-free patients (i.e. those without death, MI or revascularization within 1 year)

BARC, Bleeding Academic Research Consortium; MI, myocardial infarction; NR, not reported.