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FASTTRACK – CLINICAL RESEARCH
Cardiac and vascular surgery

Coronary bypass surgery guided by computed tomography in a low-risk population

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Abstract

Background and Aims In patients with three-vessel disease and/or left main disease, selecting revascularization strategy based on coronary computed tomography angiography (CCTA) has a high level of virtual agreement with treatment decisions based on invasive coronary angiography (ICA).

Methods In this study, coronary artery bypass grafting (CABG) procedures were planned based on CCTA without knowledge of ICA. The CABG strategy was recommended by a central core laboratory assessing the anatomy and functionality of the coronary circulation. The primary feasibility endpoint was the percentage of operations performed without access to the ICA. The primary safety endpoint was graft patency on 30-day follow-up CCTA. Secondary endpoints included topographical adequacy of grafting, major adverse cardiac and cerebrovascular (MACCE), and major bleeding events at 30 days. The study was considered positive if the lower boundary of confidence intervals (CI) for feasibility was ≥75% (NCT04142021).

Results The study enrolled 114 patients with a mean (standard deviation) anatomical SYNTAX score and Society of Thoracic Surgery score of 43.6 (15.3) and 0.81 (0.63), respectively. Unblinding ICA was required in one case yielding a feasibility of 99.1% (95% CI 95.2%–100%). The concordance and agreement in revascularization planning between the ICA- and CCTA-Heart Teams was 82.9% with a moderate kappa of 0.58 (95% CI 0.50–0.66) and between the CCTA-Heart Team and actual treatment was 83.7% with a substantial kappa of 0.61 (95% CI 0.53–0.68). The 30-day follow-up CCTA in 102 patients (91.9%) showed an anastomosis patency rate of 92.6%, whilst MACCE was 7.2% and major bleeding 2.7%.

Conclusions CABG guided by CCTA is feasible and has an acceptable safety profile in a selected population of complex coronary artery disease.

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Structured Graphical Abstract

Key Question

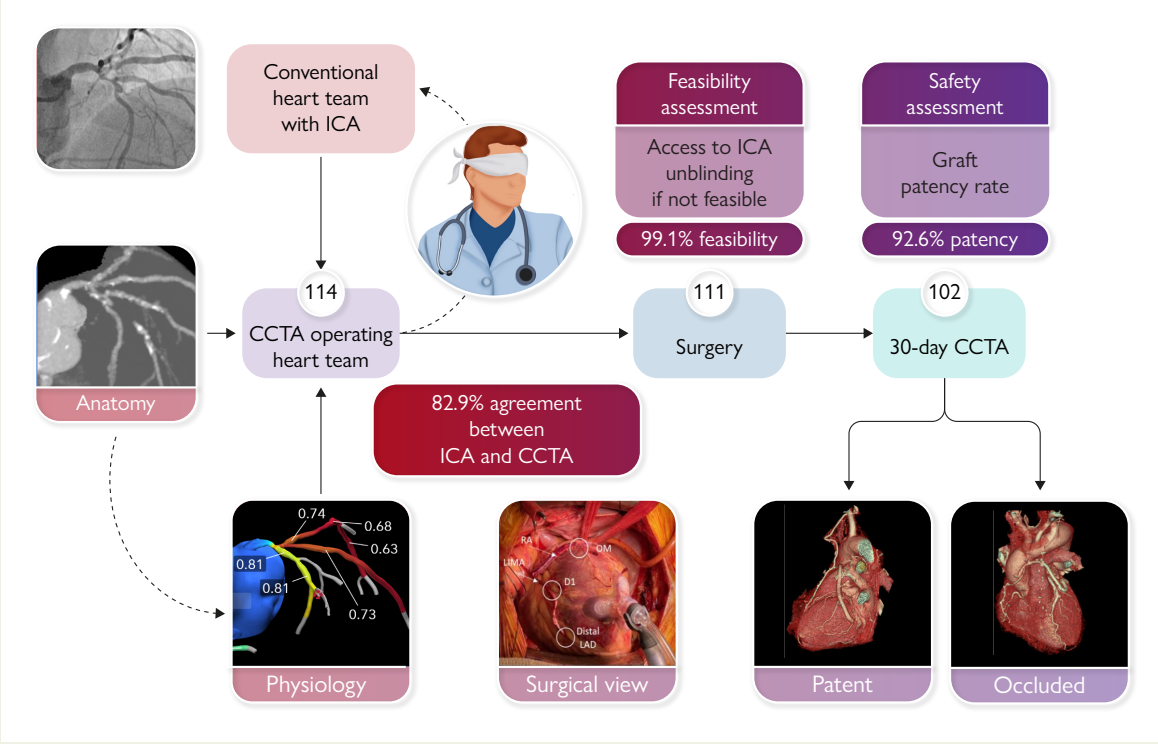
Is it safe and feasible to skip invasive coronary angiography before coronary artery bypass grafting (CABG)?

Key Finding

Planning and execution of CABG based on coronary computed coronary angiography (CCTA) alone was feasible in a cohort of 114 patients with chronic coronary syndrome and low surgical risk. The 30-day follow-up CCTA in 92% of patients showed an anastomosis patency rate of 93%, whilst major cardiovascular event and bleeding rates were 7.2% and 2.7%, respectively.

Take Home Message

CABG based on CCTA alone is feasible. Efficacy and safety of this innovative approach needs to be demonstrated in randomized control studies.



Overview of the FAST TRACK CABG trial. ICA, invasive coronary angiography; CABG, coronary artery bypass grafting; CCTA, coronary computed tomography angiography; LAD, left anterior descending coronary artery; RA, radial artery; OM, obtuse marginal branch; LIMA, left internal mammary artery; D1, diagonal branch.

Keywords Coronary computed tomography • Coronary artery bypass grafting • First-in-human • Proof-of-concept • Feasibility • Safety

Introduction

Selecting the optimal modality of revascularization in patients with three-vessel disease (3VD) and/or left main (LM) coronary artery disease (CAD) remains a topic of discussion between cardiologists and cardiac surgeons.[1] Deciding between percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG) should be made by consensus during a Heart Team consultation as endorsed by the European Society of Cardiology (ESC) and the American College of Cardiology/American Heart Association (ACC/AHA).[2,3]

Since 2009, both societies have incorporated the anatomical SYNTAX score (aSS) in their guidelines for revascularization.[2,3] In 2013, the aSS was adapted to use coronary computed tomography angiography (CCTA), as opposed to invasive coronary angiography (ICA), whilst its combination with clinical characteristics yielded the SYNTAX score II prediction model, which was recalibrated in 2020 after the integration of long-term all-cause mortality from the SYNTAX trial. These risk scores remain pivotal when selecting the revascularization strategy in contemporary practice.[4–7]

In patients with 3VD and/or LM CAD, the SYNTAX III REVOLUTION trial concluded that clinical decision-making between CABG and PCI using CCTA had a high level of agreement with treatment decisions based on ICA (93% concordance and Cohen's kappa 0.82), a finding which prompted the hypothesis that CCTA might

provide sufficient, or even superior, information to ICA in planning and performing CABG.[6,7] However, the SYNTAX III REVOLUTION trial was virtual, as prior to treatment, each Heart Team (ICA and CCTA) was ultimately unblinded. Nevertheless, it is worth mentioning that vital prognosis at 5-year follow-up, using either ICA or CCTA, was comparable.[8] In addition, physiological assessment with fractional flow reserve derived from CCTA (FFR_{CT}, HeartFlow, Mountain View, CA, USA) has refined the planning of the optimal revascularization strategy in patients with multivessel disease.[9–11]

The logical next step could have been to plan a trial truly randomizing patients between CCTA and ICA in a blinded fashion. However, for ethical reasons, an intermediate step was felt to be mandatory and this is the essence of the FAST TRACK CABG trial: can the surgeon plan his surgery without the visual knowledge of the conventional cineangiography whilst knowing that other surgeons have decided on surgical revascularization?

The present study aims to assess the feasibility and safety of using CCTA and FFR_{CT} as guidance for planning and performing CABG in patients with 3VD and/or LM CAD.[5]

Methods

Trial design and oversight

The trial was designed by the steering committee and sponsored by the University of Galway (Galway, Ireland). Research grants were given by GE HealthCare (Chicago, IL, USA) and HeartFlow (Mountain View, CA, USA).

The FAST TRACK CABG study is an investigator-initiated, single-arm, multicentre, prospective, proof-of-concept trial in patients with 3VD and/or LM CAD referred for CABG.

Treatment planning and surgical revascularization were based on CCTA and FFR_{CT} without knowledge of the anatomy delineated by ICA, which was used initially to select the modality of revascularization (e.g. PCI or CABG) by a Conventional Heart Team (ICA-Heart Team) which was not subsequently involved in the CCTA Planning and Operating Heart Team (CCTA-Heart Team) or in the actual surgical treatment. Coronary computed tomography angiography was repeated 30 days after CABG to assess graft patency and the topographical adequacy of revascularization with respect to the planned surgical technique, which was based wholly on non-invasive imaging.

The composition of the Conventional Heart Team and Operational/CCTA-Heart Team remained the same during the entire course of the trial. The CTA Planning and Operating Heart Team did not have access to the cineangiography and was completely blind to any information provided by the conventional Heart Team and ICA. The research nurse/study coordinator was responsible for the logistics to ensure that all required actions were in place to keep the CTA planning and operating Heart Team members blind to the conventional cineangiography. Furthermore, a monitor from an independent organization (Freelance Clinical Research Professional at CRA-Services, Utrecht, The Netherlands) visited sites and reviewed all source records, i.e. cath lab reports (to check who was present during angiography) and CABG reports (to check who was present during the bypass operation).

The study was approved by the ethics committee of each enrolling site. This trial is registered with ClinicalTrials.gov, number NCT04142021 (see Supplementary data online, *Text S1*).

An independent data and safety monitoring board approved the trial protocol and monitored patient safety. The trial design and methods have been published previously and are described in the protocol (which includes the statistical analysis plan).[5]

Trial population

Four study sites in Europe and the USA enrolled 114 patients with equivalent angina, silent ischaemia, and chronic (angina class from the Canadian Cardiovascular Society, CCS) or stabilized acute coronary syndrome (Braunwald's classification) who had been referred by the ICA-Heart Team for surgical revascularization.

Specific inclusion and exclusion criteria are listed in Supplementary data online, *Text S2*. The risk of surgical revascularization was evaluated by the EuroSCORE II and the Society of Thoracic Surgery score (STS), whilst the SYNTAX score 2020 (SS-2020) was used to predict major adverse cardiac and cerebrovascular events (MACCE) and all-cause mortality at 5 years.[12,13]

Coronary computed tomography angiography, fractional flow reserve derived from coronary computed tomography angiography acquisition, and academic core lab

Coronary computed tomography angiography was performed with the GE HealthCare Revolution computed tomography (CT) scanner that enables imaging of the heart in one heartbeat.[14] Image quality was measured using the five-point Likert scale at patient and segment levels.[15] The severity and extent of CAD were assessed by applying the aSS to all coronary segments with visual diameter stenosis ≥50% on CCTA and ICA, producing the CCTA-aSS and ICA-aSS, respectively.[16]

The reconstructed CCTA images were transferred to an independent core laboratory, blind to the ICA assessment (CORRIB Core Lab, Ireland, Galway) for anatomic analysis and to HeartFlow for FFR_{CT}, which enabled the calculation of the functional SYNTAX score (fSS), derived from the aSS by subtracting the weighing points of those lesions with an $FFR_{CT} > 0.80$ that were not intended to be bypassed.[17] The procedural CABG technique and post-operative management were left to surgeon's discretion. The FFR_{CT} and fSS were not available in 8/114 patients (7.0%).

The intraclass correlation coefficient (ICC) and the kappa value for the inter-observer reproducibility of the CCTA-aSS score were 0.96 [95% confidence interval (CI) 0.94–0.97] and 0.81 (kappa value almost perfect), respectively.[18]

The residual post-CABG SYNTAX score (post-CABG-aSS) was assessed on the 30-day follow-up CCTA as previously described. A score > 21 has been associated with poor long-term outcomes.[19] Definitions related to the SYNTAX score were summarized in Supplementary data online, *Text S3*.

Primary endpoints

The primary feasibility endpoint was defined as the percentage of CABG operations performed guided by CCTA and without the surgeon formally requesting access to the ICA.

The safety endpoint was the rate of anastomosis occlusion located either at the ostium, side-to-side, or end-to-side of the grafted site and diagnosed by follow-up CCTA at 30 days.

Secondary endpoints

Secondary feasibility endpoints were concordance and agreement between revascularization (i) planned by the ICA-Heart Team and CCTA-Heart Team and (ii) planned by the CCTA-Heart Team and actual treatment. Planned revascularization referred to all coronary segments defined according to the SYNTAX score segments and regrouped into the three major epicardial vessel territories (MEVT) with secondary branches targeted for revascularization (see Supplementary data online, *Text S4*).

Theoretically to be considered graftable, two conditions were mandatory: (1) to have a diameter stenosis ≥50% in main and/or secondary branches and (2) to have a reference diameter > 1.5 mm. The impact of the FFR_{CT} was left at the discretion of the surgeon as well as the assumed amount of myocardium subtended by the vessels to be grafted or deferred. The intended types of bypass graft [e.g. left intrathoracic artery (LITA), right intrathoracic artery (RITA), radial artery (RA), and saphenous vein graft (SVG)] and the planned grafting techniques (e.g. end-to-end, side-to-end,

jump graft, and X/Y graft) were also recorded among the ICA-Heart Team, CCTA-Heart Team, and actual treatment.

The secondary safety points were net adverse clinical events (NACE) at 30 days, defined as the combination of (i) MACCE, a composite of any death, stroke, myocardial infarction (MI), and repeat revascularization by PCI and/or CABG, and (ii) bleeding according to the Bleeding Academic Research Consortium criteria (BARC 4 and 5).[5,20] Definitions of these major adverse events are listed in the design paper and supplement (see Supplementary data online, *Text S5*).[5]

All clinical events were adjudicated by an independent clinical events committee (CEC).

Statistical analysis

The sample size calculation in this single-arm safety and feasibility study was not guided by a desired power or precision. A subsequent retrospective survey of surgeons involved in the SYNTAX III trial established that 84% were willing to perform CABG using the sole information from CCTA.[21] Arbitrarily, this was then set as the goal for the feasibility of this study. When the 95% CI of this was calculated with 100 patients, the lower boundary was 75%; assuming a 12% rate of imaging attrition as seen in SYNTAX III meant that 114 patients were required. The feasibility of CCTA was categorized according to the proportion of patients in whom the completion of CABG planning and execution was based using CCTA alone, based on the lower-bound of the CI using the following categories: poor < 50%; 50% ≥ acceptable < 75%; 75% ≥ excellent ≤ 100%. The trial is considered positive and successful when the results exceed 75%.

For evaluating the concordance and agreement between treatment strategies and executions, Cohen's kappa was used and the values were classified into the following categories. Values < 0 were interpreted as indicating no agreement, 0–0.20 as slight, 0.21–0.40 as fair, 0.41–0.60 as moderate, 0.61–0.80 as substantial, and 0.81–1 as almost perfect agreement.

Descriptive summaries of continuous variables are presented as mean and standard deviation (SD) whilst categorical variables as absolute numbers and percentages. Concordance between the decisions via different methods (actual decision, ICA-guided, and CCTA-guided) was evaluated by the proportion of agreeing cases and with Cohen's kappa. The 30-day follow-up CCTA ($n = 102$ patients) allowed the assessment of the anastomosis patency rate in 91.6% of the operated patients ($n = 111$ patients), whilst MACCE and major bleeding were assessed in the 111 operated patients and censored at 30 days.

All statistical analyses were performed using R 4.1.1 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Baseline characteristics

The study flow chart is shown in *Figure 1*. From September 2020 to May 2023, a total of 114 patients were enrolled from the 4 sites (Italy, 56; Belgium, 34; Germany, 12; and the USA, 12). During the inclusion period, 258 patients were operated in Monzino, 320 patients in Brussels, 128 in Mount Sinai, and 178 in Jena; thus, the average inclusion rate in the trial was 12.9%. Patient and lesion characteristics are shown in *Table 1*. The patient's mean age was 65.9 (8.7), 87.8% were men, and approximately a third had medically treated diabetes. Mean EuroSCORE II was 1.06 (0.62) and STS score was 0.80 (0.62). Of the 114 patients, 83 (72.8%) had a high aSS-CCTA (>32), 23 (20.2%) an intermediate aSS-CCTA (23–32), and 8 (7.0%) a low aSS-CCTA (<23). In eight patients, FFR_{CT} were not analysable due to motion artefact and therefore, no fSS could be evaluated.

The mean paired aSS-CCTA and fSS-CCTA ($n = 106$) were 43.6 (15.3) and 41.2 (16.5), respectively; the difference in absolute numbers was modest, indicating that the majority of stenoses was functionally significant (637/689 lesions in 106 patients).

According to the SS-2020, the 5-year predicted MACCE was 15.7% and mortality 10.7%.

Coronary computed tomography angiography radiation exposure was 16.0 (12.8) mGy for radiation dose and 3.9 (2.7) mSv for effective dose, whilst ICA radiation dose was 273.6 (204.6) mGy which is compatible to 4.9 (3.7) mSv.[22]

Feasibility of coronary artery bypass graft guided by coronary computed tomography angiography

The CCTA in one patient was hampered by major motion artefacts so the core lab recommended that the CCTA-Heart Team was unblinded and consequently given access to the ICA, resulting in a feasibility rate of 99.1% (95% CI 95.2%–100%).

The monitor concluded that blinding was 100% correctly executed at all four sites, with no blinding violations detected.

Coronary artery bypass grafting procedure

Off-pump surgery was performed in 17.1% of the patients, the duration of CABG procedure was 333.4 (66.6) minutes, and no circulation-supporting device except for the heart–lung machine during the on-pump surgery was used. Procedure details are presented in *Table 2*, and graft details were presented in Supplementary data online, *Table S1*. Procedure complications not related to the MACCE and NACE are presented in Supplementary data online, *Table S2*.

Topographical adequacy of anatomic revascularization

Based on the MEVT assessment, the mean (SD) number of lesions per patient seen on CCTA and ICA was 4.7 (1.1) and 4.1 (1.2), respectively. According to SYNTAX segments, the mean number of stenotic/occluded coronary segments per patient was 6.5 (4.1) on CCTA and 5.0 (2.1) on ICA.

Figure 2 illustrates the agreement in revascularization of the 533 MEVT in 111 operated patients between what was planned by the ICA- and CCTA-Heart Teams vs. what was actually performed. The concordance and agreement in the planning of revascularization between the ICA- and CCTA-Heart Teams was 82.9% (95% CI 79.5%–86.0%) with a moderate kappa 0.58 (95% CI 0.50–0.66), whilst between the revascularization planned by the CCTA-Heart Team and actual treatment, it was 83.7% (95% CI 80.3%–86.7%) with a substantial kappa of 0.61 (95% CI 0.53–0.68; *Figure 2*, and Supplementary data online, *Figure S1*). According to the surgical report, 329 (87.0%, 95% CI 83.2%–90.3%) out of 378 stenotic/occluded coronary segments detected by CCTA were anastomosed, whereas 319 (83.5%, 95% CI 79.4%–87.1%) out of 382 stenotic/occluded coronary segments detected by ICA were grafted.

Anastomosis patency at 30 days

The patency of anastomoses on 30-day follow-up CCTA was 92.6% (339/366, 95% CI 89.4%–95.1%) with the 27 occlusions seen in all types of graft (LITA, $n = 8$; RITA, $n = 3$; RA $n = 5$; and SVG $n = 11$) and located at the ostium (3.0%) or the end-to-side anastomosis (4.4%; *Table 3*). These occlusions were not specifically related to the major

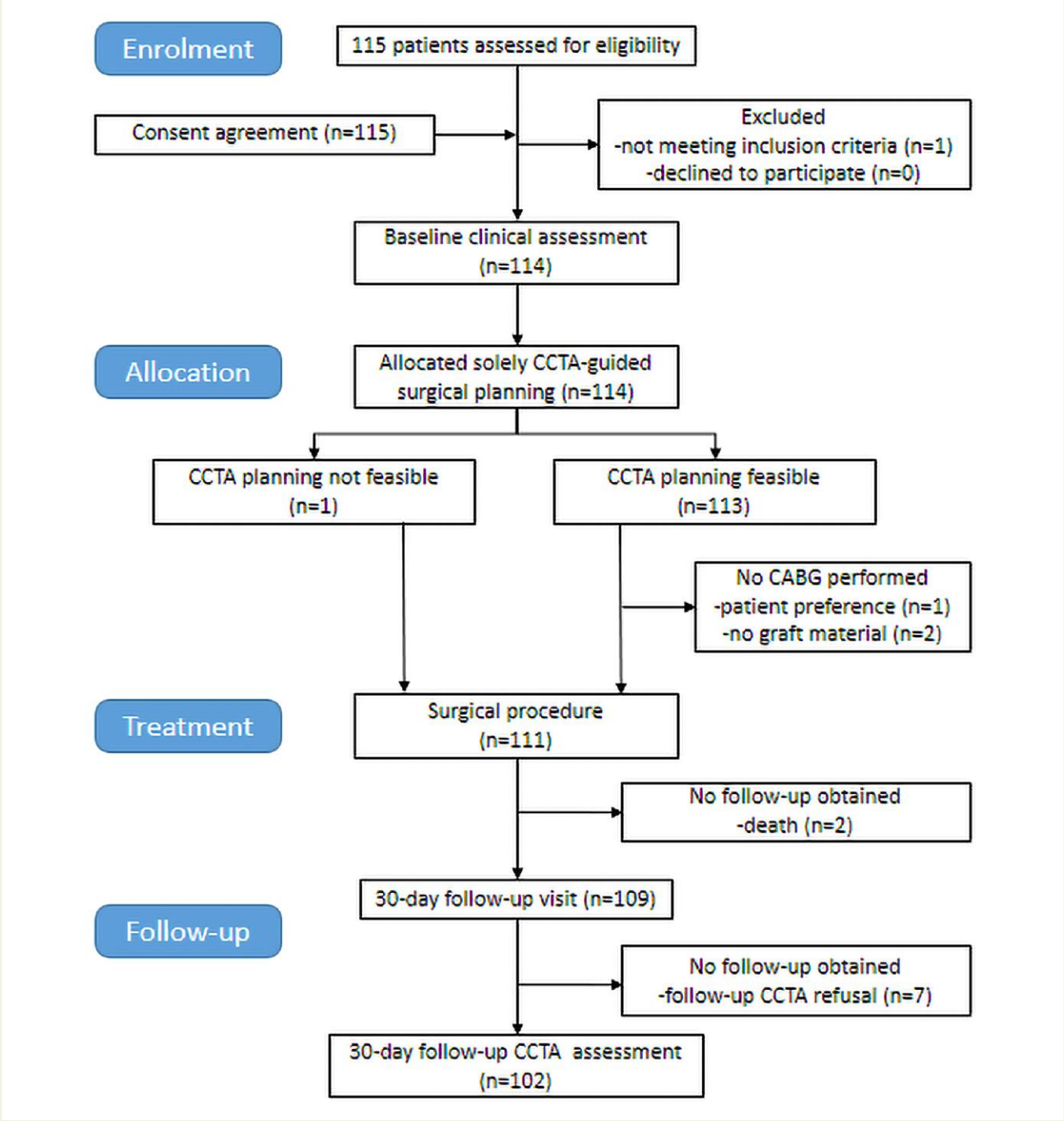


Figure 1 Flow chart of the study and number of patients at each stage. CABG, coronary artery bypass grafting; CCTA, coronary computed tomography angiography

epicardial vessel or secondary side branch FFR_{CT}, with 26 graft occlusions occurring when the $FFR_{CT} \leq 0.80$ vs. 1 with an $FFR_{CT} > 0.80$.

Overall safety

Death occurred in two patients (1.8%); one suffered a major stroke with haemiplegia 12 days after surgery and died the next day. The second developed ventricular fibrillation 3 h post-surgery and was resuscitated; following successful defibrillation, there were signs of major internal bleeding (BARC 5b) prompting urgent re-sternotomy that revealed a dehisced jump graft, a perforated right ventricle, and a ruptured ascending aorta. The graft was reattached, the perforation closed, and the aorta replaced with a Dacron graft; however, the patient died from multiorgan failure.

Out of four (4/111, 3.6%) peri-procedural MIs (PPMI), only one was an ST-elevation MI, which was due to early occlusion of the LITA graft on the LAD and this patient underwent urgent PCI to the LM and left anterior descending artery (LAD) on the same day. Three other PPMIs were adjudicated by the CEC (*Table 2*), but none were directly imputed to non-invasive imaging guidance.

Table 1 Baseline patient characteristics ($n = 114$)

Clinical characteristics	
Age, years, mean (SD)	65.9 (8.7)
Body mass index, kg/m^2, mean (SD)	26.8 (4.2)
Male sex, *n* (%)	101 (87.8%)
Prior myocardial infarction, *n* (%)	9/114 (7.9%)
Prior heart failure, *n* (%)	4/114 (3.5%)
Prior stroke, *n* (%)	4/114 (3.5%)
Prior revascularization, *n* (%)	0
Angina status	
Silent ischaemia, *n* (%)	29/114 (25.4%)
Chronic coronary syndrome, *n* (%)	69/114 (58.7%)
Angina class I Canadian Cardiovascular Society	7
Angina class II Canadian Cardiovascular Society	35
Angina class III Canadian Cardiovascular Society	27
Angina class IV Canadian Cardiovascular Society	0
Unstable angina, *n* (%)	7[a]/114 (6.1%)
Braunwald's classification IA	1
Braunwald's classification IB	2
Braunwald's classification IC	1
Braunwald's classification IIA	1
Braunwald's classification IIB	2
Equivalent angina, *n* (%)	6/114 (5.3%)
Asymptomatic but history of angina[b]	3 (2.6%)
Current smoker, *n* (%)	26 (22.8%)
Chronic obstructive lung disease, *n* (%)	9 (7.9%)
Peripheral artery disease, *n* (%)	10 (8.8%)
Creatinine clearance, mL/min (SD)	81.2 (20.1)
Hypertension, *n* (%)	97 (85.1%)
Systolic blood pressure, mmHg (SD)	126.7 (14.4)
Diastolic blood pressure, mmHg (SD)	77.2 (9.0)
Heart rate, b.p.m. (SD)	67.7 (11.9)
Dyslipidaemia, *n* (%)	82 (71.9%)
Medically treated diabetes mellitus, *n* (%)	38 (33.3%)
Insulin-dependent, *n* (%)	3 (2.6%)
Haemoglobin (g/dL), mean (SD)	14.2 (1.6)
White blood cell (10^3/μL), mean (SD)	7.5 (2.1)
Left ventricular ejection fraction, %, mean (SD)	56.5 (8.7%)
Coronary anatomy	
Left main disease, *n* (%)	28 (24.8%)
Three-vessel disease, *n* (%)	85 (75.2%)
Total number of lesions according to the anatomic SYNTAX coronary segmentation	735 (CCTA) 565 (ICA)
Total occlusion diagnosed by CCTA, *n* (%)	86/735 (11.7%)
Total occlusion diagnosed by ICA, *n* (%)	74/565 (13.1%)
Number of lesions per patient according to the SYNTAX coronary segmentation diagnosed by CCTA, mean (SD)	6.51 (4.09)
Total number of lesions per major epicardial vessel territory[c] diagnosed by CCTA, mean (SD)	4.7 (1.1)
Total number of lesions per major epicardial vessel territory[c] diagnosed by ICA, mean (SD)	4.1 (1.2)
ICA-derived anatomical SYNTAX score, mean (SD)	34.0 (12.9)
CCTA-derived anatomical SYNTAX score, mean (SD)	43.6 (15.3)
FFR_{CT}-derived functional SYNTAX score, mean (SD)	41.2 (16.5)
Clinical prediction	$N = 114$
EuroSCORE II 30-day predicted mortality, %, mean (SD)	1.06 (0.62)
STS score 30-day predicted mortality, %, mean (SD)	0.80 (0.62)
SS-2020 predicted 5-year CABG MACCE, %, mean (SD)	15.7 (9.7)
SS-2020 predicted 5-year PCI MACCE, %, mean (SD)	25.1 (14.8)
SS-2020 predicted 5-year CABG mortality, %, mean (SD)	10.7 (9.7)
SS-2020 predicted 5-year PCI mortality, %, mean (SD)	17.0 (14.2)

SD, standard deviation; SYNTAX, The SYNergy between percutaneous coronary intervention with TAXus and cardiac surgery; ICA, invasive coronary angiography; CCTA, coronary computed tomography angiography; FFR_{CT}, computed tomography–derived fractional flow reserve; STS, Society of Thoracic Surgeons; SS-2020, SYNTAX score 2020; CABG, coronary artery bypass grafting; PCI, percutaneous coronary intervention; MACCE, major adverse cardiac and cerebrovascular event.

[a]None of the unstable angina patients had elevated cardiac biomarkers. However, seven additional patients clinically classified as CCS ($n = 6$) and silent ischaemia ($n = 1$) had elevated cardiac biomarkers > ULN (upper limit of normal).

[b]History of angina, however, asymptomatic at the time of inclusion.

[c]See online supplementary material for the definition.

One patient underwent unplanned CABG after resuscitation in the second death case. Three patients underwent an unplanned PCI on the day of their surgery with a detailed description of each in the supplement (see Supplementary data online, *Text S6*). Nevertheless, according to the independent CEC, none of these unplanned PCIs were directly related to the fact that CABG had been performed under the guidance of CCTA.

Overall, at 30 days, the MACCE rate was 7.2% (*Table 4*), whilst three BARC 4 and one BARC 5 (above-mentioned) bleeds occurred.

Table 2 Coronary artery bypass grafting procedure

Operated ($N = 111$)		95% CI
Sternotomy, *n* (%)	111 (100%)	
Duration of CABG[a], min (SD)	333.4 (66.6)	320.9–345.9
Off-pump surgery, *n* (%)	19/111 (17.1%)	10.6%–25.4%
On-pump surgery, *n* (%)	92/111 (82.9%)	74.6%–89.4%
On-pump duration, min (SD)	106 (77.5)	91.4–120.6
On-pump with beating heart, *n* (%)	11/92 (12.0%)	6.1%–20.4%
Cardioplegia	81/92 (88.0%)	79.6%–93.9%
Blood	79	
Crystalloid	2	
Endarterectomy	3/111 (2.7%)	0.6%–7.7%
Days of hospitalization, day (SD)	7.7 (5.5)	6.7–8.7
$N = 111$[b]		
CK-MB post-CABG > 10 ULN, PPMI, *n* (%)[c]	1/65 (1.5%)	0%–8.3%
CK-MB post-CABG > 5 ULN, *n* (%)[d]	7/65 (10.8%)	4.4%–20.9%
Troponin post-CABG > 70 ULN, PPMI, *n* (%)[c]	1/46 (2.2%)	0.1%–11.5%
Troponin post-CABG > 35 ULN, *n* (%)[d]	4/46 (8.7%)	2.4%–20.8%

CABG, coronary artery bypass grafting; SD, standard deviation; CI, confidence interval; CK-MB, creatine kinase-MB; ULN, upper limit of normal; PPMI, peri-procedural myocardial infarction; U, unit.
[a]See the definition in the design paper and online supplementary material.
[b]Centro Cardiologico Monzino measured CK-MB post-CABG, University Hospital Jena and Universitair Ziekenhuis Brussel measured troponin, Mount Sinai measured CK-MB in 11 patients, and troponin was measured in 1 remaining patient.
[c]Enzymatic threshold definition of peri-procedural myocardial infarction; see definition in the design paper[5] and the online supplementary material.
[d]Not qualified the rise of cardiac enzymes as peri-procedural myocardial infarction; without electrocardiogram Q-wave in two contiguous leads, without abnormal wall motion loss of viable myocardium, or occlusion of the vessel.

Serious adverse events other than MACCE are presented in Supplementary data online, *Table S2*.

Medication at 30-day follow-up is presented in Supplementary data online, *Table S3*.

Discussion

The key finding of this first-in-human study is the 99.1% feasibility, which is driven by the relatively good diagnostic concordance between CCTA and ICA (*Structured Graphical Abstract*). Overall, the safety and adequacy of surgical revascularization did not appear to be negatively impacted by just relying on CCTA guidance, although it is obviously premature to draw any definitive conclusions, and ultimately, this study will serve as a foundation for large comparative and controlled investigations.

Inherently, a first-in-human trial is limited in terms of patient number, and typically, the feasibility and safety of the novel approach is evaluated without a comparative arm since at that stage of the investigation, there are no clinical data available to justify any rational sample size or to guarantee the safety of a large, powered randomization study.

Appropriateness of the selection of the coronary artery bypass grafting candidates

The individual vital prognosis at 5 years (*Table 1*) provided by the SS-2020 confirms that both Heart Teams in the study selected the appropriate patients for CABG (see Supplementary data online, *Figure S2*), with only two patients having a lower predicted mortality at 5 years if they had undergone PCI instead of CABG.

However, the STS and EuroSCORE II are low in our selected population, which is attributable to the exclusion, as per the study protocol, of complex comorbidities (not directly related to the extent and complexity of coronary disease), which are significant components of these scores.

Comparative assessment of invasive coronary angiography and coronary computed tomography angiography

The ICA-aSS and CCTA-aSS are major components of the global prognostic SS-2020, and therefore, it is critical to compare them. The mean CCTA-aSS 43.6 (15.3) was higher than the ICA-aSS 33.7 (12.5), which may relate on one hand to slightly different methodologies of assessment of the ICA and CCTA scores[18] and on the other hand to calcium blooming artefact on CCTA causing lesion severity to be overestimated, thereby increasing the number of stenoses visually ≥50%. Coronary computed tomography angiography has accuracy for detecting diameter stenosis ≥50% of 94.3% when compared with ICA.[23,24] Notably, whilst severe calcifications were seen frequently in this study, HeartFlow uses its own proprietary algorithms for de-blooming calcified stenoses. Currently, the resolution of conventional cine fluoroscopic angiography is in the range of 200 microns/pixel. The current multislice CT technology offers a resolution of 400 μ/voxel but offers, on top of this, the aforementioned advantages and the capability to display 3D multiplanar contours of the coronary artery. The increase in the resolution of the photon CT scanner into the 200 μ/pixel (can be a maximum of 110 μ/pixel according to the literature) range will further boost the diagnostic capability of CCTA.[25–28] Novel high-resolution hardware (photon-counting CT), high-resolution reconstructions, subtraction techniques, and post-processing with deep learning de-blooming algorithms can also effectively decrease this artefact, improving the diagnostic accuracy of CCTA.[29,30]

Although on average 1.5 more lesions were detected on CCTA than on ICA, the difference in the average number of MEVT which needed bypass grafting was only 0.6. The current CCTA-aSS allows reporting of more than one serial bifurcation/trifurcation and total occlusion within the same coronary segment, which may account for this difference. Furthermore, at variance with ICA, lesions located distal to total occlusions are visualized on CCTA. Using the criteria of a 6 mm occlusion length (absence of contrast), more total occlusions were seen on CCTA ($n = 86$) than ICA ($n = 74$), further contributing to the difference in lesion numbers. Notwithstanding, the new version of CCTA-aSS had a high inter-observer reproducibility when tested in this study cohort ($n = 113$, $\kappa = 0.82$).[18]

In the FAST TRACK CABG, FFR_{CT} of the native coronary artery was mandatory and provided functional information (FFR_{CT})

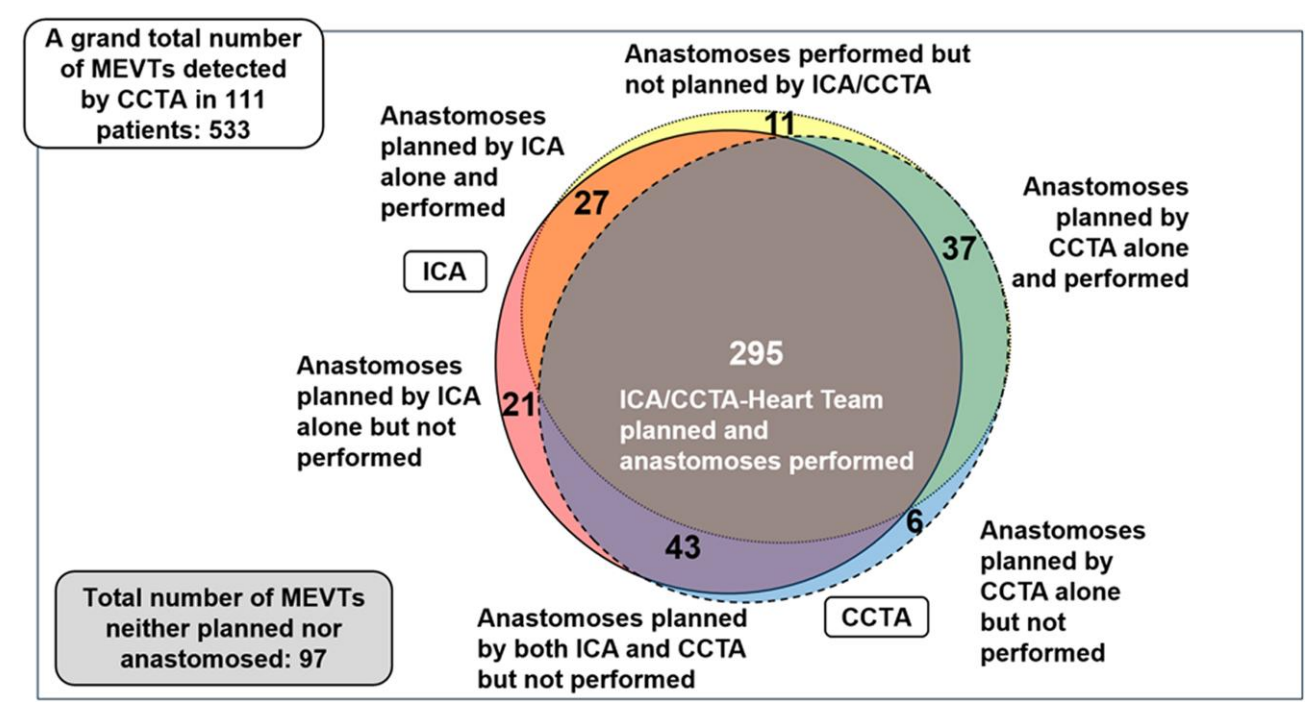


Figure 2 Agreement between revascularization planned by the Heart Teams against actual treatment by using major epicardial vessel territories (MEVTs). Text incorporated in the manuscript describing the Venn diagram: a total of 533 MEVTs (diameter stenosis ≥50% with reference diameter > 1.5 mm) were detected by CCTA in 111 operated patients. In a clockwise fashion, from 9 o'clock, the total number of bypassed MEVTs (367) consists of 292 bypassed MEVTs targeted both by ICA- and CCTA-Heart Teams (centre), 27 bypassed MEVTs targeted only by ICA-Heart Team (ten O'clock), 11 bypassed MEVTs but not originally targeted by ICA- and CCTA-Heart Teams (twelve O'clock), and 37 bypassed MEVTs targeted only by CCTA-Heart Team (two O'clock). Six MEVTs targeted only by CCTA-Heart Team but not bypassed are depicted at five O'clock, and 43 MEVTs targeted by both ICA- and CCTA-Heart Teams but not bypassed are depicted at seven O'clock. Twenty MEVTs targeted only by ICA-Heart Team but not bypassed are depicted at eight O'clock. Ninety-seven MEVTs have to be added to all the options depicted in the Venn diagram (436) and constitute the overall denominator of the kappa calculation. CCTA, coronary computed tomography angiography; ICA, invasive coronary angiography

complimenting the anatomical data from the CCTA. The average number of lesions with a visual diameter stenosis of 50% was 6.51 (4.09) per patient; notably, the cath lab time that would have been needed to evaluate that number of lesions with invasive pressure wire FFR would have been prohibitive. The fSS 41.2 (16.5) was lower than the anatomical SYNTAX score 43.6 (15.3) which ensured that only the most important ischaemia-proven vessels were grafted considering the limited availability of anatomic graft material. As already mentioned, out of 689 anatomic stenoses, 52 were not functionally significant ($FFR_{CT} > 0.8$) and 42 of these were not grafted.

For the surgeon, 'complete revascularization' in 3VD means, in many scientific reports, successfully intended revascularization of the three MEVT (RCA, LAD, LCX) including secondary side branches (e.g. diagonal, obtuse marginal, posterolateral branch), whilst a PCI operator may report a more granular description of all the stenotic/occluded coronary segments involved in each MEVT as depicted in the SYNTAX score segments (see Supplementary data online, *Table S4*).[14,31–33]

Despite significant differences in the aSS calculated using ICA and CCTA and the reliance on different imaging modalities, there was reasonable concordance between the planning of the two Heart Teams and the actual treatment delivered during surgery (*Figure 2*, Supplementary data online, *Figure S1*), with no significant difference in the number of MEVT targeted for grafting by each individual Heart Team (95% CI difference −0.019 to 0.081). Therefore, the topographical adequacy of anatomic grafting guided by ICA or CCTA seems to be comparable, as were grafting techniques and the types of graft used (95% CI difference −0.015 to 0.086).

Anatomic vs. functional revascularization

The CABG strategies recommended by the core lab were based on a combination of anatomical (visual) and functional assessment with FFR_{CT}. In the SYNTAX III REVOLUTION trial, FFR_{CT} was analysable in 196 out of 223 patients with 3VD, with the mean (SD) CCTA-aSS and CCTA-fSS 33.9 (13.0) and 30.5 (13.0), respectively. In that trial, FFR_{CT} changed the recommended treatment (PCI or CABG) in 7% of cases and modified the target vessel in 12%.[6]

Out of 689 anatomic stenoses, only 52 were not functionally significant ($FFR_{CT} > 0.80$), and 42 of them were not bypassed. Since the number of narrowed coronary segments far exceeds the number of available grafts, a $FFR_{CT} > 0.80$ was an important factor in selecting the vessels to be bypassed.

Doenst *et al.*[34] have advocated and promoted the concept of CABG ('surgical collateral flow', in their wording) as a preventative treatment of high-risk lesions located proximal to the anastomosis since a thin cap rupture of a vulnerable plaque located proximal or distal to a stent would jeopardize the whole myocardial territory distal to the stent, whereas a similar event occurring proximal to the graft anastomosis would not have a major ischaemic bearing on the myocardial territory distal to the anastomosis. In keeping with that concept, surgical collateral flow may provide flow in a retrograde and anterograde fashion to coronary

Table 3 Angiographic outcome at 30 days

Angiographic outcome based on 30-day CCTA	N = 102	95% CI
Anastomoses performed at surgery	N = 366	
Anastomoses per patient, n (SD) (n = 111 operated)	3.57 (0.86)	3.41–3.73
30-day follow-up CCTA, n (%)	102/111 (91.9%)	85.2%–96.2%
Anastomoses patent (patency rate, %)	339/366 (92.6%)	89.4%–95.1%
Anastomoses occluded (occlusion rate, %)	27/366 (7.4%)	4.9%–10.6%
Site of occlusion		
Ostium, n (%)	11/366 (3.0%)	1.5%–5.3%
Side-to-side, n (%)	0	
End-to-side, n (%)	16/366 (4.4%)	2.5%–7.0%
Post-CABG SYNTAX score, mean (SD)	11.7 (10.6)	9.6–13.8
Post-CABG SYNTAX score ≥ 22, n (%)	15/102 (14.7%)	8.5%–23.1%

SD, standard deviation; CCTA, coronary computed tomography angiography; CI, confidence interval; SYNTAX, The SYNergy between percutaneous coronary intervention with TAXus and cardiac surgery; CABG, coronary artery bypass grafting.

Table 4 Clinical outcome at 30 days

Clinical endpoint in operated patients	N = 111	95% CI
Unblinded to ICA, n (%)	1/111 (0.9%)	0%–4.9%
Composite endpoint of MACCE, n (%)	8/111 (7.2%)	3.2%–13.7%
Cardiovascular death, n (%)	2/111 (1.8%)	0.2%–6.4%
Stroke, n (%)	3/111 (2.7%)	0.6%–7.7%
Ischaemic, n (%)	3/111 (2.7%)	0.6%–7.7%
Haemorrhagic, n (%)	0	
Death or stroke, n (%)	4/111 (3.6%)	1.0%–9.0%
Peri-procedural myocardial infarction, n (%)	4/111 (3.6%)	1.0%–9.0%
Spontaneous myocardial infarction, n (%)	0	
Death or stroke or myocardial infarction, n (%)	8/111 (7.2%)	3.2%–13.7%
Revascularization, n (%)	4/111 (3.6%)	1.0%–9.0%
PCI, n (%)	3/111 (2.7%)	0.6%–7.7%
CABG, n (%)	1/111 (0.9%)	0%–4.9%
Death or stroke or MI or revascularization, n (%)	8/111 (7.2%)	3.2%–13.7%
Bleeding (BARC 4 and 5), n (%)	4/111 (3.6%)	1.0%–9.0%
BARC 4, n (%)	3/111 (2.7%)	0.6%–7.7%
BARC 5, n (%)	1/111 (0.9%)	0%–4.9%
Net adverse clinical events[a], n (%)	11/111 (9.9%)	5.1%–17.0%

CI, confidence interval; ICA, invasive coronary angiography; MACCE, major adverse cardiac and cerebrovascular event; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; MI, myocardial infarction; BARC, Bleeding Academic Research Consortium; CCTA, coronary computed tomography angiography; SD, standard deviation.
[a]Net adverse clinical events is MACCE plus BARC 4 or 5 bleeding events.

segments located distal to a subtotal lesion and contribute retrograde blood flow to large amounts of post-stenotic myocardial territory.

Spadaccio *et al.*[35] have reviewed the literature on FFR and CABG which is contradictory and not univocal. Two randomized trials, FARGO and GRAFFITI, could not demonstrate a detrimental effect of a pressure wire FFR > 0.80 on the occurrence of graft failure, at variance with three retrospective and two prospective studies that tended to demonstrate a negative impact of an FFR > 0.80 on graft patency. Based on this evidence, Lytle and Gaudino[36] concluded that FFR assessments may be useful when deciding whether or not to use an arterial conduit to graft a certain vessel but not to determine whether or not that vessel should be grafted.

The FFR_{CT} aids surgeons to be more selective in their revascularization strategy by avoiding the grafting of narrowed vessels with an FFR_{CT} > 0.80, thereby sparing graft material for vessels with an FFR_{CT} < 0.80. Only 1 of the 27 occluded anastomoses in our study were connected with a vessel having a baseline FFR_{CT} > 0.80, and thus, the other occlusions must have been due to technical reasons generating a rheology prone to thrombosis. In contrast to pressure-derived FFR which is a focal measurement in a specific vessel, FFR_{CT} is analysable over all the entire coronary circulation.

Coronary computed tomography angiography with FFR_{CT} might provide better anatomical and functional analysis of the coronary circulation leading to more appropriate anatomical and functional revascularization and thereby contributing to a better outcome. A presentation at the ESC congress 2023 of 90 000 CCTAs from the UK without (not available before 2018) or with FFR_{CT} (available after 2018) demonstrated a 14% reduction in cardiovascular death in favour of those patients diagnosed using CCTA + FFR_{CT}.[37]

Anastomosis occlusion at 30 days

At 30-day follow-up CCTA in 102 patients, 339 (92.6%) of the 366 anastomoses [average number of anastomoses per patient 3.57 (0.86)] were patent. The 27 anastomosis occlusions (21 patients) were documented both in arterial and venous grafts and located both at the graft ostium and at the site of the anastomosis; in 19 patients, the anastomosis occlusion(s) were silent. The two remaining patients had acute graft occlusion on the same day. A previous single centre study of 346 patients with 955 bypass grafts reported an incidence of early asymptomatic graft failure of 4.7% at pre-discharge CCTA,[38] with the independent risk factors: female sex, composite grafting, pulse index value, and new post-procedural atrial fibrillation. Károlyi *et al.*[39] reported a graft occlusion or high-grade stenosis rate of 15% amongst 305 consecutive patients who underwent CABG and had a post-operative CCTA at a median of 6 days post-surgery. Sousa *et al.*[40] randomized 150 patients to on- or off-pump

Table 5 Comparison of the graft patency rate with the previous trials

Trial name	FAST TRACK CABG	Károlyi *et al.*[39]	Han *et al.*[38]	Sousa *et al.*[40]
Patient population	*N* = 102	*N* = 305	*N* = 346	*N* = 150
Anastomoses performed at surgery	*N* = 366	*N* = 943	*N* = 955	*N* = 487
Follow-up period after procedure	30 days	6 days	Pre-discharge (4–34 days)	5 weeks
Anastomoses patent (patency rate, %)	339/366 (92.6%)	912/943 (96.7%)	910/955 (95.3%)[a]	450/487 (92.4%)
Anastomoses occluded (occlusion rate, %)	27/366 (7.4%)	31/943 (3.3%)	45/955 (4.7%)	37/487 (7.6%)

[a]The report excluded 25 patients with symptom and/or signs of myocardial infarction.

CABG and reported rates of graft patency on CCTA at 30 days of 89.9% and 95.0% after off- and on-pump surgery, respectively [intrathoracic artery (ITA) 94% vs. 97%, RA 86% vs. 94%, and SVG 86% vs. 93%]. The rate of anastomosis occlusion in our trial is in keeping with these studies (*Table 5*). Typically, in a first-in-human study, feasibility and safety at a patient level are essential, and in the absence of a comparative outcome, which is the prerequisite and basis of a first-in-human, we need to rely on performance indices that have already been described in the literature. If surgical performance is comparable with historical series, then it can be assumed that CCTA is an appropriate guide for the surgeon; however, this needs confirmation in randomized control trials.

Safety assessment and patient-oriented composite endpoint

In this first-in-human trial, two deaths occurred: one due to a massive stroke and the other a BARC 5 bleed; the death rate (1.8%) in this small cohort is possibly at variance with the 30-day mortality predicted by the STS score (0.80, 95% CI 0.68–0.91) and EuroSCORE II (1.06, 95% CI 0.94–1.17).

The study used the same definition for PPMI as the EXCEL trial, which enrolled patients with LM CAD of low or intermediate anatomical complexity, and our rate of 3.6% (4/111) is on par with the 6.1% in EXCEL.[41]

In a contemporary series of 2209 patients from a large quaternary healthcare system in the USA, the incidence of re-PCI within 30 days of CABG was 2.5% (55/2209) which is comparable with the 2.7% (3/111) we observed.[42] The median time from CABG to angiography was 3 days (interquartile range, 1–7) in the referred study. Having considered these results, our results (2.7%, 95% CI 0.6%–7.7%) are not significantly different from the numbers published in the literature (95% CI of difference between the current trial and Serruys *et al.*[1] −2.5% to 3.7%).

Among 111 patients of this series who underwent ICA within 30 days of CABG, the incidence of stroke was 2.7% (3/111), which is identical to ours. According to the independent CEC, none of these unplanned PCIs were directly related to the CABG being performed under the guidance of CCTA.

The eagerness to develop non-invasive diagnostic testing is increasing given the benefits to patients in terms of improved safety and accessibility and the impact on the wider healthcare economy. Recently, the DISCHARGE trial has provided the first randomized comparison between an invasive and non-invasive diagnostic assessment in patients with stable chest pain who had an intermediate pre-test probability of obstructive CAD.[43] During initial management (<48 h), the study showed rates of major procedure-related complications of 0.5% with CCTA and 1.9% with ICA (hazard ratio 0.26, 95% CI 0.13–0.55).

Our single-arm, proof-of-concept study showed excellent feasibility and satisfactory 30-day safety profile that may pave the way to a randomized comparison of invasive and non-invasive diagnostic assessment, decision-making, and procedural guidance in patients with the most complex CAD.

Limitations

One of the major limitations of this first-in-human study is that the CCTA-Heart Team had the pre-knowledge that these patients had 3VD with/without LM disease, were amenable to surgical revascularization, and had been accepted for CABG. However, the CCTA-Heart Team remained strictly blinded to the actual coronary anatomy and the surgical strategy devised using the ICA by the separate ICA-Heart Team. Obviously, this single-arm study has no randomized comparators.

Second, the four surgical sites have previously participated in a virtual randomized trial testing the equivalence of decision-making either based on conventional ICA or CCTA and it remains to be demonstrated whether their expertise can be conveyed to other surgical centres and tested in a randomized trial.[6,21]

Third, due to the first-in-human nature of this trial, it included selective patients who mainly had CCS and were of low surgical risk. The seven patients enrolled with unstable angina (no troponin rise) did not need urgent revascularization.

Fourth, the recruitment started in September 2020 and ended in May 2023. At the beginning of the study, enrolment was slowed down due to the administrative and logistic restrictions associated with the COVID-19 pandemic that have impacted the duration of recruitment and the interpretation of the true feasibility in time of our first-in-man trial.

Conclusions

The planning and execution of CABG with the sole knowledge of anatomy from CCTA, and without any visual information from conventional coronary angiography, in patients referred for CABG is feasible and deemed safe in a select population with chronic coronary syndrome and low surgical risk. Efficacy and confirmed safety will have to be demonstrated in randomized controlled studies.

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Supplementary data

Supplementary data are available at *European Heart Journal* online.

Declarations

Disclosure of Interest

P.W.S. reported consulting fees from SMT, Novartis, Meril Life, Philips, and Xeltis. J.L. reported the grants from GE HealthCare, consulting fees and stock options from HeartFlow and Circle CVI, and speaker fees from GE HealthCare and Philips. S.G. reported consulting fee from Biosensors. J.N. reported consulting fee from HeartFlow. G.P. reported grants and consulting fees from GE HealthCare, Bracco, and HeartFlow, honoraria from GE HealthCare and HeartFlow, and payment for expert testimony from GE HealthCare. All other authors have nothing to declare.

Data Availability

The data underlying this article will be shared on reasonable request to the corresponding author.

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Ethical Approval

The study was approved by the ethics committee of each enrolling site. Ethical approvals from the ethics committee/institutional review board of the Centro Cardiologico Monzino (R1158/20-CCM 1220), University Hospital of Brussels (B1432020000236), University Hospital Jena (2020-1889-1-BO), and Mount Sinai School of Medicine (STUDY-22-00201) have been obtained. Each patient provided written informed consent as approved by the ethical committee of the respective clinical site.

Pre-registered Clinical Trial Number

This trial is registered with ClinicalTrials.gov, number NCT04142021.

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