"Randomized Comparison of HARVesting the Left Internal Thoracic Artery in a skeletonized versus pedicled technique: the HARVITA trial – study protocol"

Hannes Abfalterer[1*], Elfriede Ruttmann-Ulmer[1], Michael Grimm[1], Gudrun Feuchtner[2], Sarah Maier[3], Hanno Ulmer[3], Sigrid Sandner[4], Daniel Zimpfer[5], Torsten Doenst[6], Martin Czerny[7], Matthias Thielmann[8], Andreas Böning[9], Mario Gaudino[10], Matthias Siepe[11], Nikolaos Bonaros[1]

[1] Department of Cardiac Surgery, Medical University of Innsbruck, Innsbruck, Austria

[2] Department of Radiology, Medical University of Innsbruck, Innsbruck, Austria

[3] Institute of Medical Statistics and Informatics, Medical University of Innsbruck, Innsbruck, Austria

[4] Department of Cardiac Surgery, Medical University of Vienna, Vienna, Austria

[5] Department of Surgery, Division of Cardiac Surgery, Medical University of Graz, Graz, Austria

[6] Department of Cardiac Surgery, University of Jena, Jena, Germany

[7] Department of Cardiovascular Surgery, University of Freiburg, Freiburg, Germany

[8] Department of Thoracic and Cardiovascular Surgery, West-German Heart & Vascular Center, University Hospital Essen, University of Duisburg-Essen, Essen, Germany

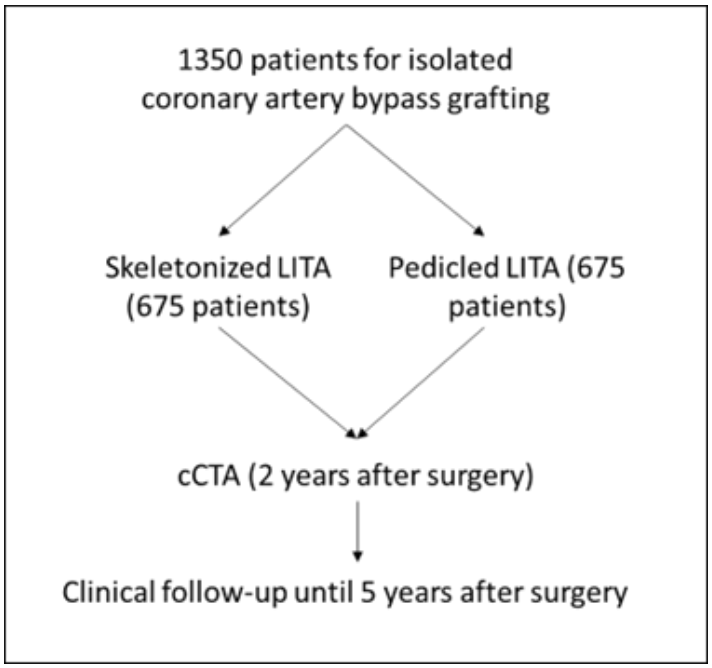
[9] Department of Cardiovascular Surgery, University Hospital Giessen, Giessen, Germany

[10] Department of Cardiothoracic Surgery, Weill Cornell Medicine, New York City, NY, USA

[11]Department of Cardiac Surgery, University Hospital Bern, University of Bern, Switzerland

* corresponding author/principal investigator: Department of Cardiac Surgery, Medical University of Innsbruck, Anichstraße 35, 6020 Innsbruck, Austria. Tel: +43-51250482988, e-mail: hannes.abfalterer@i-med.ac.at

Visual abstract:



Legend: LITA… left internal thoracic artery, cCTA… coronary computed tomography angiography

Summary:

Hereby we present the study protocol of the HARVITA trial, the first adequately powered, prospective, randomized, multi-centre trial comparing skeletonized and pedicled harvesting technique of internal thoracic arteries.

Abstract:

Latest research has posed a potential adverse effect of skeletonizing left internal thoracic artery on graft patency rates and clinical outcomes. With this trial, we aim to provide a prospective, randomized, multi-centre trial to compare skeletonized versus pedicled harvesting technique of left internal thoracic artery concerning graft patency rates and patient survival. 1350 patients will be randomized to either skeletonized or pedicled harvesting technique and undergo surgical revascularization. Follow-up will be performed at 30 days, 1 year, 2 years and 5 years after surgery. The primary outcome will be death or left internal thoracic artery graft occlusion in coronary computed tomography angiography or invasive angiography within 2 years (+/- 3 months) after surgery. The secondary outcome will be major adverse cardiac events (composite outcome of all-cause death, myocardial infarction and repeated revascularization) within 1 year, 2 years and 5 years after surgery. The primary endpoint will be compared in the modified intention-to-treat population between the two treatment groups using Kaplan-Meier graphs, together with log-rank testing.

Hereby, we present the study protocol of the first adequately powered prospective, randomized, multi-centre trial, which compares skeletonized and pedicled harvesting technique of left internal thoracic artery regarding graft patency rates and patient survival.

Keywords: left internal thoracic artery, skeletonized versus pedicled, harvesting technique, graft patency rate

Abbreviations and acronyms:

BMI… body mass index

CABG… coronary artery bypass grafting

CAG… coronary angiography

cCTA… coronary computed tomography angiography

CT… computed tomography

ECG… electrocardiography

e.g. … example given

et al. … et alii

GFR… glomerular filtration rate

ITA… internal thoracic artery

ITT… intention-to-treat

LAD… left anterior descending artery

LITA… left internal thoracic artery

MACE… major adverse cardiac events

mITT… modified intention-to-treat

mmHg… millimetre of mercury

PCI… percutaneous coronary intervention

PI… pulsatility index

RA… radial artery

RITA… right internal thoracic artery

SVG… saphenous vein graft

TTFM… transit time flow measurement

Objectives:

Since the landmark study by Loop et al. in 1986 (1), the left internal thoracic artery (LITA) is the preferred bypass conduit to the left anterior descending artery (LAD), owing to its survival benefit over the saphenous vein graft (SVG), which has also been noticed in other observational studies (2) (3) and one small randomized trial (4).

Since occlusion of the proximal LAD more often leads to fatal myocardial infarction than occlusion of non-LAD coronary vessels (except from the left main coronary artery), the LAD has an extremely important role in myocardial revascularization (1).

Therefore, current European and American guidelines (5) (6) recommend the use of the LITA to the LAD to improve patient`s outcome.

Two techniques exist for surgical harvesting the LITA during coronary artery bypass grafting (CABG): pedicled and skeletonized harvesting technique (7). While a pedicle contains the artery, together with its accompanying veins, fatty tissue and endothoracic fascia, in skeletonized harvesting technique, only the artery is harvested.

Skeletonizing the internal thoracic artery (ITA) may be more time-consuming and more challenging, but it provides a graft of longer-length and better free-flow (8). Furthermore, various studies describe a reduced incidence of sternal wound infections for skeletonized harvesting technique (9) (10) (11) (12) (13). On the other hand, when only one ITA is used, skeletonization does not provide any additional effect on preventing sternal wound complications (9). Deep sternal wound infections especially, are associated with increased mortality and morbidity (14), but they are caused by multiple factors, not solely by harvesting technique of ITAs (15). Lazar et al. was indeed able to eliminate any form of sternal wound

infection by 3 perioperative measures (perioperative intravenous antibiotics, topical vancomycin to the sternal edges and tight glycaemic control) (16).

Besides the potential beneficial effects, skeletonizing the ITAs is supposed to be more prone to injury (17).

Latest research by Lamy et al. and Gaudino et al. has posed a potential adverse effect of skeletonizing LITA on graft patency rates and clinical outcomes (18) (19). In a post-hoc analysis of the COMPASS trial Lamy et al. saw a significant reduced short-term graft patency at one year and a significant higher risk for major adverse cardiac events (MACE) at 23 months after CABG for skeletonized harvesting technique. In a post-hoc analysis of the ART trial Gaudino et al. did not provide data on graft patency rates, but at 10 years, the risk for MACE was significantly higher for skeletonized versus pedicled ITA grafts. A difference in 10-year mortality rate was not seen. Interestingly, the impaired outcome was only observed in surgeons who enrolled less than 51 patients to the study, implying that surgeon`s experience plays a key role.

Furthermore, a significant learning curve has been described, for LITA graft harvesting (20).

To date, no adequately powered randomized trial has ever been performed investigating the influence of harvesting technique of ITAs on graft patency rates and clinical outcome.

Due to the ongoing debate on the potential adverse outcome of skeletonizing harvesting technique of ITA, only prospective randomized trials will tell, if skeletonizing of ITA is a safe procedure or contains potential adverse effects.

Therefore, with the HARVITA trial, we aim to provide a prospective, randomized, multi-centre trial to compare skeletonized versus pedicled harvesting technique of LITA concerning patency rates.

Methods:

Study design:

The HARVITA trial is a 2-arm, prospective, randomized, multi-centre clinical trial aiming to evaluate the impact of harvesting technique of LITA on patency rates. All patients who are referred to isolated CABG will be screened for inclusion and exclusion criteria. For eligible patients, informed consent will be required. Patients will be randomized to skeletonized or pedicled harvesting technique of LITA. Coronary CT angiography (cCTA) will be performed, in order to evaluate LITA graft status, 2 years (+/- 3 months) after surgery. Follow up will be performed at 30 days, 1 year, 2 years and 5 years after surgery.

Hypotheses:

Primary hypothesis:

Harvesting technique of LITA (skeletonized versus pedicled) is associated with a difference in the rate of death or LITA graft occlusion within 2 years (+/- 3 months) after surgery.

Eligibility:

Inclusion criteria:

Primary isolated CABG patients with multi-vessel disease (defined as ≥70 % stenosis of the left anterior descending artery (LAD) and ≥50% stenosis of circumflex and right coronary territory, with or without a ≥50% stenosis of the left main artery).

Exclusion criteria:

- Age > 80 years
- Planned CABG without LITA use
- Preoperative mediastinal radiation therapy
- Emergency operation
- Minimal invasive coronary artery bypass surgery
- Any concomitant cardiac or non-cardiac procedures
- Previous cardiac surgery
- Known contrast agent allergy
- Severe stenosis of the left subclavian artery/ left-sided subclavian steal syndrome
- Chronic kidney disease (GFR <60ml/min/1.73m²)
- Life expectancy of less than 5 years
- Pregnancy
- Hyperthyroidism
- Iodine allergy

Intraoperative exclusion criteria:

- Y/T graft off the LITA graft
- LITA sequential grafting
- LITA target vessel other than LAD

Randomization, stratification and enrolment:

All patients with planned isolated CABG procedure are screened according to inclusion and exclusion criteria. In case of eligibility and patient informed consent, patients will be randomized to one of the two treatment arms (skeletonized or pedicled harvesting technique).

Patients will be randomized in a 1:1 fashion. Permuted block randomization with variable block sizes and stratification by centre will be performed with a web-based randomization system, in order to achieve an equal distribution in both groups. Log will be held for all screened patients with reasons for inclusion and exclusion.

Surgical procedure:

Surgery should take place within 4 weeks of randomization. Surgery is carried out via median sternotomy and either on-pump or off-pump. Harvesting of LITA is performed by surgeons who are technically capable of both harvesting techniques and who have harvested at least 50 ITAs. LITA is either harvested with electrocautery or harmonic scalpel, independently of allocated harvesting technique and according to the established method in each centre. Only topical, but not intravasal application (in order to decrease the risk of a potential endothelial damage) of spasmolytic agents will be used. If randomized to skeletonized harvesting technique, only the LITA itself is harvested, in case of pedicle harvesting technique, the LITA, it`s accompanying veins and parts of the endothoracic fascia is harvested, creating a 1-2 cm broad pedicle. Through an incision in the pericardium, the LITA is brought intrapericardial and then anastomosed with running suture to the LAD. In case of pedicled harvesting technique, the pedicle is stabilized without tension at the height of anastomosis with sutures at the

surface of the heart, to avoid twisting of the pedicle. Any other target vessel for LITA other than LAD is against protocol. For LITA, sequential or T/Y graft configuration is not allowed. LITA is primarily used as in-situ graft. The remaining diseased coronary vessels (≥1.5mm and target vessel stenosis ≥50%) will receive SVG, RA or right ITA (RITA). SVG can be either harvested in open (conventional or no-touch) or endoscopic technique. RA can be harvested in open or endoscopic technique, both as a pedicle. RITA can be harvested in either skeletonized or pedicled harvesting technique, independent of the randomization process. Surgeons are encouraged to attach the proximal part of the SVG and/or RA to the ascending aorta. It is recommended to not use RA which has been used for coronary angiography (CAG) prior to surgery. It is also recommended to anastomose RA to a target vessel with high grade stenosis. After de-cannulation and administration of protamine, transit time flow measurements (TTFM) are used for final evaluation of all grafts. All TTFM measurements are performed at a mean arterial pressure of 70 to 80 mmHg, as much distally as safely possible. Mean graft flow (ml/min), pulsatility index (PI) and mean arterial blood pressure (mmHg) is recorded.

Recommendations to prevent sternal wound infections:

Sternal wound infections are associated with high mortality and morbidity (14). The European Association for Cardio-Thoracic Surgery and the American Association for Thoracic Surgery provide guidelines for the prevention and treatment of sternal wound infections (14) (21). We recommend obtaining the following measures, in both treatment groups (skeletonized and pedicled harvesting technique), in order to prevent the occurrence of sternal wound infections:

- routine screening for nasal carriers of Staphylococcus aureus

- topical mupirocin to the nares for all patients without negative screening for staphylococcus in nasal swab within 24 hours of the surgery and up to 5 days after surgery
- continuous insulin therapy to keep blood glucose level <180mg/dl within the first 24 hours after surgery or for the duration of intensive care unit stay
- a cephalosporin (either cefuroxime or cefazolin) as a first choice should be administered 60 minutes prior to skin incision and up to a maximum of 72 hours (individual institutional protocols are accepted)
- topical application of vancomycin to the bone edges immediately after median sternotomy and prior to sternal closure
- avoiding the use of bone wax

Postoperative treatment:

Postoperative treatment will be carried out according to local standards and current guidelines (22). Treatment with antiplatelet agents should be re-started within 24 hours to surgery, in case there is no concern regarding surgical bleeding. In case RA was used as a graft, the decision to use spasmolytic medication (agent, duration and time of initiation) will be left to local practice. Secondary prophylaxis should be carried out according to current guidelines (5) (23) (24). We generally recommend the use of aspirin as antiplatelet agent (indefinitely), the use of angiotensin-converting-enzyme inhibitors/angiotensin receptor blockers (sartane), the use of a beta-blocker and the use of a statin for guideline-conform secondary prophylaxis. In case of dual antiplatelet therapy (off-pump, previous acute coronary syndrome, previous elective/acute coronary stent implantation) we recommend the use of aspirin in combination with clopidogrel, in order to ensure uniformity.

Outcome measures:

Primary outcome:

Death or LITA graft occlusion in cCTA or invasive angiography within 2 years (+/- 3 months) after surgery.

Secondary outcome:

MACE-free survival (composite outcome of all-cause death, myocardial infarction and repeated revascularization) within 1 year, 2 years and 5 years after surgery.

Additional secondary outcomes:

1) Death/LITA graft occlusion (in cCTA or invasive angiography)/intraoperative LITA graft injury within 2 years (+/- 3 months) after surgery
2) LITA graft occlusion (and LITA graft dysfunction) in cCTA or invasive angiography at 2 years (+/- 3 months)
3) LITA graft occlusion at cCTA or invasive angiography for patients with cCTA or invasive angiography for clinical reasons
4) Repeated revascularization at 2 years and 5 years after surgery.
5) Repeated revascularization of the left anterior descending artery (LAD target vessel revascularization) at 2 years and 5 years after surgery.
6) Sternal wound complications at 1 year after surgery
7) Composite endpoint of LITA graft occlusion/dysfunction (cCTA or invasive angiography), myocardial infarction, repeat-revascularization within 2 years (+/- 3 months) after surgery.
8) Perioperative outcome at 30 days

Further analyses:

- Primary and secondary endpoints for male versus female sex
- Primary and secondary endpoints according to the severity of target vessel stenosis (moderate 50 - <70%, severe ≥70% or occlusion)
- Competing risk analyses

Follow-up:

Patients will receive cCTA at 2 years (+/- 3 months) postoperatively. 1 week prior to cCTA, blood samples (glomerular filtration rate, creatinine and thyroid stimulating hormone for the upcoming cCTA; LDL-cholesterol and HbA1c for follow-up) will be collected. At 30 days, 1 year, 2 years and 5 years postoperatively, phone calls will be used for follow-up. cCTA should be performed within a time span of 6 months (-3 months to + 3 months) for 2 year`s cCTA. If cCTA or invasive angiography is performed for clinical reasons (e.g., signs of acute or chronic ischemia, acute myocardial infarction, heart failure, or recurrence of symptoms), prior to the above-mentioned time interval (> 3 months prior to 2 year`s cCTA) and LITA graft is not occluded, cCTA will be performed according to protocol. If cCTA or invasive angiography is performed due to other reasons prior to the above-mentioned time interval (> 3 months prior to 2 year`s cCTA) and LITA graft is occluded, cCTA will not be performed and the findings of cCTA/CAG will be used for statistical analysis. If CAG is performed due to other reasons within the above-mentioned time intervals (≤ 3 months prior to 2 year`s cCTA) and LITA graft does or does not show LITA graft occlusion, cCTA will not be repeated and the findings of the CAG will be used for statistical analysis. In case of occlusion or dysfunction of other grafts rather than LITA, patients with clinical symptoms and/or pathological findings in non-invasive testing,

should be referred to invasive angiography. This decision will be left to the clinical assessment of the participating centres.

Table 1 describes the process of follow-up.

cCTA:

At each participating centre two independent experienced radiologists, blinded to patient data (especially allocated harvesting cohort) (but not to the type of graft (LITA/RA/RITA/SVG) and their target vessels), will evaluate the cCTA results according to graft patency status. Graft status will be analysed for all bypass grafts. Graft patency by cCTA will be determined and classified as: 1 = patent, 2 = dysfunctional and 3 = 100% occlusion.

In case of equal assessment of graft status by the two independent radiologists, no further assessment is necessary. In case of unequal assessment, cCTA image data will be sent anonymized as a DICOM file to the core-centre. The cCTA will be assessed by a third experienced radiologist (blinded to patient data (especially allocated harvesting cohort) (but not to the type of graft (LITA/RA/RITA/SVG) and their target vessels) at the core centre. This is considered as the final evaluation. In inconsistent cases and if asked by the core centre, an invasive angiography will be performed.

CT Scan: Cardiac computed tomography angiography will be performed by using a CT scanner with ≥ 64 slices, in each centre.

Medical University Innsbruck: A 128-slice dual-source CT (Definition FLASH or DRIVE, Siemens Healthineers, Erlangen, Germany) with a detector collimation of 2×64×0.6 mm and a rotation time of 0.28 s will be used, and high-pitch (3.2) scanning (Flash mode). Scans will be triggered into arterial phase using bolus tracking (threshold of 100 HU, ascending aorta) and by injecting an intravenous iodine contrast agent (Iopromide, Ultravist 370™, Bayer Healthcare, Berlin, Germany, 70 – 120 ml pending on BMI). Prospective ECG-triggering will be applied and images reconstructed at an end-diastolic phase (70% of RR-interval). Thin slice images will be reconstructed with 0.75 mm slice width (increment, 0.4) and transferred to a 3D-postprocessing software (SyngoVIA, Siemens Healthineers, Erlangen, Germany) for cCTA image analysis. Estimated radiation exposure will be 1-3 mSv.

Beta blockers may be given to lower heart rate, pending on the centre's individual internal guidelines (scanner-specific), prior to the scan. Patients will be advised not to drink coffee prior to the CT exam (in order to avoid an increase in heart rate).

Outcome definitions:

LITA graft occlusion in cCTA: absence of contrast detection in the lumen of the graft indicating a 100% occlusion of LITA graft in cCTA

LITA graft dysfunction in cCTA: Suspicion of LITA graft dysfunction in cCTA either anatomical (anatomical stenosis ≥ 50% (for example due to plaques, stricture) at anastomotic site or in the course of the graft), functional (due to competitive flow) or unclear (diffuse small sized vessel without clear anatomical obstruction)

LITA graft occlusion in CAG: complete occlusion (100%) of LITA graft

LITA graft dysfunction in CAG: ≥ 50% stenosis of the LITA graft, string-sign of the graft due to competitive flow or graft spasm

Intraoperative LITA graft injury: surgeon`s decision to not use LITA as a conduit after the harvesting process

MACE: composite outcome of all-cause death, myocardial infarction and repeated revascularization

all-cause death: death from any cause (cardiac or non-cardiac) from the time of the surgical procedure

cardiac death: death due to myocardial infarction, cardiogenic shock, sudden cardiac death or cardiac arrhythmias

non-cardiac death: death from any cause rather than cardiac (e.g. cancer, trauma, pulmonary embolism, …)

myocardial infarction: composition of periprocedural myocardial infarctions and non-periprocedural *myocardial infarctions.*

-periprocedural myocardial infarction during CABG: defined as type 5 myocardial infarction according to the criteria of 4th universal definition of myocardial infarction (25)

- spontaneous myocardial infarction: defined as type 1-3 myocardial infarction according to criteria of the 4th universal definition of myocardial infarction (25)

repeat revascularization: any form of repeat revascularization (CABG, PCI (balloon angioplasty or stent implantation) after the index operation

343 *target vessel repeat revascularization:* any form of repeat revascularization (CABG, PCI
344 (balloon angioplasty or stent implantation)) to the LAD after the index operation

345 *sternal wound complication:* superficial or deep sternal wound infection requiring external
346 vacuum therapy, surgical treatment including wound debridement, open vacuum-assisted
347 therapy or sternal reconstruction with concomitant antibiotic therapy

348 *perioperative mortality:* death within 30 days after primary surgery

349 Supportive clinical centres:

350 The following centres will participate to the trial:

351 Department of Cardiac Surgery, Medical University of Innsbruck, Innsbruck, Austria (Dr. med.
352 univ. Hannes Abfalterer/Assoc.-Prof. Dr. Nikolaos Bonaros) (core clinical centre)

353 Department of Cardiac Surgery, Division of Surgery, Medical University of Vienna, Vienna,
354 Austria (Assoc. Prof. Priv. Doz. Dr. Sigrid Sandner, PhD)

355 Department of Surgery, Division of Cardiac Surgery, Medical University of Graz, Graz, Austria
356 (Univ.-Prof. Daniel Zimpfer)

357 Department of Cardiac Surgery, University of Jena, Jena, Germany (Univ.-Prof. Dr. Torsten
358 Doenst)

359 Department of Cardiovascular Surgery, University of Freiburg, Freiburg, Germany (Univ.-Prof.
360 Dr. Martin Czerny)

Department of Thoracic and Cardiovascular Surgery, West-German Heart & Vascular Center, University Hospital Essen, University of Duisburg-Essen, Essen, Germany (Univ.-Prof. Dr. Matthias Thielmann)

Department of Cardiovascular Surgery, University Hospital Giessen, Giessen, Germany (Univ.-Prof. Dr. Andreas Böning)

Department of Cardiac Surgery, University Hospital Bern, Bern, Switzerland (Univ.-Prof. Dr. Matthias Siepe)

Statistics:

Study design and objectives:

This is a 2-arm, prospective, randomized, observer-blinded, multi-centre clinical trial aiming to evaluate the impact of harvesting technique of LITA on graft occlusion-free survival. The primary endpoint is defined as death or LITA graft occlusion in cCTA or invasive angiography within 2 years (+/- 3 months), secondary endpoints include MACE (composite outcome of all-cause death, myocardial infarction and repeated revascularization) free-survival, occlusion rate and other graft related outcomes. LITA graft occlusion-free survival and MACE-free survival are treated as time-to-event variables with observation time ranging from date of surgery (time zero) to either date of event or censoring date.

Sample Size Rationale/Number of Patients:

A sample size estimation was performed using data of a post-hoc analysis of the COMPASS trial (18). In this trial at 1 year, LITA to LAD graft occlusion occurred in 7.3% (21/289) of

skeletonized and in 3.4% (25/725) of pedicled grafts (the COMPASS trial did not provide 2 year`s results). In addition, within two years, five of 1014 patients died. Rounding up this numbers, we consider event rates of 4% (pedicled) versus 8% (skeletonized) at 2 years as a realistic, conservative scenario for our study. In order to detect this difference of 4%, (corresponding to a hazard ratio of 0.49), as statistically significant with a two-sample log-rank test, a sample size of 558 patients in each treatment group is needed, assuming a type I error of 0.05 (alpha = 5%) and a power of 0.8 (beta = 20%), requiring 62 events (death or LITA occlusion) in total. To account for dropouts and withdrawals we increase the sample size to 675 patients in each group, resulting in a total sample size of 1350 patients for the trial.

Study population:

The following populations will be used for statistical analysis:

Intention-to-treat population:

The intention-to-treat (ITT) population consists of all individuals who are randomized to one of the arms of the HARVITA trial, regardless of adherence, treatment or protocol deviations.

Modified intention-to-to treat (mITT) population:

The mITT population consists of individuals who are randomized, undergo surgical procedure and have a LITA graft anastomosed to the LAD.

Data Analysis:

Demographic and Baseline Characteristics:

A flow-chart will be produced, showing the number of patients screened, excluded, randomized, receiving surgery and having follow up. Baseline demographic data will be presented as absolute numbers with percentages for categorical variables and as mean+/- standard deviation or median (interquartile range) for continuous variables.

Efficacy Analysis:

The primary endpoint LITA graft occlusion-free survival will be compared between the two treatment groups using Kaplan-Meier graphs and a center stratified two sample log-rank test. In addition, Cox proportional hazards regression analysis adjusting for clinically relevant confounders will be performed. Hazard ratios and their 95% confidence intervals will be estimated.

The primary efficacy hypotheses will thus be formulated as:

H_0: hazard ratio$_{\text{skeletonized vs. pedicled}} = 1$

H_1: hazard ratio$_{\text{skeletonized vs. pedicled}} \neq 1$

Primary efficacy analysis will be performed in the mITT population.

MACE-free survival and other secondary endpoints that follow the time-to-event format will be analysed with Kaplan-Meier, log rank test and Cox proportional hazards regression analysis. Categorical endpoints will be compared between treatment groups using a chi-square test. P values < 0.05 will be considered statistically significant, however, formal significance testing will be applied to the primary hypothesis only. Statistical tests for secondary endpoints will be applied in a descriptive manner only.

Safety Analysis:

Safety variables will be summarised using descriptive statistics and tabulated by treatment group.

Safety monitoring committee: A safety monitoring committee composed of three independent consultants (two consultants in cardiac surgery, one consultant in cardiology) will annually meet and inspect follow up data. The primary safety outcome composed of death, myocardial infarction and stroke as well as the secondary safety outcome composed of periprocedural major complications (re-operation due to bleeding, perioperative myocardial infarction, dialysis, tracheostomy, stroke and deep sternal wound infections) will be compared. In case of over 10% difference between the two treatment groups, the safety monitoring committee, together with the trial steering committee will temporarily pause the randomization of further patients, until a final decision is made. This final decision could either be the early termination of the trial or a change in the study protocol or a continuation of the trial.

Software:

All statistical analyses will be performed with SPSS Version 28 (IBM Corporation, Armonk, NY, USA), MedCalc Version 19.4, GraphPad Prism version 9.0. and R 3.2.2 (The R Foundation for Scientific Computing, Vienna, Austria).

Ethics:

Permission for this study was approved from the local institutional review board on 1st of December 2023 (Medical University of Innsbruck) (EK Nr: 1135/2023). All participating centres will apply for approval of the study-protocol at their local institutional review board before proceeding with enrolling patients to the trial.

Registration:

444 The HARVITA trial has been registered on ClinicalTrials.gov (NCT05931783)

445 Funding statement: in process

446 Conflict of interest statement: none declared

447 Data Availability Statement: data will be available upon request from the journal

448 Author contribution statement:

449 Hannes Abfalterer: conceptualization, writing-original draft, writing-review and editing,
450 visualization

451 Elfriede Ruttmann-Ulmer: conceptualization, writing-review and editing

452 Michael Grimm: conceptualization, writing-review and editing

453 Gudrun Feuchtner: conceptualization, writing-original draft, writing-review and editing

454 Sarah Maier: conceptualization, writing-original draft, writing-review and editing

455 Hanno Ulmer: conceptualization, writing-original draft, writing-review and editing

456 Sigrid Sandner: conceptualization, writing-review and editing

457 Daniel Zimpfer: conceptualization, writing-review and editing

458 Torsten Doenst: conceptualization, writing-review and editing

459 Martin Czerny: conceptualization, writing-review and editing

460 Matthias Thielmann: conceptualization, writing-review and editing

Andreas Böning: conceptualization, writing-review and editing

Mario Gaudino: conceptualization, writing-review and editing

Matthias Siepe: conceptualization, writing-review and editing

Nikolaos Bonaros: conceptualization, writing-review and editing, supervision

Tables:

Table 1 describes the process of follow-up (cCTA… coronary computed tomography angiography)

References:

1. Loop FD, Lytle BW, Cosgrove DM, Stewart RW, Goormastic M, Williams GW, et al. Influence of the Internal-Mammary-Artery Graft on 10-Year Survival and Other Cardiac Events. N. Engl. J. Med. 1986; 314(1):1-6.

2. Boylan MJ, Lytle BW, Loop FD, Taylor PC, Borsh JA, Goormastic M, et al. Surgical treatment of isolated left anterior descending coronary stenosis: Comparison of left internal mammary artery and venous autograft at 18 to 20 years of follow-up. J. Thorac. Cardiovasc. Surg. 1994; 107(3):657-62.

3. Cosgrove DM, Loop FD, Lytle BW, Gill CC, Golding LA, Gibson C, et al. Determinants of 10-year survival after primary myocardial revascularization. Ann. Surg. 1985; 202(4):480-90.

4. Zeff RH, Kongtahworn C, Iannone LA, Gordon DF, Brown TM, Phillips SJ, et al. Internal Mammary Artery versus Saphenous Vein Graft to the Left Anterior Descending Coronary

480 Artery: Prospective Randomized Study with 10-Year Follow-up. Ann. Thorac. Surg. 1988;
481 45(5):533-6.

482 5. Neumann FJ, Sousa-Uva M, Ahlsson A, Alfonso F, Banning AP, Benedetto U, et al. 2018
483 ESC/EACTS Guidelines on myocardial revascularization. Eur. Heart J. 2019; 40(2):87–165.

484 6. Lawton JS, Tamis-Holland JE, Bangalore S, Bates ER, Beckie TM, Bischoff JM, et al. 2021
485 ACC/AHA/SCAI Guideline for Coronary Artery Revascularization: A Report of the American
486 College of Cardiology/American Heart Association Joint Committee on Clinical Practice
487 Guidelines. Circulation. 2021; 145(3):e18-e114.

488 7. Keeley SB. The Skeletonized Internal Mammary Artery. Ann. Thorac. Surg. 1987;
489 44(3):324-5.

490 8. Athanasiou T, Crossman MC, Asimakopoulos G, Cherian A, Weerasinghe A, Glenville B,
491 et al. Should the internal thoracic artery be skeletonized? Ann. Thorac. Surg. 2004; 77(6):2238-
492 46.

493 9. Benedetto U, Altman DG, Gerry S, Gray A, Lees B, Pawlaczyk R, et al. Pedicled and
494 skeletonized single and bilateral internal thoracic artery grafts and the incidence of sternal
495 wound complications: Insights from the Arterial Revascularization Trial. J. Thorac. Cardiovasc.
496 Surg. 2016; 152(1):270-6.

497 10. De Paulis R, de Notaris S, Scaffa R, Nardella S, Zeitani J, Del Giudice C, et al. The effect
498 of bilateral internal thoracic artery harvesting on superficial and deep sternal infection: The
499 role of skeletonization. J. Thorac. Cardiovasc. Surg. 2005; 129(3):536-43.

11. Hu X, Zhao Q. Skeletonized Internal Thoracic Artery Harvest Improves Prognosis in High-Risk Population After Coronary Artery Bypass Surgery for Good Quality Grafts. Ann. Thorac. Surg. 2011; 92(1):48-58.

12. Peterson MD, Borger MA, Rao V, Peniston CM, Feindel CM. Skeletonization of bilateral internal thoracic artery grafts lowers the risk of sternal infection in patients with diabetes. J. Thorac. Cardiovasc. Surg. 2003; 126(5):1314-9.

13. Saso S, James D, Vecht JA, Kidher E, Kokotsakis J, Malinovski V, et al. Effect of Skeletonization of the Internal Thoracic Artery for Coronary Revascularization on the Incidence of Sternal Wound Infection. Ann. Thorac. Surg. 2010; 89(2):661-70.

14. Lazar HL, Salm TV, Engelman R, Orgill D, Gordon S. Prevention and management of sternal wound infections. J. Thorac. Cardiovasc. Surg. 2016; 152(4):962-72.

15. Lazar HL. The risk of mediastinitis and deep sternal wound infections with single and bilateral, pedicled and skeletonized internal thoracic arteries. Ann. Cardiothorac. Surg. 2018; 7(5):663-72.

16. Lazar HL, Ketchedjian A, Haime M, Karlson K, Cabral H. Topical vancomycin in combination with perioperative antibiotics and tight glycemic control helps to eliminate sternal wound infections. J. Thorac. Cardiovasc. Surg. 2014; 148(3):1035-40.

17. Deja MA, Gołba KS, Malinowski M, Woś S, Kolowca M, Biernat J, et al. Skeletonization of internal thoracic artery affects its innervation and reactivity. Eur. J. Cardiothorac. Surg. 2005; 28(4):551-7.

18. Lamy A, Browne A, Sheth T, Zheng Z, Dagenais F, Noiseux N, et al. Skeletonized vs Pedicled Internal Mammary Artery Graft Harvesting in Coronary Artery Bypass Surgery: A Post Hoc Analysis From the COMPASS Trial. JAMA Cardiol. 2021; 6(9):1042-9.

19. Gaudino M, Audisio K, Rahouma M, Chadow D, Cancelli G, Soletti GJ, et al. Comparison of Long-term Clinical Outcomes of Skeletonized vs Pedicled Internal Thoracic Artery Harvesting Techniques in the Arterial Revascularization Trial. JAMA Cardiol. 2021; 6(12):1380-6.

20. Oehlinger A, Bonaros N, Schachner T, Ruetzler E, Friedrich G, Laufer G, et al. Robotic Endoscopic Left Internal Mammary Artery Harvesting: What Have We Learned After 100 Cases? Ann. Thorac. Surg. 2007; 83(3):1030-4.

21. Abu-Omar Y, Kocher GJ, Bosco P, Barbero C, Waller D, Gudbjartsson T, et al. European Association for Cardio-Thoracic Surgery expert consensus statement on the prevention and management of mediastinitis. Eur J Cardiothorac Surg. 2017; 51(1):10-29.

22. Sousa-Uva M, Head SJ, Milojevic M, Collet JP, Landoni G, Castella M, et al. 2017 EACTS Guidelines on perioperative medication in adult cardiac surgery. Eur J Cardiothorac Surg. 2018; 53(1):5-33.

23. Knuuti J, Wijns W, Saraste A, Capodanno D, Barbato E, Funck-Brentano C, et al. 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes The Task Force for the diagnosis and management of chronic coronary syndromes of the European Society of Cardiology (ESC). Eur. Heart J. 2020; 41(3):407-77.

24. Visseren FLJ, Mach F, Smulders YM, Carballo D, Koskinas KC, Bäck M, et al. 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice: Developed by the Task

542 Force for cardiovascular disease prevention in clinical practice with representatives of the
543 European Society of Cardiology and 12 medical societies With the special contribution of the
544 European Association of Preventive Cardiology (EAPC). Eur. Heart J. 2021; 42(34):3227-337.

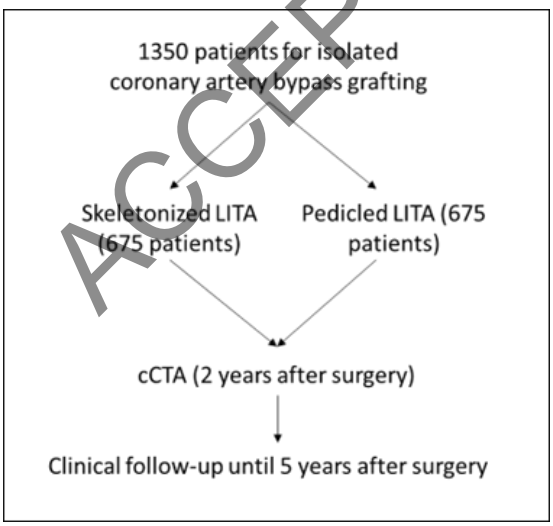
545 25. Thygesen K, Alpert JS, Jaffe AS, Chaitman BR, Bax JJ, Morrow DA, et al. Fourth Universal
546 Definition of Myocardial Infarction (2018). Circulation. 2018; 138(20):e618-51.

547 Table 1

Follow-up	30 days	1 year	2 years	5 years
Telephone interview	x	x	x (2 years + 3 months)	x
cCTA			x (2 years +/- 3 months)	

548 Table 1 describes the process of follow-up. (cCTA… coronary computed tomography
549 angiography)

550 Central Image



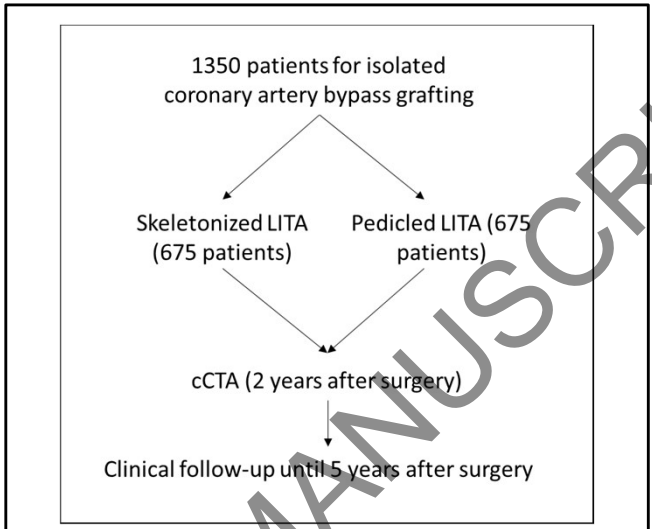
551

552 Legend: LITA… left internal thoracic artery, cCTA… coronary computed tomography
553 angiography

The HARVITA trial – study protocol

Summary

Hereby we present the study protocol of the HARVITA trial, the first adequately powered, prospective, randomized, multi-centre trial comparing skeletonized and pedicled harvesting technique of internal thoracic arteries.



Legend: LITA… left internal thoracic artery; cCTA… coronary computed tomography angiography