



Taggart, D. P., Gaudino, M. F., Gerry, S., Gray, A., Lees, B., Sajja, L. R., Samvar, V., Flather, M., & Benedetto, U. (2020). Ten-year outcomes after off-pump versus on-pump coronary artery bypass grafting: Insights from the Arterial Revascularization Trial. *Journal of Thoracic and Cardiovascular Surgery*.
<https://doi.org/10.1016/j.jtcvs.2020.02.035>

Peer reviewed version

License (if available):
CC BY-NC-ND

Link to published version (if available):
[10.1016/j.jtcvs.2020.02.035](https://doi.org/10.1016/j.jtcvs.2020.02.035)

[Link to publication record in Explore Bristol Research](#)
PDF-document

This is the author accepted manuscript (AAM). The final published version (version of record) is available online via Elsevier at [https://www.jtcvs.org/article/S0022-5223\(20\)30427-X/fulltext](https://www.jtcvs.org/article/S0022-5223(20)30427-X/fulltext) . Please refer to any applicable terms of use of the publisher.

University of Bristol - Explore Bristol Research

General rights

This document is made available in accordance with publisher policies. Please cite only the published version using the reference above. Full terms of use are available:
<http://www.bristol.ac.uk/red/research-policy/pure/user-guides/ebr-terms/>

**10-year outcomes after off-pump vs on-pump coronary artery bypass grafting.
Insights from the Arterial Revascularization Trial.**

Running Title: off-pump vs on-pump surgery

David P Taggart¹ PhD, Mario F Gaudino MD², Stephen Gerry³ MSc, Alastair Gray⁴ PhD,
Belinda Lees¹ BSc PhD, Lokeswara R Sajja⁵ MD, Vipin Zamvar⁶ MD, Marcus Flather⁷ MD,
Umberto Benedetto⁸ MD PhD; on behalf of the ART investigators

¹Nuffield Department of Surgical Sciences, University of Oxford, John Radcliffe Hospital, Oxford, UK;

²Cardiothoracic Surgery at Weill Cornell Medical Center, New York, US

³Centre for Statistics in Medicine, Nuffield Department of Orthopaedics, Rheumatology & Musculoskeletal Sciences, University of Oxford, Oxford, UK;

⁴Department of Public Health, Health Economics Research Centre, University of Oxford, Oxford, UK;

⁵Division of Cardiothoracic Surgery, Star Hospitals, Banjara Hills, Hyderabad, India

⁶Royal Infirmary of Edinburgh, Department of Cardio-thoracic Surgery

⁷Research and Development Unit, Norfolk and Norwich University Hospitals NHS Foundation Trust, Norwich, UK

⁸Bristol Heart Institute, University of Bristol, School of Clinical Sciences, United Kingdom

Conflict of interest: DT is Consultant/Advisor for Medtronic

Funding: British Heart Foundation, UK Medical Research Council and the UK National Institute of Health Research. UB contribution was supported by the NIHR Bristol Cardiovascular Biomedical Research Unit

Word count: 3418

Corresponding Author

Mario Gaudino, MD

Department of Cardiothoracic Surgery

Weill Cornell Medicine

525 East 68th Street, New York, NY 10065

Email: mfg9004@med.cornell.edu

Abstract

Objectives: We performed a post hoc analysis of the Arterial Revascularization Trial to compare 10-year outcome after off-pump vs on-pump surgery.

Methods: Among 3102 patients enrolled, 1252 (40% of total) and 1699 patients received off-pump and on-pump surgery (and 151 were excluded because of other reasons); 2792 (95%) patients completed 10-year follow-up. Propensity matching and mixed effect Cox model were used to compare long term outcomes. Interaction term analysis was used to determine whether bilateral internal thoracic artery grafting was a significant effect modifier.

Results: 1078 matched pairs were selected for comparison. A total of 27 patients (2.5%) in the off-pump group required conversion to on-pump surgery. The off-pump and on-pump group received a similar number of grafts (3.2 ± 0.89 vs 3.1 ± 0.8 ; $P=0.88$). At 10 years, when compared to on-pump, there was no significant difference in death (adjusted HR for off-pump: 1.1; 95%CI 0.84-1.4; $P=0.54$) or the composite of death, myocardial infarction, stroke and repeat revascularization (adjusted HR 0.92; 95%CI 0.72-1.2; $P=0.47$). However, off-pump surgery performed by low volume off-pump surgeons was associated with a significantly lower number of grafts, increased conversion rates and an increased cardiovascular death (HR 2.39; 95%CI 1.28-4.47; $P=0.006$) when compared to on-pump surgery performed by “on-pump only” surgeons.

Conclusions: The present findings showed that in the Arterial Revascularization Trial off-pump and on-pump techniques achieved comparable long-term outcomes. However, when off-pump surgery was performed by low volume surgeons, it was associated with a lower number of grafts, increased conversion and a higher risk of cardiovascular death.

Abstract word count: 249

63 Ultra-mini abstract

64 In experienced hands, off-pump surgery can achieve long term outcomes comparable to those
65 observed after on-pump surgery and can therefore be considered a valid alternative to on-pump
66 to reduce surgical morbidity. The choice of bilateral vs. single internal thoracic artery grafts
67 should not influence the decision to adopt the off-pump technique.

68

69 Introduction

70 Whether off-pump coronary artery bypass graft (CABG) surgery is as safe and effective as on-
71 pump surgery remains one of the most controversial areas of cardiac surgery.¹ Some
72 randomized controlled trials (RCT) have found increased mortality following off-pump
73 surgery^{1,2} but limited surgeon off-pump experience has been advocated to explain these
74 results.² On the other hand, off-pump has been shown to achieve results comparable to on-
75 pump surgery when performed by experienced surgeons.^{3,4} However, available RCTs are
76 limited by relatively short follow-up duration (5 years) and differences in clinical outcomes
77 may become evident with longer follow-up duration.⁵

78 Moreover, available data comparing off-pump and on-pump surgery were based on a single
79 internal thoracic artery graft (SITA) supplemented by saphenous vein grafts (SVGs).²⁻⁴ There
80 is growing concern that off-pump surgery is associated with a significantly higher graft failure
81 rate when SVGs but not arterial grafts are used.⁶ Therefore, it has been suggested that a more
82 extensive use of arterial grafts including bilateral internal thoracic artery (BITA) grafts should
83 be adopted during off-pump surgery.^{6,7}

84 The Arterial Revascularization Trial (ART) was designed to compare 10-year survival after
85 BITA versus SITA grafting and the final results have recently reported.⁸ In the ART, the choice
86 of off-pump versus on-pump was based on the surgeon's preference in accordance with their
87 clinical expertise. As such, the ART trial may provide useful insights into the long-term effect
88 of off-pump surgery when performed by surgeons who use it routinely in clinical practice.
89 Moreover, the ART trial can provide further information regarding the role of BITA vs. SITA
90 grafting in patients undergoing off-pump surgery. We performed a post-hoc analysis to
91 compare 10-year outcomes after off-pump vs on-pump surgery and the effect of BITA vs. SITA
92 grafting.

93

94 **Materials and Methods**

95 The present study is a post hoc retrospective analysis of 10-year outcomes of the ART trial.

96 The study was approved by an institutional review committee and the subjects gave informed

97 consent. The data that support the findings of this study are available from the corresponding

98 author upon reasonable request. The study adheres to the principles set forth in the Declaration

99 of Helsinki (<http://www.wma.net/en/30publications/10policies/b3/index.html>). In the ART,

100 the choice of off-pump versus on-pump surgery was based on individual surgeon discretion in

101 accordance with their routine clinical practice. The off-pump versus on-pump strategy adopted

102 was available for all patients enrolled.

103 Among all patients enrolled in the ART (n = 3102, from 2004 to 2007), we excluded a total of

104 151 patients including those who did not undergo surgery (n = 24), incomplete information

105 regarding the use of cardiopulmonary bypass and myocardial protection strategy (n=6),

106 patients who received on-pump beating heart surgery (n = 23) and 98 patients who received

107 cross clamp fibrillation. The present analysis compared 1252 patients who underwent off-pump

108 surgery versus 1699 patients who underwent on-pump with cardioplegic arrest. Off-pump

109 surgery requiring intraoperative conversion to on-pump was included in the off-pump group in

110 the primary analysis (**Supplementary Figure 1**).

111 *Trial Design*

112 The ART was approved by the institutional review board of all participating centers, and

113 informed consent was obtained from each participant. The protocol for the ART has been

114 published.⁹ Briefly, the ART is a 2-arm, randomized multicenter trial conducted in 28 hospitals

115 in 7 countries, with patients being randomized equally to SITA or BITA grafting. Eligible

116 patients were those with multivessel coronary artery disease undergoing coronary artery bypass

117 grafting, including patients requiring urgent treatment. Only patients requiring emergency

118 treatment (refractory myocardial ischemia/cardiogenic shock) and patients requiring single

119 grafts or redo surgery were excluded.

120 Follow-up

121 Questionnaires were sent to study participants by mail at 12 months and then every year after
122 surgery. No clinic visits were planned apart from the routine clinical 6-week postoperative
123 visit. Participants were sent stamped addressed envelopes to improve the return rates of postal
124 questionnaires. Study coordinators contacted participants by telephone to alert them to the
125 questionnaire's arrival and to ask them about medications, adverse events, and health services
126 resource use. A total of 2792 (95%) patients completed 10-year follow-up. Median follow-up
127 time was 10.0 [interquartile range 9.3-10.0] years.

128 Study Outcomes

129 The 2 strategies were compared in terms of hospital and 10-year outcomes. The primary
130 endpoint was all-cause mortality. We also investigated the incidence cardiovascular death,
131 nonfatal myocardial infarction (MI), nonfatal stroke, and repeat revascularization and a
132 combined endpoint of death, MI, stroke and repeat revascularization. Adverse events were
133 adjudicated blind to surgical procedure by a member of the Clinical Event Review Committee.

134 Outcomes Definitions

135 Death was classified into cardiovascular and non-cardiovascular, when possible, using autopsy
136 reports and death certificates. Congestive heart failure, arrhythmia or MI, pulmonary embolus,
137 and dissection were considered cardiovascular causes of death. MI was diagnosed when 2 of
138 the following 3 criteria were present: (1) unequivocal electrocardiogram changes; (2) elevation
139 of cardiac enzyme(s) above twice the upper limit of normal or diagnostic troponin increases;
140 and (3) chest pain typical for acute MI that lasted more than 20 minutes. Cerebro-vascular
141 accident (CVA) was defined as new neurologic deficit evidenced by clinical signs of paresis,
142 plegia, or new cognitive dysfunction including any mental status alteration lasting more than
143 24 hours or evidence on computed tomography or magnetic resonance imaging scan of recent
144 brain infarct (<6 months). Repeat revascularization was defined as coronary bypass surgery or
145 percutaneous coronary intervention performed after trial procedure. Acute kidney injury was

146 defined as a 0.3 mg/dL (≥ 26.5 mmol/L) creatinine increase from baseline within 48 hours of
147 surgery.

148 *Statistical Analysis*

149 Multiple imputation ($m = 3$) was used to address missing data. Rubin's method was used to
150 combine results from each of the imputed data sets (Amelia R package).¹⁰ Because of the lack
151 of randomization with regard to receiving off-pump, a propensity score was generated for each
152 patient from a multivariable logistic regression model based on pretreatment covariates listed
153 in **Table 1**. Pairs of patients were derived using greedy 1:1 matching with a caliper of width of
154 0.005 (nonrandom R package). As the sample size of the two groups was comparable as well
155 as the prevalence of most pre-matching features, we used a more restrictive value than the 0.2
156 standard deviation of the logit of PS in order to obtain comparable pairs. The quality of the
157 match was assessed by comparing selected pretreatment variables in propensity score-matched
158 patients using the standardized mean difference, with an absolute standardized mean difference
159 (SMD) of greater than 0.10 taken to represent meaningful covariate imbalance.¹¹ McNemar's
160 test and paired t test were used to assess the statistical significance of the risk difference for
161 hospital outcomes. In absence of competing events, the 1 minus Kaplan-Meier estimator was
162 used to calculate cumulative incidence function with its relative 95% standard error while the
163 Fine and Gray approach was used to account for presence of competing risk on a
164 subdistribution hazard function.

165 Event rates for 10-years outcomes were calculated according to Kaplan-Meier estimates and
166 were compared using a stratified log-rank test. The treatment effect on the 10-year outcomes
167 was investigated by means of mixed effect Cox regression models stratified by matched pairs
168 (coxme R package). This approach accounts for the within-pair homogeneity by allowing the
169 baseline hazard function to vary across matched sets.¹¹ Individual surgeon ID was used as a
170 random effect to account for any clustering effect due to different individual surgeons. Risk
171 competing framework was used to estimate the treatment effect on non-fatal events and

172 cardiovascular death. The Schoenfeld residuals test was used to test the independence between
173 residuals and time, and thus to test the proportional hazards assumption in Cox models.
174 Treatment effect was reported as hazard ratio (HR) and 95% confidence interval (95%CI).
175 As sensitivity analysis, the treatment effect was re-estimated by further adjustment for
176 medications at discharge. Subgroup and interaction term analyses were performed to
177 investigate whether BITA vs SITA grafting was a potential effect modifier in the comparison
178 between off-pump vs. on-pump surgery. We also investigate the interaction between off-pump
179 vs on-pump surgery and the use of the radial artery (RA) and the use of multiple arterial grafting
180 (MAG) defined as the use of 2 or more arterial grafts.

181 To account for the potential influence of individual surgeons' off-pump experience, we
182 compared off-pump vs on-pump surgery stratified by surgeon expertise in off-pump surgery.
183 The number of off-pump procedure within the trial was used as proxy for individual surgeon
184 expertise in off-pump surgery. The cut-off to define high off-pump volume surgeons
185 corresponded to the 75th percentiles of total number of off-pump cases performed by each off-
186 pump surgeon (10 off-pump surgeries). Five groups were compared: 1) off-pump surgery
187 performed by “high off-pump volume” surgeon; 2) off-pump surgery performed by “low off-
188 pump volume” surgeon; 3) on-pump surgery performed by “high off-pump volume” surgeon;
189 4) on-pump surgery performed by “low off-pump volume” surgeon; 5) on-pump surgery
190 performed by “on-pump only” surgeon. The treatment effect on outcomes of interest was
191 investigated using mixed Cox models using individual surgeon as random effect (random
192 intercept) and all baseline characteristics as fixed effect. On-pump surgery performed by “on-
193 pump only” surgeons was considered as reference group. To investigate the effect of surgeon
194 off-pump volume, the original sample was used. A p-value less than 0.05 was considered
195 statistically significant. All statistical analysis was performed using R Statistical Software
196 (version 3.2.3; R Foundation for Statistical Computing, Vienna, Austria).

197

198 **Results**

199 The unmatched sample consisted of 1699 and 1252 patients undergoing off-pump vs on-pump
200 surgery respectively (**Supplementary Table 1, Supplementary Table 2**). Overall, the off-
201 pump group presented a trend toward a higher risk profile including increased creatinine level
202 and higher prevalence of unstable angina. The prevalence of 3 vessel disease was also higher
203 among off-pump patients and the quality of native vessels tended to be worse. BITA grafts
204 were more likely to be used in the off-pump group while a radial artery was more likely to be
205 used in the on-pump group. Propensity score matching identified 1078 pairs (total matched
206 sample = 2156) for final comparison, balanced for all baseline characteristics (SMD<0.10,
207 **Table 1**) and propensity score distribution was comparable between the two matched groups
208 (**Figure 1**).

209 *Hospital outcomes*

210 In-hospital outcomes in the matched sample are reported in **Table 2**. A total of 27 patients
211 (2.5%) in the off-pump group required conversion to on-pump surgery. The off-pump and on-
212 pump group received a comparable number of total grafts (3.2 ± 0.89 vs 3.1 ± 0.8 ; $P=0.88$). Off-
213 pump surgery resulted in a lower rate of transfusion and a lower incidence of post-operative
214 atrial fibrillation and peri-operative MI with a marginally non-significant reduction of CK-MB
215 release postoperatively. In-hospital mortality, stroke and repeat revascularization was
216 comparable between the two groups. Patients undergoing off-pump surgery were more likely
217 to be discharged on dual antiplatelet therapy, but they were less likely to receive statins
218 (**Supplementary Table 3**).

219 *10-year outcomes*

220 10-year outcomes and treatment effect are summarized in Table 3. The incidence of all-cause
221 mortality and the composite of death, MI, stroke and revascularization was 232 (21.5%) vs 215
222 (19.9%) and 355 (32.7) vs 356 (33.0) in the off-pump and on-pump group respectively (**Figure**

223 2). When compared to on pump, off-pump surgery was not associated with increased risk of
224 all-cause death (HR 1.1; 95%CI 0.84-1.4; P=0.47) nor the composite of death, MI, stroke and
225 revascularization (HR 0.92; 95%CI 0.72-1.2; P=0.47). No significant differences were
226 recorded for composite outcome individual components (**Figure 3**). The equipoise between the
227 two groups persisted after adjusting for medications at discharge.

228 When the analysis was stratified by BITA vs SITA grafting, the presence of BITA vs. SITA
229 grafting did not significantly influence the comparison between off-pump and on-surgery for
230 all outcomes of interest (**Table 4, Figure 4**). However, when compared to on-pump, off-pump
231 surgery was associated with a non-significant excess of cardiovascular deaths when SITA (off-
232 pump vs on-pump HR 2.0174; 95%CI 1.1-3.7) but not BITA grafts (off-pump vs on-pump
233 HR1; 95%CI 0.45-2.3) were used (interaction P=0.21). Off-pump and on-pump surgery were
234 comparable in terms of 10-year mortality and incidence of major adverse cardiac and
235 cerebrovascular outcomes regardless the use of the RA (**Supplementary Figure 2**) or any
236 multiple arterial grafting configuration (**Supplementary Figure 3**).

237 A total of 159 participating surgeons were involved (**Supplementary Figure 4**). Ninety-eight
238 surgeons performed on-pump only while off-pump was performed by 61 surgeons including
239 21 surgeons who performed off-pump only. For 133 patients (59 off-pump, 74 on-pump), no
240 information on participating surgeon was available and these were not included in this analysis.
241 High off-pump volume surgeons were defined those performing over the 75th percentile. Based
242 on the identified cut-off of least 10 off-pump procedures, 21 surgeons were classified as high
243 volume off-pump performing 1075 procedures and the remaining 40 surgeons were classified
244 as low-volume off-pump performing a total of 118 off-pump procedures. A total of 98 surgeons
245 performed on-pump only. Patients characteristics, hospital outcomes stratified for off-pump vs.
246 on-pump surgery and surgeon off-pump volume are summarized in **Supplementary Table 4**
247 **and 5**. The use of BITA vs SITA graft (as treated) according to off-pump surgeon volume is
248 summarized in **Supplementary Table 6**. High volume off-pump surgeons were more likely to

249 perform BITA grafting. For low-volume off-pump surgeons, the use of off-pump technique did
250 not influence the use of BITA or SITA grafting. Surgeons only performing on-pump surgery
251 had the lowest rate of BITA grafting usage.

252 10-year outcomes and adjusted treatment effect estimation on these outcomes stratified by
253 surgeon off-pump volume are presented in **Supplementary Table 7 and 8**. When performed
254 by low volume off-pump surgeons, off-pump surgery resulted in a significantly lower number
255 of grafts and higher conversion rates while this trend was not observed when off-pump was
256 performed by high volume off-pump surgeons. When compared to on-pump surgery
257 performed by “on-pump only” surgeons, off-pump surgery performed by low volume off-pump
258 surgeons was associated with a significantly increased risk-adjusted incidence of
259 cardiovascular death (HR 2.39; 95%CI 1.28-4.47; P=0.006) and increased risk of late stroke
260 (HR 3.97; 95%CI 1.81-7.95; P<0.001) at 10 years. No difference in long term outcomes were
261 demonstrated for off-pump surgery performed by high volume off-pump surgeons and for on-
262 pump surgery performed by high and low volume off-pump surgeons. BITA vs SITA grafting
263 was not an effect modifier in the comparison between off-pump vs. on-pump surgery.

264

265

266 Discussion

267 The main finding of the present post-hoc analysis of the ART was that at 10 years, off-pump
268 and on-pump surgery were associated with comparable outcomes including all-cause mortality
269 and the composite of death, MI, stroke and repeat revascularization. When compared to on-
270 pump, off-pump surgery was associated some advantage in terms of hospital outcomes
271 including a lower rate of transfusion and post-operative atrial fibrillation.

272 The use of SITA or BITA grafts was not found to be a significant effect modifier in the
273 comparison between off-pump vs. on-pump surgery. It has been suggested that off-pump
274 surgery may increase the risk of SVG failure⁶ without affecting graft patency of arterial
275 conduits including BITA grafts. However, other reports have shown that both arterial and vein
276 grafts durability is not reduced when off-pump surgery is performed by experienced
277 surgeons.¹² Available randomized comparative studies on long-term survival after off-pump
278 vs. on-pump surgery included mainly procedure with SITA grafting.²⁻⁴ Observational studies
279 have suggested that off-pump surgery with multiple arterial grafts but not vein grafts provides
280 long-term outcomes comparable with those observed on-pump surgery with multiple arterial
281 grafts.⁷

282 Our findings suggest that off-pump surgery can safely performed regardless the use of BITA
283 or SITA grafts. As the choice to perform on-pump or off-pump was based on individual
284 surgeon's preference, the overall experience in off-pump surgery in the ART was likely to be
285 adequate and this can explain the equipoise between the two techniques regardless the graft
286 selection adopted.¹² However, it must be noticed that although not statistically significant, off-
287 pump surgery was associated with a non-significant excess of cardiovascular deaths in patients
288 who received SITA graft but not in those with BITA grafts and this observation requires further
289 investigation.

290 We further analyzed the effect of off-pump surgery according to individual surgeon off-pump
291 volume. When compared to on-pump performed by on-pump only surgeons, off-pump surgery
292 performed by low-volume off-pump surgeons was associated with a significantly lower
293 number of grafts and significantly increased risk of on-pump conversion, cardiovascular death
294 and late stroke at 10 years. On contrary, off-pump surgery performed by high off-pump volume
295 surgeon was associated with comparable number of grafts and 10 years outcomes.

296 Off-pump volume at individual surgeon or hospital level are intuitive measures of “expertise”
297 and a proxy of enhanced safety and quality⁵ and studies suggesting an increased risk of late
298 mortality after off-pump surgery have been criticized by those who believe that surgeon
299 experience plays a major role in determining outcomes. In the ROOBY trial,² 53 participating
300 surgeons enrolled an average of only 8 patients per year during the study period and had
301 unacceptably high conversion rates to on-pump surgery (12%) and incomplete
302 revascularization (18%). Moreover, in 60% of the cases, a resident was the primary surgeon.
303 These aspects might have contributed to the higher mortality observed in the off-pump group.
304 In the CORONARY trial³ where each procedure was performed by a surgeon who had
305 expertise in the specific type of surgery (completion of >100 cases of the specific technique,
306 off-pump or on-pump), the difference in terms of number of grafts (3.0 vs 3.2) and incidence
307 of incomplete revascularization (11.8% vs 10.0%) were only marginal and off-pump and on-
308 pump surgery showed similar 5-year outcomes, including mortality with both techniques.
309 Similar results were observed in the German off pump CABG trial in elderly patients study,⁴
310 where surgeons were established experts with an average of 514 OPCAB procedures (median,
311 322) performed, and where no significant differences between OPCAB and on-pump outcomes
312 were found.

313 A potential limitation of studies supporting the equipoise between the two techniques is the
314 limited follow-up duration of 5 years and the ART trial, with 10-year follow-up, can provide
315 further insights into the long-term comparison between off-pump vs on-pump surgery. Off-

316 pump surgery was performed at the individual surgeon's discretion. Furthermore it is likely
317 that the overall off-pump experience in the ART trial was adequate as witnessed by a similar
318 number of grafts in the off-pump and on-pump groups, the very low off-pump to on-pump
319 conversion rate and the equipoise between the two groups at 10 years. This hypothesis is
320 supported by other reports from high off-pump volume centers.¹³

321 Of note, the number of grafts performed with off-pump surgery and the incidence of conversion
322 from off-pump to on-pump surgery in the ART trial was lower than those reported in other
323 series.² Finally, we also found that off-pump surgery was also associated with a non-significant
324 reduction of myocardial enzymes and a lower rate of peri-operative MI as defined by the study
325 protocol. It is well recognized that off-pump surgery is associated with a lower release of
326 myocardial enzymes,¹⁴ but the clinical relevance of this observation remains unclear
327 (**Supplementary Table 8**) also in view of comparable long-term outcomes between the two
328 techniques. Moreover, the definition of perioperative MI after myocardial revascularization
329 remains controversial.¹⁵

330

331 **Limitations**

332 The main limitation of the present study is its observational nature. The propensity technique
333 can adjust only for measurable and included variables, and we cannot exclude a selection bias
334 based on a nonmeasurable "eye-balling," including the quality of the targets. We had no
335 information on specific surgeon off-pump expertise, and we used the total number of off-pump
336 procedures performed in the ART as a surrogate of off-pump expertise. We had no information
337 on reasons for preferring off-pump over on-pump and vice versa across surgeon subgroups.
338 The number of off-pump surgeries performed by low off-pump volume surgeons was relatively
339 small thus increasing the risk of type I error. Therefore, subgroup analysis based on surgeon
340 off-pump volume should be considered only as descriptive and hypothesis generating.

341 It should also be noted by today's standards that the ART population might be considered a
342 relatively low risk subset of CABG patients (although the only formal exclusion criteria were
343 evolving myocardial infarction, redo surgery or the need for a single graft). It is possible that
344 a difference between the two techniques could exist in patients at higher surgical risk.

345 In conclusion, we found that when performed by experienced surgeons, off-pump was as safe
346 and effective as on-pump surgery at long term follow-up regardless the use of BITA vs. SITA
347 grafts. In the current era, an increasing number of patients with a high-risk profile are being
348 referred for surgical revascularization, and off-pump surgery represents an attractive strategy
349 to potentially reduce operative morbidity. However, the unique technical challenges of off-
350 pump surgery may lead to poorer outcomes during each surgeon's "learning curve" and this
351 further emphasizes the need for recognition of off-pump surgery as a subspecialty with a
352 formally structured training program.¹⁶

353

355 **Central Message:**

356 In the Arterial Revascularization Trial, off-pump surgery long term outcomes were
357 comparable to those of on-pump; this was not influenced by the use of single vs. bilateral
358 internal thoracic artery.

359

360 **Perspective Statement:**

361 Off-pump surgery in experienced hands can achieve long term outcomes comparable to those
362 observed after on-pump surgery and therefore off-pump should be considered a valid
363 alternative to on-pump to reduce surgical morbidity following coronary bypass surgery. The
364 choice of bilateral vs. single internal thoracic artery grafts should not influence the decision
365 to adopt the off-pump technique.

366

367 **Abbreviated legend for Central Picture:**

368 Cumulative outcome incidence in the matched sample in the off-pump vs on-pump groups.

369

370 **References**

- 371 1. Smart NA, Dieberg G, King N. Long-Term Outcomes of On- Versus Off-Pump
372 Coronary Artery Bypass Grafting. *J. Am. Coll. Cardiol.* 2018;71:983–991.
- 373 2. Shroyer AL, Hattler B, Wagner TH, Collins JF, Baltz JH, Quin JA, et al. Five-Year
374 Outcomes after On-Pump and Off-Pump Coronary-Artery Bypass. *N. Engl. J. Med.*
375 2017;377:623–632.
- 376 3. Lamy A, Devereaux PJ, Prabhakaran D, Taggart DP, Hu S, Straka Z, et al. Five-Year
377 Outcomes after Off-Pump or On-Pump Coronary-Artery Bypass Grafting. *N. Engl. J. Med.*
378 2016;375:2359–2368.
- 379 4. Diegeler A, Börgermann J, Kappert U, Hilker M, Doenst T, Böning A, et al. Five-
380 Year Outcome After Off-Pump or On-Pump Coronary Artery Bypass Grafting in Elderly
381 Patients. *Circulation.* 2019;139:1865–1871.
- 382 5. Gaudino M, Benedetto U, Bakaeen F, Rahouma M, Tam DY, Abouarab A, et al. Off-
383 Versus On-Pump Coronary Surgery and the Effect of Follow-Up Length and Surgeons’
384 Experience: A Meta-Analysis. *J. Am. Heart Assoc.* 2018;7:e010034.
- 385 6. Zhang B, Zhou J, Li H, Liu Z, Chen A, Zhao Q. Comparison of graft patency between
386 off-pump and on-pump coronary artery bypass grafting: an updated meta-analysis. *Ann.*
387 *Thorac. Surg.* 2014;97:1335–1341.
- 388 7. Benedetto U, Caputo M, Mariscalco G, Gaudino M, Chivasso P, Bryan A, et al.
389 Impact of multiple arterial grafts in off-pump and on-pump coronary artery bypass surgery. *J.*
390 *Thorac. Cardiovasc. Surg.* 2017;153:300-309.e6.
- 391 8. Taggart DP, Benedetto U, Gerry S, Altman DG, Gray AM, Lees B, et al. Bilateral
392 versus Single Internal-Thoracic-Artery Grafts at 10 Years. *N. Engl. J. Med.* 2019;380:437–
393 446.
- 394 9. Taggart DP, Lees B, Gray A, Altman DG, Flather M, Channon K, et al. Protocol for
395 the Arterial Revascularisation Trial (ART). A randomised trial to compare survival following
396 bilateral versus single internal mammary grafting in coronary revascularisation
397 [ISRCTN46552265]. *Trials.* 2006;7:7.
- 398 10. Rubin D. Multiple Imputation for Nonresponse in Surveys. J Wiley & Sons. New
399 York: 1987.
- 400 11. Benedetto U, Head SJ, Angelini GD, Blackstone EH. Statistical primer: propensity
401 score matching and its alternatives. *Eur. J. Cardio-Thorac. Surg.* 2018;53:1112–1117.
- 402 12. Puskas JD, Williams WH, Mahoney EM, Huber PR, Block PC, Duke PG, et al. Off-
403 pump vs conventional coronary artery bypass grafting: early and 1-year graft patency, cost,
404 and quality-of-life outcomes: a randomized trial. *JAMA.* 2004;291:1841–1849.
- 405 13. Kirmani BH, Holmes MV, Muir AD. Long-Term Survival and Freedom From
406 Reintervention After Off-Pump Coronary Artery Bypass Grafting: A Propensity-Matched
407 Study. *Circulation.* 2016;134:1209–1220.
- 408 14. Chowdhury UK, Malik V, Yadav R, Seth S, Ramakrishnan L, Kalaivani M, et al.
409 Myocardial injury in coronary artery bypass grafting: on-pump versus off-pump comparison
410 by measuring high-sensitivity C-reactive protein, cardiac troponin I, heart-type fatty acid-
411 binding protein, creatine kinase-MB, and myoglobin release. *J. Thorac. Cardiovasc. Surg.*
412 2008;135:1110–1119, 1119.e1–10.
- 413 15. Cho MS, Ahn J-M, Lee C-H, Kang D-Y, Lee J-B, Lee PH, et al. Differential Rates
414 and Clinical Significance of Periprocedural Myocardial Infarction After Stenting or Bypass
415 Surgery for Multivessel Coronary Disease According to Various Definitions. *JACC*
416 *Cardiovasc. Interv.* 2017;10:1498–1507.
- 417 16. Song HK, Petersen RJ, Sharoni E, Guyton RA, Puskas JD. Safe evolution towards
418 routine off-pump coronary artery bypass: negotiating the learning curve. *Eur. J. Cardio-*
419 *Thorac. Surg.* 2003;24:947–952.

421 **Figure Legend**

422 **Figure 1.** Mirrored histogram showing propensity score distribution in the off-pump vs on-
423 pump groups before (white) and after (blue and red respectively) matching.

424
425 **Figure 2.** Cumulative incidence of all-cause death (left) and the composite of all-cause death,
426 myocardial infarction (MI), stroke and revascularization (right) in the matched sample in the
427 off-pump vs on-pump groups.

428
429 **Figure 3.** Cumulative incidence of cardiovascular (CV) death, myocardial infarction (MI),
430 stroke and revascularization in the matched sample in the off-pump vs on-pump groups.

431
432 **Figure 4.** Cumulative incidence of all-cause death (left) and the composite of all-cause death,
433 myocardial infarction (MI), stroke and revascularization (right) in the matched sample in the
434 off-pump vs on-pump groups stratified for the use of single vs bilateral internal thoracic
435 artery (SITA vs. BITA) grafts.

436

437

438

439

440

441

442 **Table 1.** Baseline characteristics in the off-pump and on-pump group (matched sample)

| | Off-pump surgery | On-pump surgery | P-value | SMD |
|--|------------------|-----------------|---------|--------|
| n | 1078 | 1078 | | |
| Age year, mean (sd) | 63.83 (8.88) | 63.97 (8.74) | 0.71 | 0.02 |
| Female n(%) | 144 (13.4) | 139 (12.9) | 0.79 | 0.01 |
| Ethnicity n(%) | | | 0.08 | 0.09 |
| Caucasian | 1001 (92.9) | 1023 (94.9) | | |
| East Asian | 1 (0.1) | 4 (0.4) | | |
| South Asian | 63 (5.8) | 41 (3.8) | | |
| Afro-Caribbean | 0 (0.0) | 2 (0.2) | | |
| African | 0 (0.0) | 4 (0.4) | | |
| Other | 13 (1.2) | 4 (0.4) | | |
| Body Mass Index, mean (sd) | 28.22 (4.18) | 28.33 (3.91) | 0.51 | 0.02 |
| Serum Creatinine mmol/l, mean (sd) | 99.07 (20.02) | 97.86 (21.93) | 0.18 | 0.05 |
| Unstable Angina n(%) | 83 (7.7) | 71 (6.6) | 0.35 | 0.04 |
| Treated Hypertension n(%) | 813 (75.4) | 824 (76.4) | 0.61 | 0.02 |
| Treated Hyperlipaemia n(%) | 1012 (93.9) | 1019 (94.5) | 0.58 | 0.03 |
| Diabetes n(%) | | | 0.59 | 0.04 |
| No | 850 (78.8) | 847 (78.6) | | |
| Insulin Dependent | 51 (4.7) | 61 (5.7) | | |
| Non-Insulin Depended | 177 (16.4) | 170 (15.8) | | |
| Smoking n(%) | | | 0.31 | 0.05 |
| Current smoker | 157 (14.6) | 136 (12.6) | | |
| Ex-smoker | 585 (54.3) | 642 (59.6) | | |
| Never | 336 (31.2) | 300 (27.8) | | |
| COPD n(%) | 28 (2.6) | 30 (2.8) | 0.89 | 0.01 |
| Asthma n(%) | 53 (4.9) | 53 (4.9) | 1 | <0.001 |
| Extracardiac arteriopathy n(%) | 72 (6.7) | 68 (6.3) | 0.79 | 0.01 |
| Stroke n(%) | 29 (2.7) | 23 (2.1) | 0.48 | 0.03 |
| Myocardial infarction n(%) | 435 (40.4) | 450 (41.7) | 0.54 | 0.02 |
| PCI n(%) | 182 (16.9) | 190 (17.6) | 0.69 | 0.02 |
| History of AF n(%) | 15 (1.4) | 15 (1.4) | 1 | <0.001 |
| LVEF n(%) | | | 0.30 | 0.03 |
| ≥50%(good) | 842 (78.1) | 811 (75.2) | | |
| 31-49% (moderate) | 205 (19.0) | 253 (23.5) | | |
| ≤30% (poor) | 31 (2.9) | 14 (1.3) | | |
| APLT within 3 days n(%) | 156 (14.5) | 166 (15.4) | 0.58 | 0.02 |
| RCA disease n(%) | 695 (64.5) | 703 (65.2) | 0.75 | 0.02 |
| Mean vessel quality (1 good, 2 moderate, 3 poor) mean (sd) | 1.73 (0.59) | 1.69 (0.54) | 0.11 | 0.07 |
| Endarterectomy n(%) | 12 (1.1) | 14 (1.3) | 0.84 | 0.02 |
| BITA n(%) | 497 (46.1) | 483 (44.8) | 0.57 | 0.03 |
| Radial artery usage n(%) | 224 (20.8) | 223 (20.7) | 1 | 0.002 |
| Saphenous vein graft n(%) | 804 (74.6) | 815 (75.6) | 0.61 | 0.02 |

443 COPD: chronic obstructive pulmonary disease; PCI: percutaneous coronary intervention; AF: atrial fibrillation;
444 LEFT: left ventricular ejection fraction, APLT: antiplatelet therapy; RCA: right coronary artery; BITA: bilateral
445 internal thoracic arterial

446 **Table 2.** Hospital outcomes in the off-pump and on-pump group (matched sample)

| | Off-pump surgery | On-pump surgery | P-value |
|---|------------------|-----------------|-------------|
| | 1078 | 1078 | |
| n grafts | 3.21 (0.89) | 3.10 (0.79) | 0.88 |
| Conversion | 27 (2.5) | | |
| Red Blood Cell transfusion n(%) | 107 (10.1) | 138 (13.2) | 0.04 |
| Re-exploration n(%) | 32 (3.0) | 41 (3.8) | 0.34 |
| Need for IABP n(%) | 50 (4.6) | 42 (3.9) | 0.45 |
| Renal Replacement Therapy n(%) | 61 (5.7) | 58 (5.4) | 0.85 |
| Acute Kidney Injury n(%) | 179 (17.4) | 174 (17.1) | 0.90 |
| Creatinine peak at 48 hours mmol/l, mean (sd) | 111 (44) | 107 (61) | 0.18 |
| CK-MB at 24 hours, U/Lmean (sd) | 36(194) | 78(122) | 0.06 |
| Troponin at 24 hours U/L mean (sd) | 6.5 (24) | 7.5 (61) | 0.85 |
| Sternal Wound Complication n(%) | 30 (2.8) | 45 (4.2) | 0.10 |
| Death n(%) | 9 (0.8) | 12 (1.1) | 0.66 |
| Myocardial Infarction n(%) | 10 (0.9) | 28 (2.6) | 0.01 |
| Stroke n(%) | 14 (1.3) | 15 (1.4) | 1 |
| Repeat Revascularization n(%) | 7 (0.6) | 6 (0.6) | 1 |
| Postoperative atrial fibrillation n(%) | 247 (22.9) | 295 (27.4) | 0.02 |

447 IABP: intra-aortic balloon pump

448

449

Table 3. 10-year outcomes in the off-pump and on-pump group (matched sample)

| | Off-pump Surgery | On-pump Surgery | PSM-model only | | PSM-model + medication at discharge | P-value |
|--|---------------------|--------------------|----------------|---------|---|---------|
| | | | HR [95%] | P-value | | |
| N | 1078 | 1078 | HR [95%] | P-value | HR [95%] | P-value |
| All-cause death n(%) | 232 (21.5) | 215 (19.9) | 1.1[0.84-1.4] | 0.54 | 1.25[0.98-1.6] | 0.07 |
| Cardiovascular death n(%) | 90 (8.3) | 70 (6.5) | 0.97[0.57-1.6] | 0.91 | 1.07[0.61-1.8] | 0.82 |
| MI n(%) | 49 (4.5) | 64 (5.9) | 0.78[0.53-1.2] | 0.21 | 0.79[0.51-1.2] | 0.28 |
| Stroke n(%) | 50 (4.6) | 47 (4.4) | 1.2[0.45-1.5] | 0.52 | 0.95[0.47-1.9] | 0.88 |
| Revascularization n(%) | 114 (10.6) | 111 (10.3) | 0.75[0.47-1.2] | 0.21 | 0.70[0.44-1.1] | 0.10 |
| Death/MI/stroke/revascularization n(%) | 353 (32.7) | 356 (33.0) | 0.92[0.72-1.2] | 0.47 | 0.95[0.75-1.2] | 0.66 |

PSM: propensity score matching; HR: hazard ratio; CI: confidence interval; MI: myocardial infarction

Table 4. 10-year outcomes in the off-pump and on-pump group in the matched sample stratified for single vs bilateral internal thoracic artery

(SITA vs. BITA) grafts with treatment effect and interaction term analysis for outcomes of interest.

| | SITA grafting | | | BITA grafting | | | Interaction P |
|--|------------------|-----------------|----------------|------------------|-----------------|----------------|---------------|
| | Off-pump Surgery | On-pump Surgery | HR [95%CI] | Off-pump Surgery | On-pump Surgery | HR [95%CI] | |
| n | 581 | 595 | | 497 | 483 | | |
| All-cause death n(%) | 136 (23.4) | 125 (21.0) | 1.2[0.84-1.8] | 96 (19.3) | 90 (18.6) | 1.1[0.74-1.7] | 0.68 |
| Cardiovascular death n(%) | 54 (9.3) | 39 (6.6) | 2[1.1-3.7] | 36 (7.2) | 31 (6.4) | 1[0.45-2.3] | 0.21 |
| MI n(%) | 28 (4.8) | 32 (5.4) | 0.89[0.34-2.4] | 21 (4.2) | 32 (6.6) | 0.77[0.34-1.8] | 0.82 |
| Stroke n(%) | 34 (5.9) | 29 (4.9) | 1.1[0.46-2.4] | 16 (3.2) | 18 (3.7) | 0.78[0.29-2.1] | 0.68 |
| Revascularization n(%) | 66 (11.4) | 54 (9.1) | 1.1[0.68-1.9] | 48 (9.7) | 57 (11.8) | 0.75[0.41-1.4] | 0.27 |
| Death/MI/stroke/revascularization n(%) | 204 (35.1) | 199 (33.4) | 1[0.72-1.5] | 149 (30.0) | 157 (32.5) | 0.9[0.63-1.3] | 0.41 |

HR: hazard ratio; CI: confidence interval; SITA: single internal thoracic artery; BITA: bilateral internal thoracic arteries; MI: Myocardial infarction