A comparison of survival between on-pump and off-pump left internal mammary artery bypass graft surgery for isolated left anterior descending coronary artery disease: An analysis of the UK National Adult Cardiac Surgery Audit Registry

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ABSTRACT

Objective: To determine if the use of cardiopulmonary bypass is associated with all-cause in-hospital and mid-term survival for patients undergoing left internal mammary artery (LIMA) to left anterior descending (LAD) coronary artery bypass grafting (CABG) for single coronary vessel disease.

Methods: Data from the National Adult Cardiac Surgery Audit registry for all elective and urgent isolated CABG procedures performed between April-2003 and March-2013 in first-time cardiac surgery patients were extracted. Experienced surgeons (those with ≥300 records) were classified by their technique preference (as 'off-pump preference', 'mixed practice', 'on-pump preference') based on their entire isolated CABG data. In-hospital mortality and time-to-death were analyzed using logistic and Cox proportional hazards regression models respectively.

Results: From a total of 3402 records, 65.5% were performed off-pump. There were 16 (0.47%) in-hospital deaths: 6 (0.51%) in the on-pump group and 10 (0.45%) in the off-pump group. The risk-adjusted odds ratio of in-hospital mortality in the direction of on-pump was 1.09 (95% CI: 0.39 to 3.04; *P*=0.86). The overall 5-year survival in the on- and off-pump groups was 93.1% and 93.4% respectively. The adjusted hazard ratio for mortality in the direction of on-pump CABG was 1.15 (95% CI: 0.89 to 1.49; *P*=0.28). Comparing off-pump cases performed by experienced CABG surgeons with a preference for the off-pump technique to on-pump cases performed by surgeons with a preference for the on-pump technique indicated a significant difference (HR for on-pump=1.72; 95% CI: 1.19 to 2.47; *P*=0.004).

Conclusions: Elective and urgent first-time CABG for isolated LAD disease is associated with excellent mid-term survival in the England and Wales population, conferring 5-year survival of 93.1% and 93.4% in the on-pump and off-pump groups respectively. There was no difference in risk-adjusted survival between on-pump and off-pump techniques when analysing all procedures; however supportive analysis demonstrated that off-pump surgery performed by experienced surgeons with a preference for the off-pump technique in their CABG caseload is associated with improved mid-term survival when compared to on-pump surgery performed by surgeons with a preference for the on-pump technique.

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INTRODUCTION

58 Debate still ensues with regard to the merits or detrimental effects of off-pump versus on-pump coronary artery bypass surgery (CABG) [1–4]. To date this has been exclusively with
60 regard to multi-vessel disease. The left internal mammary artery (LIMA) to left anterior descending artery (LAD) is the main prognostic component of a CABG operation and is a
62 primary reason why CABG surgery has not yet been overtaken by coronary artery stenting [5].

Comparing outcomes between patients undergoing on-pump surgery for multi-vessel
64 disease with those undergoing off-pump surgery is frequently confounded by surgical and patient factors, such as saphenous vein quality, radial artery usage, composite and sequential grafting,
66 aortic calcification, and extent of coronary atheroma. Isolated LIMA-to-LAD surgery for single vessel disease should, in principle, eliminate many of these confounding factors, potentially
68 enabling the simple comparison of the on- or off- pump technique to be made, as no top ends, sequential or composite grafting is required.

70 Our objective is to investigate if in-hospital mortality and mid-term survival (up to 10-years) of all-cause mortality following isolated LIMA-to-LAD surgery for single coronary vessel
72 disease were significantly associated with the use of cardiopulmonary bypass or not by retrospectively analysing the United Kingdom National Adult Cardiac Surgery Audit (NACSA)
74 registry.

METHODS

Data extraction and preprocessing

Data were extracted from The National Institute for Cardiovascular Outcomes Research (NICOR) NACSA registry (version 4.1.2) on 10th October 2014 for all adult cardiac surgery procedures performed in the United Kingdom. All data for one private hospital was deleted prior to any analysis as it was awaiting validation at the time of extraction. Reproducible cleaning algorithms were applied to the database, which are regularly updated as required [6]. Briefly, duplicate records and non-adult cardiac surgery entries were removed; transcriptional discrepancies harmonized; and clinical conflicts and extreme values corrected or removed. The data is returned regularly to each unit for local validation as part of the NASCA in the United Kingdom [7].

Study design

This is a cross-sectional observational study, which was approved by the NICOR NACSA Research Board (study reference 13-ACS-21), and the need to obtain informed consent from patients was waived as patient identifiable information was either removed or pseudonymised.

The initial inclusion criteria for this study were: 1) first-time cardiac surgery; 2) isolated CABG surgery; 3) elective or urgent procedure; 4) performed in England and Wales; 5) operation performed between 1st April 2003 and 31st March 2013; 6) responsible consultant surgeon identifiable (identified by a unique General Medical Council registration number in the registry). At this stage, for each responsible consultant cardiac surgeon we determined the total number of cases matching the aforementioned inclusion criteria, and the proportion of cases performed off-pump. Following this intermediary calculation, we applied our final inclusion criterion: 7) surgery for single vessel disease using a single pedicle LIMA graft going to either the proximal, mid- or distal LAD. Free LIMA, saphenous vein grafts and other arteries were not included. Exclusion criteria for this study were records with: 1) missing CPB status, or 2) missing discharge status. Data from Scotland, Northern Ireland and the Republic of Ireland were not included as post-discharge mortality tracking data was not available.

104 **Study variables**

For each operation, data are recorded on administrative factors, patient characteristics,
106 comorbidities, surgical team, intra-operative factors, and post-operative outcomes. For this study we extracted data on patient age at time of operation (years); gender; body mass index (BMI;
108 defined as weight [kg] / height^2 [m^2]); operative urgency; dyspnoea (NYHA grade); history of neurological dysfunction; diabetes (diet or insulin controlled); history of hypertension; recent
110 myocardial infarction (defined as within 90-days of surgery); serum creatinine >200 µmol/l; history of pulmonary disease; extracardiac arteriopathy; previous percutaneous coronary
112 intervention (PCI); preoperative heart rhythm (atrial fibrillation or flutter vs. all other rhythms); left ventricular ejection fraction (LVEF; classified as <30%, 30-50%, and >50%); critical
114 preoperative state (defined as per the EuroSCORE group); preoperative use of IV nitrates or heparin for treatment of unstable angina.

116 As expected with a national clinical registry, there were missing data. Reasons include inputting invalid choices, which were mapped to missing data during the pre-processing stage,
118 and incomplete data form filling. There were few missing data (all >95% complete with the exception of BMI). Missing data were therefore imputed as follows: continuous variables were
120 replaced by the median values of the observed data; categorical (and binary) data were replaced by the mode (i.e. most frequent value) of the observed data.

122 Administrative data was also extracted including: patient procedure and discharge dates, admission hospital, and responsible consultant cardiac surgeon. For each record we also
124 calculated the logistic EuroSCORE [8]. Further details of variable definitions are available at http://www.ucl.ac.uk/nicor/audits/adultcardiac/datasets (last accessed 4th February 2015).

126 **Study outcomes**

The primary outcome for this study was mid-term survival from all-cause mortality. The
128 secondary outcome was in-hospital mortality, defined as death due to any cause during admission to the base hospital for cardiac surgery. Patients who died in-hospital on the day of
130 surgery were recorded as having a nominal survival time of 0.5 days. Follow-up data up until the point of discharge was collected by the NACSA clinical registry system and post-discharge
132 survival data was collected by linking the records via patient NHS numbers to the Office for

National Statistics (ONS) death registry, which records all deaths in England and Wales. The final date of follow-up was 30th July 2013. Data on cause of death was unavailable. An attempt to back-fill missing in-hospital mortality data was made by record linkage to the ONS registry prior to applying the extraction criteria.

Statistical analysis

Patient and operative data were contrasted between the on-pump and off-pump groups. The independent samples Student *t*-test or Mann-Whitney *U*-test was used to compare approximately normal and non-normal continuous variables respectively. The chi-squared test for independence with Yates' continuity correction was used to compare categorical variables. To quantify the actual degree of imbalance between the on- and off-pump groups for each variable, we also calculated the standardized difference as:

$$\Delta = 100(\bar{x}_{\text{on}} - \bar{x}_{\text{off}}) \,/\, \sqrt{\{(s^2_{\text{on}} + s^2_{\text{off}})/2\}},$$

where $\bar{x}_{\text{off}}$ and $\bar{x}_{\text{on}}$ denotes the sample means for the off- and on-pump groups respectively, and s^2_{off} and s^2_{on} the respective sample variances. Typically, variables with absolute standardized differences <10% are considered to be adequately balanced [9].

We estimated survival curves, stratified by CPB use (on-pump vs. off-pump), using the Kaplan-Meier method. All variables were initially included in a multivariable Cox proportional hazards regression model [10]. In order to capture the non-linear association with the outcome, BMI was included as a restricted cubic spline on 4-knots placed at the 5th, 35th, 65th and 95th percentiles. Variables corresponding to statistically non-significant and clinically counterintuitive coefficients were eliminated from the model, and it was re-fitted. In order to assess linearity in log hazard for patient age at time of surgery, graphical plots of Martingale residuals were plotted against age, and a LOWESS smoothing curve overlaid [11]. As indicated, a piecewise linear spline was appropriate with a single knot at 70-years. The proportional hazards assumption was checked in the final model using graphical inspection of scaled Schoenfeld residuals plotted against time, and also by the Grambsch and Therneau test [12]. The final model is summarized by reporting the hazard ratios and 95% confidence intervals.

By the nature of data inclusion, there was expected to be few in-hospital deaths, which would translate into a small event per variable ratio for a saturated binary outcome regression model. Therefore we only included two variables in a multivariable logistic regression model for modelling in-hospital: logit (log-odds) transformed logistic EuroSCORE and CPB status. The odds ratios and 95% confidence intervals are reported for each.

All analyses and data cleaning were performed in R (Version 3.1.2; R Foundation for Statistical Computing, Vienna, Austria; http://www.R-project.org/). Survival analysis was performed using the survival package (version 2.37-7) [13]. Restricted cubic splines were calculated using the Hmisc package (version 3.14-5) [14]. In all cases, a *P*-value <0.05 was considered statistically significant.

Supportive analyses

Whilst there is heterogeneity in CPB practice between consultant surgeons, many adopt a preference. A supportive analysis was performed to assess whether there was a treatment effect for surgery performed according to the responsible consultant surgeons preferred technique. Based on all isolated CABG (elective and urgent) procedures for first-time cardiac surgery patients in England and Wales during the study period (irrespective of the number of grafts or conduit types), surgeons were categorized as one of the following groups:

I. Preference for off-pump: off-pump rate ≥80%;

II. Preference for on-pump: off-pump rate ≤20%;

III. Mixed practice: off-pump rate between >20% and <80%.

The thresholds of ≥80% for classifying a surgeon preference were predefined. For surgeons with experience in isolated CABG, defined here to be those contributing 300 or more such cases to the NACSA registry during the study period, we performed two supportive analyses:

1. Comparing the survival in off-pump cases performed by surgeons with a preference for the off-pump technique to on-pump cases performed by surgeons with a preference for the on-pump technique. Cases corresponding to either (i) on-pump surgery performed by surgeons with a preference for the off-pump technique, (ii) off-pump surgery performed

by surgeons with a preference for the on-pump technique, and (iii) all surgery performed
188 by mixed practice surgeons were excluded.

2. Comparing the survival between the three categories of surgeon preference within the
190 off-pump surgery group only. All on-pump cases were excluded.

The first analysis aims to address the question of whether there are any differences in outcome
192 between CPB techniques when performed by experienced surgeons using their preferred operative technique. The second analysis attempts to tease out whether preference for the off-
194 pump technique in experienced surgeons is associated with survival specifically in the off-pump surgery cases. Whilst the first supportive analysis was predefined, the second was performed
196 following the findings of the first analysis and should therefore be interpreted with caution.

RESULTS

Data

A total of 173,244 records met the initial inclusion criteria. Of these, 3266 (1.9%) records did not have data for whether CPB was used or not, and they were assumed as on-pump for the purposes of calculating the overall off-pump surgery rate. The overall rate of off-pump use in the isolated first-time surgery CABG group was 18.1%. We then filtered 3456 records that met the criteria of being a single pedicle LIMA graft to the LAD for single vessel disease. We excluded 52 records for missing CPB status followed by 2 records for missing outcome data (one had missing status at discharge and the other had missing discharge date, neither of which had ONS tracking data). A final dataset of 3402 records spanning 37 hospitals and 260 unique responsible consultant surgeons was then analysed (**Figure 1**). The overall rate of off-pump use was 65.5% in the core study dataset. There were little missing data for clinical variables of interest, with all variables ≤2% missing except BMI (5.2%). EuroSCORE could only be calculated for 83.6% of records, mainly due to a large number of missing pulmonary hypertension data (11.0%).

Patient and operative characteristics are compared between the on- and off-pump surgery groups in **Table 1**. Patient age (P=0.026) and left ventricular function (P=0.018) were the only variables that showed a statistically significant difference between groups. However, all variables were adequately balanced ($|\Delta| < 10\%$). Smoothed density histograms of patient age and BMI (**Figure 2**) illustrate the similarity and common support of both variables. The bypass times and cross-clamp times in the on-pump group were recorded in 93.3% and 92.1% of records respectively. For the complete data only, the mean (standard deviation; SD) bypass time was 35.6 (15.1) minutes. Similarly, the mean (SD) cross-clamp time was 21.0 (9.7) minutes.

Mid-term survival

ONS tracking was complete for 3321 (97.6%) records. Of those patients without post-discharge follow-up data, all patients had time-to-death right-censored at date of discharge. The median follow-up time was 5.0 years, with a maximum follow-up of 10.3 years, over which time 258 patients died (16 of who died in-hospital).

224 There was no difference in survivorship between on-pump and off-pump surgery (log-rank test *P*=0.50; **Figure 3**; unadjusted HR 1.09 [95% CI: 0.85 to 1.41]). The 1- and 5-year
226 survival in the on-pump group was 98.4% and 93.1% respectively. Correspondingly, the 1- and 5-year survival in the off-pump group was 98.4% and 93.4% respectively.

228 In the development of the multivariable Cox proportional hazards regression model, four variables were eliminated: history of hypertension, recent MI, critical preoperative state, and
230 preoperative use of IV nitrates or heparin for treatment of unstable angina. Age was modelled using a piecewise linear spline with a knot at age 70-years based on graphical assessment of the
232 smoothed Martingale residual plots. The final model is summarised in **Table 2**, indicating that the hazard ratio in the direction of on-pump CABG (reference level: off-pump CABG) was 1.15
234 (95% CI: 0.89 to 1.49; *P*=0.28). All variables in the final model were significantly associated with the mortality hazard rate, except CPB status, operative urgency, history of pulmonary
236 disease, and extracardiac arteriopathy. There was no evidence to reject proportional hazards assumption (Grambsch-Therneau global test, *P*=0.71; individual tests *P*>0.05 for all variables).

238 **In-hospital mortality**

Since records with missing discharge status constituted an exclusion criterion, no records
240 were missing. There were a total of 16 (0.47%) in-hospital deaths: 6 (0.51%) in the on-pump group and 10 (0.45%) in the off-pump group. The adjusted odds ratio in the direction of on-pump
242 was 1.09 (95% CI: 0.39-3.04; *P*=0.86). The coefficient for the logit transformed logistic EuroSCORE (equivalent to the log-odds ratio) was 1.11 (95%CI: 0.60 to 1.62; *P*<0.001).

244 **Supportive analyses**

There were 202 (77.7%) surgeons that contributed 300 or more first-time cardiac surgery
246 isolated CABG (elective and urgent) procedures in England and Wales during the study period. These surgeons accounted for 94.6% (*n*=3217) of all records in the LIMA-LAD dataset. After
248 applying our classification rules, 152 surgeons (75.2%; contributing 55.5% of study data) were classed as having a preference for the on-pump technique; 22 surgeons (10.9%; contributing
250 25.0% of study data) were classed as having a preference for the off-pump technique; and 28 surgeons (13.9%; contributing 19.5% of study data) as having a mixed practice. **Figure 4** shows
252 the distribution of the off-pump rate of the 202 expert surgeons. The median surgeon LIMA-to-

LAD volume for single vessel disease in the 'off-pump preference group was 26, 18 in the mixed
254 practice group and 9 in the on-pump preference group.

From a possible 152 expert CABG surgeons in the on-pump preference group, only 136
256 featured in this supportive analysis due to 16 not contributing any on-pump data to the LIMA-LAD study dataset. In total, 1832 records were extracted for the first supportive analysis. The 1-
258 and 5-year survival in the on-pump group was 98.2% and 92.6% respectively. Correspondingly, the 1- and 5-year survival in the off-pump group was 99.0% and 95.6% respectively (**Figure 5**,
260 top panel). Based on the log-rank test, the survival distributions were significantly different (*P*=0.031; unadjusted HR 1.48 [95% CI: 1.03 to 2.12]). We refitted the above Cox proportional
262 hazards regression model with slight modifications of age being included as a linear term only and removal of extracardiac arteriopathy. We infer from the model that on-pump surgery is
264 associated with increased hazards (HR for on-pump=1.72; 95% CI: 1.19 to 2.47; *P*=0.004). There was no evidence to reject the proportional hazards assumption (*P*=0.27).

266 For the second supportive analysis we restricted the data to the 2138 off-pump surgery cases performed by all expert CABG surgeons. These were performed by 22 surgeons (793
268 records; 37.1%) with a preference for the off-pump technique, 28 surgeons (598 records; 28.0%) with a mixed practice, and 94 surgeons (747 records; 34.9%) with a preference for the on-pump
270 technique. The 1-year and 5-year survival rates were 99.0% and 95.6% (expert off-pump preference), 97.9% and 93.3% (mixed practice), and 98.2% and 91.9% (expert on-pump
272 preference) (**Figure 5**, bottom panel). Based on the log-rank test, the survival distributions were not significantly different (*P*=0.15), nor after excluding mixed practice surgeons (*P*=0.064). We
274 refitted the Cox proportional hazards regression model fitted to the complete dataset with slight modifications of age being included as a linear term only and stratifying the baseline hazard
276 function by operative urgency. We infer from the model that relative to a reference level of the responsible consultant surgeon having a preference for the off-pump technique, those with a
278 mixed practice (HR = 1.61, 95% CI: 1.06 to 2.45; *P*=0.027) or preference for the on-pump technique (HR = 1.50, 95% CI: 1.02 to 2.20; *P*=0.037) are both associated with increased
280 hazards. There was no evidence to reject the proportional hazards assumption (*P*=0.90).

282 **DISCUSSION**

Elective and urgent first-time CABG for isolated LAD disease is associated with
284 excellent mid-term survival in the England and Wales population, regardless of bypass technique, conferring 5-year survival of 93.1% and 93.4% in the on-pump and off-pump groups
286 respectively. Although the on-pump technique is more frequently applied in general isolated CABG practice, a large proportion of cases are performed off-pump for LIMA-to-LAD bypass
288 surgery of single vessel disease. There was no difference in risk-adjusted survival between on-pump and off-pump techniques when analysing all procedures. Supportive analysis demonstrated
290 that off-pump surgery performed by surgeons with a preference for the off-pump technique in isolated CABG surgery is associated with better mid-term survival for isolated LAD disease
292 when compared to on-pump surgery performed by surgeons with an on-pump preference.

Neither of the recent large randomised trials with regard to off-pump surgery have
294 sufficient number of isolated LIMA-to-LAD grafts to allow analysis; hence one must appeal to observational data. Single institutions are not large enough to undertake the current study owing
296 to the low rate of isolated LIMA-to-LAD grafts performed for single vessel disease. Only 2% of elective and urgent first-time cardiac surgery patients undergoing isolated CABG had a single
298 pedicle LIMA-to-LAD graft for single vessel disease. Therefore it is logical that one must exploit multi-centre national registries in order to address this research hypothesis. This study,
300 however, presents 3402 records with follow-up data of up to 10-years. Interestingly, the rate of off-pump surgery in the overall first-time surgery isolated CABG group was 18.1%; however, it
302 was considerably higher in the core LIMA-to-LAD analysis dataset (65.5%). The reason for the observed disproportionality is unclear, but seems to be driven in part by the surgeons who
304 typically have a preference for the on-pump technique or who are mixed practice favouring the off-pump technique when performing isolated LIMA-to-LAD CABG surgery for single vessel
306 disease.

Comparison between on- and off-pump CABG procedures is frequently clouded by
308 differing surgical ethoses—single versus bilateral mammary grafts; use of the radial artery; graft number; composite grafting; endoscopic vein harvest; etc. Studying isolated LIMA-to-LAD
310 surgery for single vessel disease eliminates much of the expected confounding common to comparison of on- and off-pump techniques. We found that the data were adequately balanced

312 between the on- and off-pump groups, which suggest that there was no gross selection bias on measured variables. Therefore a propensity-score based analysis was not considered. However,
314 we would note that indication for CPB use is not recorded in the NACSA registry. Furthermore, we removed most haemodynamically unstable patients on the basis of operative urgency. A total
316 of 34 patients (1.0%) in a critical preoperative state were included, however they were balanced between the on- and off-pump groups.

318 Debate continues in the setting of isolated LAD disease with regard to stenting or invasive surgery [15,16]. Surgery is associated with a higher long term survival, and less
320 incidence of recurrent events and re-interventions [17]. Unfortunately surgery is invasive and associated with a higher initial morbidity and mortality than stenting. To minimise the risk of
322 surgery, minimally invasive LIMA-to-LAD has been proposed and studied as an alternative to conventional sternotomy [18]. These procedures are usually performed off-pump.

324 No significant difference in hospital mortality was found; however the number of operative deaths was small. There is a need to move away from in-hospital and 30-day mortality
326 towards mid- and long-term survival analysis, as the majority of patients with single vessel disease will expectedly do well initially regardless of treatment strategy. Furthermore, in the
328 absence of long-term patency and re-intervention data, mid-term survival is the most useful endpoint. Stroke remains the most devastating morbidity associated with CABG, and on-pump
330 surgery has been shown previously to be associated with an increased risk of stroke compared to the no aortic touch technique [19–21]. Unfortunately, we do not have validated data to verify this
332 in the current series, nor examine other postoperative morbidity outcomes.

A supportive analysis was performed that analysed data for experienced CABG surgeons
334 who adopt a technical preference for their isolated CABG practice, showing that off-pump cases performed by surgeons with a preference for the off-pump technique compared to on-pump cases
336 performed by surgeons with a preference for the on-pump technique led to a significantly lower hazard of death. Such a comparison might further help reduce surgeon bias with regard to case
338 selection, but referral bias is a possibility with isolated LIMA-to-LAD patients. The data partially supports this hypothesis since the median surgeon isolated LIMA-to-LAD volume in the
340 off-pump preference group was 26, 18 in the mixed practice group and 9 in the on-pump preference group. The corresponding overall median volumes for the same surgeons across all

342 isolated CABG procedures were 830, 797, 731 in the off-pump, mixed practice and on-pump preference groups respectively (**Figure 4**). The relatively larger volumes for surgeons with
344 preference for the off-pump technique might correspond to better experience, and therefore ability to make better anastomoses. Whilst others have demonstrated volume-outcome
346 relationships in CABG, this was beyond the scope of the research presented here [22].

Reasons for why experienced surgeons might deviate from their standard CABG
348 preference can never be fully captured in a national registry such as the one analysed. In particular, it is unclear why a large percentage (42%) of cases performed by experienced
350 surgeons with a preference for the on-pump technique were performed using the off-pump technique, which is generally regarded as being more technically demanding. The observed
352 disproportionality might be due to the perceived benefits of the off-pump technique in this group of patients, or possibly unmeasured variables. Whilst the pre-specified aim of this supportive
354 analysis was to compare the technique and not the ability of individual surgeons, we followed-up with a further analysis comparing technique preference in the experienced CABG surgeons for
356 off-pump cases only. It was shown that a surgical preference towards on-pump surgery is associated with worse outcome.

358 **Study limitations**

Whilst we have captured CPB status of the data, conversions from off-pump to on-pump
360 are not recorded, which might introduce a slight bias in the benefit of the off-pump group. No adjustment was made for site of LAD grafted (proximal, middle, or distal), distal runoff, and
362 distal target quality, the latter owing to no accurate way of quantifying this being available. We did not include free LIMA grafts owing to so few being included (1.7% of all single vessel grafts
364 to the LAD were recorded as free LIMA conduits), despite previous work indicating no difference in mid-term outcomes [23]. We do not have data on the technique of LIMA harvest.
366 Furthermore, the NACSA registry does not permit surgeons to record whether the LIMA was skeletonized or not.

368 Previous randomised trials with regard to on- or off-pump surgery have been criticised due to the relative inexperience of a number of the surgeons performing the procedures [1]. The
370 issue of surgeon experience in off-pump surgery in multi-vessel disease has been previously

addressed in the GOPCABE study [4]. No universally accepted definition exists that defines a
372 surgeon as experienced. By extracting all first-time cardiac surgery isolated CABG (elective and urgent) records in England and Wales during the study period from the NACSA registry—not
374 just on the LIMA-to-LAD for single vessel disease study data subset—we classified surgeons as 'experienced' as a contribution of 300 or more records to the NACSA registry during the study
376 period. We note that not all surgeons have contributed data to each of the 10 study years, for reasons including retirement before the study end date and qualification as a consultant after the
378 study start date [24]; hence some experienced surgeons might have been excluded. The use of total case load might allow for the confounding effect of institutional and surgeon volumes to be
380 addressed [25]. Whilst the choices for the off-pump rate thresholds for preference definition and the minimum volume were predefined before analyzing the data, they reflect a single subjective
382 view, and different definitions would potentially lead to different inferences. Furthermore, preference was calculated as a proportion from the total non-emergency CABG caseload of each
384 surgeon without consideration of whether differing case-mixes might be associated with the propensity to use one technique over another.

386 Like all observational data analyses, missing data and, more broadly, data quality are common issues that apply here also. The amount of missing clinical data in the final study
388 dataset were quite low for a national registry, partly due to the fact that this registry is used as part of the revalidation process for National Health Service consultant cardiac surgeons in
390 England and Wales [6]. Algorithms used to pre-process the registry undergo regular revision as part of the National Adult Cardiac Surgery Audit programme, and therefore the quality is
392 considered robust for research purposes. However, we note that data quality regarding graft data is not part of the validation exercises undertaken. Of these data, records that contained missing
394 data in database fields (including vessel disease, graft conduit used, graft site, and number of grafts) used to filter the complete NACSA registry were not included. Most notably, 8% of the
396 initial 173,244 records did not record extent of vessel disease. The lack of validated operative complications outcome data, and unmeasured potential confounders (e.g. whether minimally
398 invasive surgery was used or not) limit the conclusions that can be drawn also.

400 **CONCLUSIONS**

Elective and urgent first-time CABG for isolated LAD disease is associated with
402 excellent mid-term survival in the England and Wales population, regardless of bypass technique, conferring 5-year survival of 93.1% and 93.4% in the on-pump and off-pump groups
404 respectively. There was no difference in risk-adjusted survival between on-pump and off-pump techniques when analysing all procedures. Supportive analysis demonstrated that off-pump
406 surgery performed by experienced surgeons with a preference for the off-pump technique in their CABG caseload is associated with improved mid-term survival for isolated LAD disease when
408 compared to on-pump surgery performed by surgeons with a preference for the on-pump technique.

410

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416

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420

CONFLICTS OF INTEREST

422 No authors declare any conflicts of interest relevant to this study.

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Table 1. Patient and operative characteristics data by CPB technique with statistical comparison.

	Overall		On-pump		Off-pump		Δ (%)	*P*
Total number	*n*=3402		*n*=1173		*n*=2229			
Logistic EuroSCORE (%)	2.4 ± 2.5		2.4 ± 2.8		2.3 ± 2.3		1.8	0.965
Age (years)	61.7 ±10.6		61.1 ± 10.3		61.9 ± 10.7		-8.1	0.026
BMI (kg/m^2)	28.5 ± 4.6		28.7 ± 4.7		28.4 ± 4.5		6.1	0.090
	N	**%**	***N***	**%**	***N***	**%**		
Female	880	25.9%	325	27.7%	555	24.9%	6.4	0.083
Preoperative AF	69	2.0%	28	2.4%	41	1.8%	3.8	0.343
Urgent	733	21.5%	271	23.1%	462	20.7%	5.7	0.119
NYHA III/IV	645	19.0%	225	19.2%	420	18.8%	0.9	0.846
History of neurological dysfunction	53	1.6%	25	2.1%	28	1.3%	6.8	0.070
Diabetes (insulin or diet controlled)	600	17.6%	207	17.6%	393	17.6%	0.0	>0.999
History of hypertension	2269	66.7%	764	65.1%	1505	67.5%	-5.1	0.172
Recent MI	480	14.1%	177	15.1%	303	13.6%	4.3	0.255
Creatinine >200µmol//l	33	1.0%	11	0.9%	22	1.0%	-0.5	>0.999
History of pulmonary disease	361	10.6%	115	9.8%	246	11.0%	-4.0	0.293
Extracardiac arteriopathy	226	6.6%	89	7.6%	137	6.1%	5.7	0.126

Previous PCI	815	24.0%	299	25.5%	516	23.1%	5.5	0.139
Left ventricular function								0.018
Good (LVEF >50%)	3004	88.3%	1011	86.2%	1993	89.4%	-9.9	
Fair (LVEF 30-50%)	355	10.4%	146	12.4%	209	9.4%	9.9	
Poor (LVEF <30%)	43	1.3%	16	1.4%	27	1.2%	1.4	
Critical preoperative state	34	1.0%	15	1.3%	19	0.9%	4.2	0.314
Preoperative IV nitrates or heparin for treatment of unstable angina	41	1.2%	15	1.3%	26	1.2%	1.0	0.904

* Statistics reported as mean ± standard deviation for continuous variables, and number (percentage) for categorical / binary variables.

Δ – the standardized difference: $100(\bar{x}_{\text{on}} - \bar{x}_{\text{off}}) / \sqrt{\{(s_{\text{on}}^2 + s_{\text{off}}^2)/2\}}$, where $\bar{x}_{\text{off}}$ and $\bar{x}_{\text{on}}$ denotes the sample means for the off- and on-pump groups respectively, and s_{off}^2 and s_{on}^2 the respective sample variances.

P – *P*-value: chi-square test for all categorical variables (some with Yates' continuity correction as appropriate); independent samples *t*-test for age and BMI; Mann-Whitney *U*-test for logistic EuroSCORE.

Abbreviations: BMI – body mass index; MI – myocardial infraction; PCI – percutaneous coronary intervention; LVEF – left ventricular ejection fraction; CVD – coronary vessel disease; IV – intravenous; CABG – coronary artery bypass graft; AF – atrial fibrillation; NYHA – New York Heart Association.

514 **Table 2.** Multivariable Cox proportional hazards regression model summary for all-cause mortality.

	Adjusted HR (95% CI)	***P***
On-pump	1.15 (0.89, 1.49)	0.282
Age (years)	1.06 (1.04, 1.08)	<0.001
$(\text{Age} - 70)_+$	1.03 (0.98, 1.08)	0.295
BMI (kg/m^2)	0.80 (0.73, 0.88)	<0.001
BMI 1 ¶	1.87 (1.30, 2.69)	<0.001
BMI 2 ¶	0.17 (0.05, 0.61)	0.006
Female	0.68 (0.50, 0.91)	0.009
Preoperative AF	2.20 (1.32, 3.66)	0.003
Urgent	1.27 (0.95, 1.70)	0.112
NYHA III/IV	1.55 (1.18, 2.04)	0.002
History of neurological dysfunction	2.33 (1.20, 4.52)	0.014
Diabetes (insulin or diet controlled)	1.67 (1.25, 2.23)	<0.001
Serum creatinine >200μmol/l	6.58 (3.49, 12.40)	<0.001
History of pulmonary disease	1.40 (1.00, 1.96)	0.053
Extracardiac arteriopathy	1.03 (0.68, 1.55)	0.894
Previous PCI	1.35 (1.02, 1.80)	0.034
Left ventricular function		

Fair (LVEF 30-50%)	1.44 (1.02, 2.02)	0.037
Poor (LVEF < 30%)	2.68 (1.31, 5.48)	0.007

516

Abbreviations: HR – hazard ratio; CI – confidence interval; BMI – body mass index; MI –
518 myocardial infraction; PCI – percutaneous coronary intervention; LVEF – left ventricular ejection fraction; IV – intravenous; CABG – coronary artery bypass graft; AF – atrial fibrillation;
520 NYHA – New York Heart Association.

$(\text{Age} - 70)_+$ denotes 1 year for every year aged *above* 70 years; e.g. if age was 75, then $(75 -$
522 $70)_+=5$; if age=65, then $(65 - 70)_+=0$.

¶ Higher order terms from fitting restricted cubic spline with 4-knots to describe effects of BMI
524 as non-linear function. Knots for restricted cubic spline for BMI placed at 21.9kg/m^2, 26.6 kg/m^2, 29.6 kg/m^2, and 36.7 kg/m^2.

526

FIGURE LEGENDS

528 **Figure 1.** Flow of data for the study including sensitivity analyses breakdown.

530 **Figure 2.** Density plots of patient age (left panel) and BMI (right panel) by on- and off-pump groups.

532

Figure 3. Kaplan-Meier survival curve estimates stratified by on- and off-pump groups. Note
534 that the vertical axis does not start from zero probability.

536 **Figure 4.** Distribution of experienced CABG surgeon-specific off-pump rates for all isolated first-time cardiac surgery CABG procedures ('overall' group) and the single vessel disease
538 isolated pedicle LIMA-to-LAD subset ('LIMA-to-LAD' group) performed in England and Wales over the study period. Top panel: scatterplot of rates for all data against the LIMA-to-LAD
540 subset. Size of the points is proportional to the total number of isolated first-time cardiac surgery CABG procedures performed by the surgeon. Colour of points represents the different technique
542 preference classes of each surgeon. Black dashed lines denote the cut-off thresholds (based on the overall off-pump rate) for categorising surgeon technique preference. The red dotted line
544 denotes the line of equality. Data displayed is only for surgeons included in the sensitivity analysis. Bottom panel: an alternative view of the data showing volume against off-pump rate for
546 the overall and LIMA-to-LAD subset of procedures.

548 **Figure 5.** Top panel: Kaplan-Meier survival curves stratified by on- and off-pump groups for on-pump data only from surgeons with a preference for the on-pump technique and off-pump data
550 only from surgeons with a preference for the off-pump technique. Bottom panel: Kaplan-Meier survival curves stratified by preference category, which is based on the entire isolated first-time
552 cardiac surgery non-emergency CABG caseload for each surgeon, for off-pump surgery only.

Surgeons with <300 total such cases are not included in these sensitivity analyses. Note that the vertical axes do not start from zero probability.