

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

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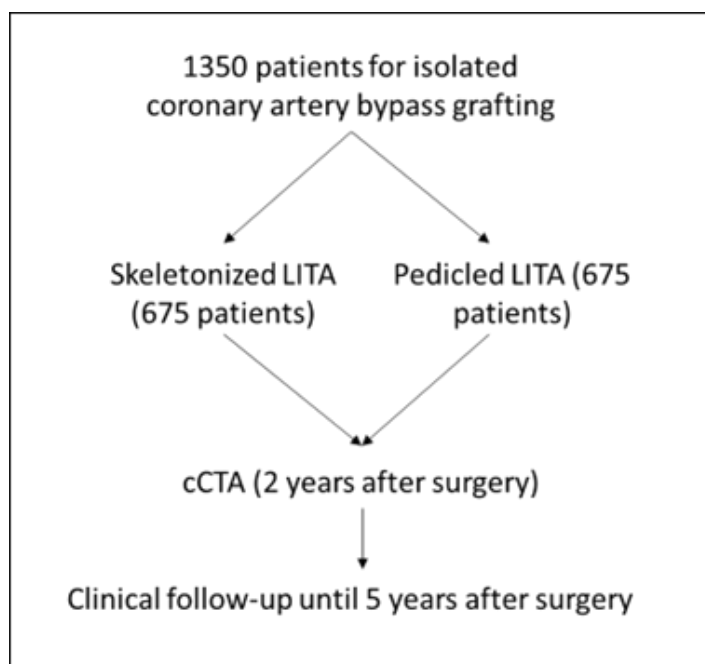
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25 Visual abstract:



26

27 Legend: LITA... left internal thoracic artery, cCTA... coronary computed tomography
28 angiography

29 Summary:

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

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41 Abstract:

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

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

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

- 65 Abbreviations and acronyms:
- 66 BMI... body mass index
- 67 CABG... coronary artery bypass grafting
- 68 CAG... coronary angiography
- 69 cCTA... coronary computed tomography angiography
- 70 CT... computed tomography
- 71 ECG... electrocardiography
- 72 e.g. ... example given
- 73 et al. ... et alii
- 74 GFR... glomerular filtration rate
- 75 ITA... internal thoracic artery
- 76 ITT... intention-to-treat
- 77 LAD... left anterior descending artery
- 78 LITA... left internal thoracic artery
- 79 MACE... major adverse cardiac events
- 80 mITT... modified intention-to-treat
- 81 mmHg... millimetre of mercury
- 82 PCI... percutaneous coronary intervention
- 83 PI... pulsatility index
- 84 RA... radial artery
- 85 RITA... right internal thoracic artery
- 86 SVG... saphenous vein graft
- 87 TTFM... transit time flow measurement
- 88

89 Objectives:

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

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

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

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

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

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

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

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

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

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

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

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

134 Methods:

135 Study design:

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

143 Hypotheses:

144 Primary hypothesis:

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

147 Eligibility:

148 Inclusion criteria:

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

152 Exclusion criteria:

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

167 Intraoperative exclusion criteria:

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

171 Randomization, stratification and enrolment:

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

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

180 Surgical procedure:

181 Surgery should take place within 4 weeks of randomization. Surgery is carried out via median
182 sternotomy and either on-pump or off-pump. Harvesting of LITA is performed by surgeons
183 who are technically capable of both harvesting techniques and who have harvested at least
184 50 ITAs. LITA is either harvested with electrocautery or harmonic scalpel, independently of
185 allocated harvesting technique and according to the established method in each centre. Only
186 topical, but not intravascular application (in order to decrease the risk of a potential endothelial
187 damage) of spasmolytic agents will be used. If randomized to skeletonized harvesting
188 technique, only the LITA itself is harvested, in case of pedicle harvesting technique, the LITA,
189 its accompanying veins and parts of the endothoracic fascia is harvested, creating a 1-2 cm
190 broad pedicle. Through an incision in the pericardium, the LITA is brought intrapericardial and
191 then anastomosed with running suture to the LAD. In case of pedicled harvesting technique,
192 the pedicle is stabilized without tension at the height of anastomosis with sutures at the

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

207 Recommendations to prevent sternal wound infections:

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

- 214 • routine screening for nasal carriers of *Staphylococcus aureus*

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

226 Postoperative treatment:

227 Postoperative treatment will be carried out according to local standards and current
228 guidelines (22). Treatment with antiplatelet agents should be re-started within 24 hours to
229 surgery, in case there is no concern regarding surgical bleeding. In case RA was used as a graft,
230 the decision to use spasmolytic medication (agent, duration and time of initiation) will be left
231 to local practice. Secondary prophylaxis should be carried out according to current guidelines
232 (5) (23) (24). We generally recommend the use of aspirin as antiplatelet agent (indefinitely),
233 the use of angiotensin-converting-enzyme inhibitors/angiotensin receptor blockers (sartane),
234 the use of a beta-blocker and the use of a statin for guideline-conform secondary prophylaxis.
235 In case of dual antiplatelet therapy (off-pump, previous acute coronary syndrome, previous
236 elective/acute coronary stent implantation) we recommend the use of aspirin in combination
237 with clopidogrel, in order to ensure uniformity.

238 Outcome measures:

239 Primary outcome:

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

242 Secondary outcome:

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

245 *Additional secondary outcomes:*

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

260 Further analyses:

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

265 Follow-up:

266 Patients will receive cCTA at 2 years (+/- 3 months) postoperatively. 1 week prior to cCTA,
267 blood samples (glomerular filtration rate, creatinine and thyroid stimulating hormone for the
268 upcoming cCTA; LDL-cholesterol and HbA1c for follow-up) will be collected. At 30 days, 1 year,
269 2 years and 5 years postoperatively, phone calls will be used for follow-up. cCTA should be
270 performed within a time span of 6 months (-3 months to + 3 months) for 2 year`s cCTA. If cCTA
271 or invasive angiography is performed for clinical reasons (e.g., signs of acute or chronic
272 ischemia, acute myocardial infarction, heart failure, or recurrence of symptoms), prior to the
273 above-mentioned time interval (> 3 months prior to 2 year`s cCTA) and LITA graft is not
274 occluded, cCTA will be performed according to protocol. If cCTA or invasive angiography is
275 performed due to other reasons prior to the above-mentioned time interval (> 3 months prior
276 to 2 year`s cCTA) and LITA graft is occluded, cCTA will not be performed and the findings of
277 cCTA/CAG will be used for statistical analysis. If CAG is performed due to other reasons within
278 the above-mentioned time intervals (\leq 3 months prior to 2 year`s cCTA) and LITA graft does or
279 does not show LITA graft occlusion, cCTA will not be repeated and the findings of the CAG will
280 be used for statistical analysis. In case of occlusion or dysfunction of other grafts rather than
281 LITA, patients with clinical symptoms and/or pathological findings in non-invasive testing,

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

284

285 Table 1 describes the process of follow-up.

286

287 cCTA:

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

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

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

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

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

315 Outcome definitions:

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

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

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

323 *LITA graft dysfunction in CAG*: $\geq 50\%$ stenosis of the LITA graft, string-sign of the graft due to
324 competitive flow or graft spasm

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

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

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

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

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

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

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

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

341 *repeat revascularization*: any form of repeat revascularization (CABG, PCI (balloon angioplasty
342 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)

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

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

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

368

369 Statistics:

370 Study design and objectives:

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

379 Sample Size Rationale/Number of Patients:

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

382 skeletonized and in 3.4% (25/725) of pedicled grafts (the COMPASS trial did not provide 2
383 year`s results). In addition, within two years, five of 1014 patients died. Rounding up this
384 numbers, we consider event rates of 4% (pedicled) versus 8% (skeletonized) at 2 years as a
385 realistic, conservative scenario for our study. In order to detect this difference of 4%,
386 (corresponding to a hazard ratio of 0.49), as statistically significant with a two-sample log-rank
387 test, a sample size of 558 patients in each treatment group is needed, assuming a type I error
388 of 0.05 (alpha = 5%) and a power of 0.8 (beta = 20%), requiring 62 events (death or LITA
389 occlusion) in total. To account for dropouts and withdrawals we increase the sample size to
390 675 patients in each group, resulting in a total sample size of 1350 patients for the trial.

391 Study population:

392 The following populations will be used for statistical analysis:

393 Intention-to-treat population:

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

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

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

399 Data Analysis:

400 Demographic and Baseline Characteristics:

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

405 Efficacy Analysis:

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

411 The primary efficacy hypotheses will thus be formulated as:

412 H_0 : hazard ratio_{skeletonized vs. pedicled} = 1

413 H_1 : hazard ratio_{skeletonized vs. pedicled} \neq 1

414 Primary efficacy analysis will be performed in the mITT population.

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

421 Safety Analysis:

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

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

434 Software:

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

438 Ethics:

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

443 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

461 Andreas Böning: conceptualization, writing-review and editing

462 Mario Gaudino: conceptualization, writing-review and editing

463 Matthias Siepe: conceptualization, writing-review and editing

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

465 Tables:

466 Table 1 describes the process of follow-up (cCTA... coronary computed tomography
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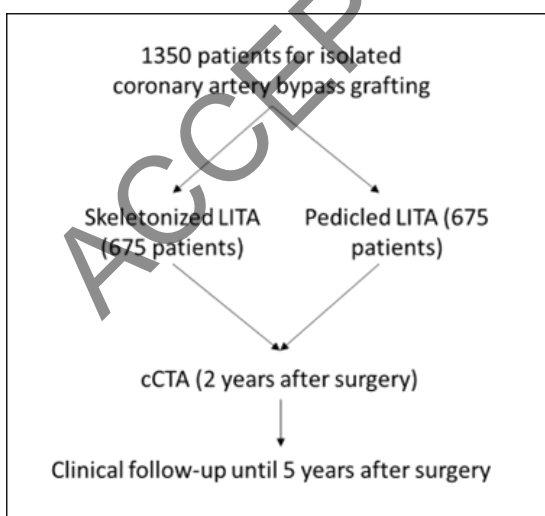
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547 Table 1

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



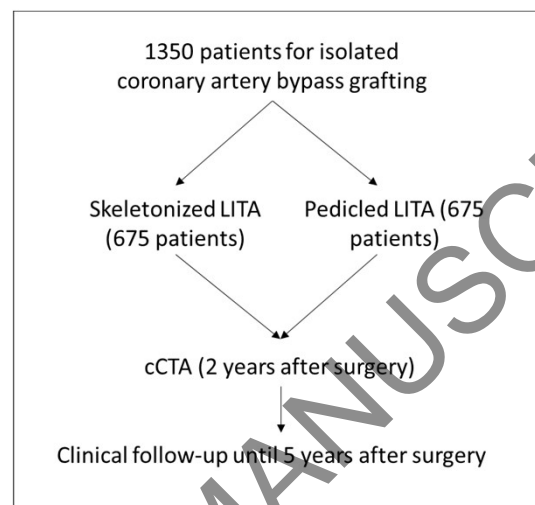
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552 Legend: LITA... left internal thoracic artery, cCTA... coronary computed tomography
 553 angiography

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

ACCEPTED MANUSCRIPT