Off-pump versus On-pump coronary artery bypass grafting. Insights from the Arterial Revascularization Trial.

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Abbreviation list

AKI: acute kidney injury

ART: Arterial Revascularization Trial

BMI: body mass index

BITA: bilateral internal thoracic artery

CK-MB: creatine kinase MB

CVA: cerebrovascular accident

COPD: chronic obstructive pulmonary disease

LMD: left main disease

LVEF: left ventricular ejection fraction

MACCE: major cardiac and cerebrovascular events

MI: myocardial infarction

ONCAB: on-pump coronary artery bypass

OPCAB: off-pump coronary artery bypass

SITA: single internal thoracic artery

PCI: percutaneous coronary intervention

PSM: Propensity score matching

RBC: red blood cell

PVD: peripheral vascular disease

SMD: standardized mean difference

SVG: saphenous vein graft

Central message: Off-pump and on-pump coronary artery bypass grafting are comparable in terms of 5-year rate of death and major cardiac and cerebrovascular events.

Perspective statement: Some studies have reported increased adverse event rates with off-pump when compared to on-pump coronary artery bypass. The present post-hoc analysis of the ART trial found no significant difference between off-pump and on-pump coronary surgery in the rate of death and major cardiac and cerebrovascular events.

Abstract

Background: The long-term effects of (OPCAB) continue to be controversial as some studies have reported increased adverse event rates with OPCAB when compared to on-pump coronary artery bypass (ONCAB). The Arterial Revascularization Trial (ART) compared survival after bilateral versus single internal thoracic artery grafting. The choice of OPCAB versus ONCAB was based on surgeon's discretion. We performed a post-hoc analysis of the ART to compare 5-year outcomes with two strategies.

Methods: Among 3102 patients enrolled in the ART, we selected 1260 patients who underwent OPCAB versus 1700 patients who underwent ONCAB with cardioplegic arrest for the preent comparison. Primary outcomes were 5-year mortality and incidence of major cardiac and cerebrovascular events (MACCE) including cardiovascular death, myocardial infarction, cerebrovascular accident and revascularization after index procedure. Propensity score matching selected 1260 pairs for final comparison. Stratified Cox models were used for treatment effect estimate.

Results: Hospital mortality was comparable between OPCAB and ONCAB groups (12[1.0%] vs 15[1.2%]; P=0.7). Conversion rate to on pump during OPCAB was 29/1260 (2.3%). When compared to OPCAB not converted, OPCAB converted to on-pump presented a remarkably higher hospital mortality (10.3% vs 0.7%; P<0.001). At 5 years, mortality rate was 110(8.9%) vs. 102(8.3%) in the OPCAB and ONCAB groups respectively with no significant difference (hazard ratio, HR 1.14; 95% confidence interval, CI 0.86-1.52; P=0.35). Incidence of MACCE was 175(14.3) vs. 169 (13.8) in the in the OPCAB and ONCAB groups respectively with no significant difference (HR 1.05 [0.84-1.31; P=0.65).

Conclusions: The present post-hoc ART analysis support the hypothesis that both OPCAB and ONCAB are equally effective and safe.

Despite the potential advantages of avoiding cardiopulmonary bypass, the postulated benefits of off-pump coronary artery bypass (OPCAB) in terms of perioperative mortality and morbidity including stroke were not realized in the majority of studies comparing the two strategies [1]. Furthermore, the long-term effects of OPCAB continue to be controversial. The increased technical complexity of OPCAB can result in less complete revascularization and reduced graft patency rates with some studies reporting increased adverse event rates with OPCAB when compared to on-pump coronary artery bypass (ONCAB) [2-5].

Two large randomized controlled trials (RCT) comparing OPCAB vs ONCABG have recently reported conflicting findings. The CABG Off or On Pump Revascularization Study (CORONARY) [6] has recently shown comparable 5 years results between the two techniques. However, CORONARY enrolled only higher risk patients and this aspect may limit the generalizability of the study findings. On the other hand, the Department of Veterans Affairs "Randomized On/Off Bypass" (ROOBY) Trial [7] has reported increased 5 years mortality with OPCAB. However, the ROOBY trial was criticized for the fact that the conversion rate to cardiopulmonary bypass was unacceptably high at 12 % and this brought some skepticism on the level of “off pump” experience of the surgeons involved in the study.

Consequently, the question whether OPCAB increases the risk of adverse events over the longer term when compared to ONCAB continues. The Arterial Revascularization Trial (ART) is designed to compare 10-year survival after bilateral internal thoracic artery (BITA) versus single left internal thoracic artery (SITA) grafting and an interim report at 5 years has not shown any clear difference between the two groups [8]. In the ART, the choice of OPCAB versus ONCAB was based on surgeon’s discretion. We sought to get further insights into the comparison between the two strategies by performing a post-hoc analysis of the ART.

Materials and Methods

The present study is a post-hoc retrospective analysis of 5 year outcomes of the ART trial. This research adheres to the principles set forth in the Declaration of Helsinki (http://www.wma.net/en/30publications/10policies/b3/index.html). In the ART, the choice of OPCAB versus ONCAB was based on surgeon's discretion. OPCAB versus ONCAB strategy adopted was available for all patients enrolled. Among patients enrolled in the ART (n=3102) from 2004 to 2007, we excluded those who did not undergo surgery (n=23). In two cases, there was no information regarding the use of cardiopulmonary bypass. We also excluded patients who received on-pump beating heart surgery (n=19) and 95 patients who received cross clamp fibrillation. The present analysis compared 1260 patients who underwent OPCAB versus 1700 patients who underwent ONCAB with cardioplegic arrest. OPCAB cases requiring intraoperative conversion to on-pump were included in the OPCAB group in the primary analysis (Figure 1). A total of 156 surgeons were involved. For 134 patients (60 OPCAB, 74 ONCAB) no information on participating surgeon was available. The total number of procedures performed by each surgeon and the choice between OPCAB vs. ONCAB presented a large variation with a large proportion of surgeons performing only few procedures (Supplementary Table 1). No information was available on individual surgeon practice pattern and OPCAB experience before they took part to the trial (i.e. number of OPCAB vs ONCAB procedure performed per year).

Trial design

The ART has been approved by the institutional review board of all participating centres, and informed consent was obtained from each participant. The protocol for the ART has been published [9]. Briefly, the ART is a 2-arm, randomized multi centre trial conducted in 28 hospitals in 7 countries, with patients being randomized equally to SITA or bilateral internal thoracic artery (BITA) grafts. Eligible patients were those with multivessel coronary artery disease undergoing coronary artery bypass grafting including urgent patients. Only emergency

patients (refractory myocardial ischemia/cardiogenic shock) and those requiring single grafts or redo surgery were excluded.

Follow-up

Questionnaires were sent to study participants by post at 12 months and then every year after surgery. No clinic visits were planned apart from the routine clinical 6-week post-operative visit. Participants were sent stamped addressed envelopes to improve the return rates of postal questionnaires. Study coordinators contacted participants by telephone to alert them to the questionnaire's arrival and to ask them about medications, adverse events and health services resource use. Mean follow-up time for the present analysis was 4.9±1.0 years. Follow-up at 5 years was completed for 2833/2960 (96%) patients.

Study outcomes

The two strategies were compared in terms of hospital outcomes and 5 years mortality and incidence of major cardiac and cerebrovascular events (MACCE) which included cardiovascular death, non-fatal myocardial infarction (MI), non-fatal cerebrovascular accident (CVA) and repeat revascularization. Treatment effect on individual MACCE components was also investigated. Adverse events were adjudicated blind to surgical procedure by a member of the Clinical Event Review Committee.

Outcomes definitions

Death was classified into cardiovascular and non-cardiovascular, where possible, using autopsy reports and death certificates. Congestive heart failure, arrhythmia or myocardial infarction, pulmonary embolus and dissection were considered cardiovascular causes of death. MI was diagnosed when two of the following three criteria were present: 1. Unequivocal ECG changes; 2. Elevation of cardiac enzyme(s) above twice the upper limit of normal or diagnostic troponin rises; 3. Chest pain typical for acute MI which lasted more than 20 minutes. CVA

was defined as new neurological deficit evidenced by clinical signs of paresis, plegia or new cognitive dysfunction including any mental status alteration lasting more than 24 hours and/or evidence on CT or MRI scan of recent brain infarct (less than 6 months). Repeat revascularization was defined as coronary bypass surgery or percutaneous coronary intervention (PCI) performed after trial procedure. Acute kidney injury (AKI) defined as a 0.3 mg/dl (≥26.5 mmol/l) creatinine increase from baseline within 48 hours of surgery.

Statistical analysis

Multiple imputation (m=3) was used to address missing data. Rubin's method [10] was used to combine results from each of the imputed data sets (Amelia R package). Due to lack of randomization with regards to receiving OPCAB, a propensity score (PS) was generated for each patient from a multivariable logistic regression model based on 23 pre-treatment covariates as independent variables with OPCAB versus ONCAB as a binary dependent variable [10]. Pairs of patients were derived using greedy 1:1 matching with a calliper of width of 0.2 standard deviation of the logit of the PS (nonrandom R package). The quality of the match was assessed by comparing selected pre-treatment variables in propensity score–matched patients using the standardized mean difference (SMD), with an absolute standardized difference of greater than 10% taken to represent meaningful covariate imbalance. [11]. McNemar's test and paired t-test was used to assess the statistical significance of the risk difference for hospital outcomes [12]. Cox regression models stratified on the matched pairs [12] were used to estimate the treatment effect on 5 years outcomes respectively. This approach accounts for the within-pair homogeneity by allowing the baseline hazard function to vary across matched sets. Risk competing framework was used to estimate the treatment effect on MACCE individual components. The Schoenfeld residuals test was used to test the independence between residuals and time and hence to test the proportional hazards assumption

in Cox models (survival R package). All p-values <0.05 were considered to indicate statistical significance.

Due to the large number of participating surgeons and the marked variability of total number of procedures and OPCAB procedures performed individually, performing surgeons could not be included into PS model. To account for the potential influence of individual surgeon's OPCAB experience, we classified each patient according to quartiles of total number of OPCAB procedures performed in the trial by the relative surgeon (0 [on-pump only], 1-5 [small OPCAB volume], 6-60 [moderate OPCAB volume], >60 [high OPCAB volume]) and outcomes in the matched sample were reported accordingly for descriptive purpose. Finally baseline characteristics and outcomes between OPCAB cases converted to on pump vs. not converted were also reported. All statistical analysis was performed using R Statistical Software (version 3.2.3; R Foundation for Statistical Computing, Vienna, Austria).

Results

Patient's characteristics and operative data.

OPCAB group was more likely to have higher creatinine and to receive BITA graft and was less likely to have treated hypertension, history of smoking and to receive saphenous vein graft. Total number of grafts per patients was comparable in the OPCAB and ONCAB groups (3.20±0.97 vs. 3.19±0.76; P=0.7). However, in the OPCAB group, the right coronary artery was less likely to be revascularized (62.1% vs 73.4%; P<0.001) whilst diagonal branches were more likely to be grafted in the OPCAB group (35.7% vs 29.2%; P<0.001). The two groups did not differ for rate of left anterior descending artery (98.1% vs 98.7%; P=0.24) and circumflex artery grafting (91.8% vs 92.6%; P=0.45).

PSM selected 1260 matched pairs for final comparison (C statistic=0.71; Supplementary Figure 1). No residual imbalance was observed between matched groups (all SMD<10%)

(Table 1 and Supplementary Figure 2). After matching number of grafts in the OPCAB and ONCAB groups was comparable (3.20±0.97 vs. 3.17±0.87; P=0.35)

Hospital outcomes

Hospital outcomes comparisons before and after matching are reported in Table 2. In hospital mortality was low and comparable between OPCAB and ONCAB groups (1.0% vs 1.2% P=0.70). OPCAB was associated with a lower creatine kinase MB (CK-MB) peak at 24hrs postoperatively and a relative lower incidence of MI. However, the rate of intra-aortic balloon pump requirement was comparable between the two groups. OPCAB was associated with a lower rate of red blood cell (RCB) transfusion and a trend towards a lower incidence of sternal wound complication. OPCAB did not reduce the incidence of postoperative CVA, AKI and renal replacement therapy.

5-year outcomes

5-year outcomes comparisons before and after matching are reported in Table 3. 5-year mortality (Figure 2) and MACCE rates were comparable in the two groups. In terms of individual MACCE components, OPCAB was associated with a marginally non-significant 1.1% absolute risk reduction in MI. CV death, CVA and Repeat revascularization rates were comparable between the two groups (Figure 3).

Impact of intraoperative conversion to on-pump on outcomes

Intraoperative conversion to on-pump occurred for 29 out of 1260 OPCAB (2.3%) procedures. Notably, distribution of risk factors between the OPCAB converted to on-pump group and OPCABG not converted group was similar (Supplementary Table 2). When compared to OPCAB not converted, OPCAB converted to on-pump presented a remarkably higher hospital mortality (10.3% vs 0.7%; P<0.001) and increased rate of hospital complications despite similar distribution of baseline risk factors. The trend towards poorer outcomes among OPCAB

cases converted to on-pump persisted at 5 years (Supplementary Table 3, Supplementary Figure 3).

Surgeon OPCAB volume and outcomes

A total of 95 surgeons performed on-pump only (951 patients); 33 surgeons performed between 1 and 5 OPCAB procedures (531 patients; 62 OPCAB; 469 ONCAB); 25 surgeons performed between 6 and 60 OPCAB procedures (in total 779 patients; 530 OPCAB; 249 ONCAB); finally, 3 surgeons performed over 60 OPCAB procedures (in total 699 patients; 668 OPCAB; 31 ONCAB)

Baseline characteristics and outcomes in the matched OPCAB and ONCAB groups stratified per surgeon OPCAB volume are reported in Supplementary Table 4 and Supplementary Table 5 and Supplementary Figure 4. OPCAB cases performed by "sporadic" OPCAB surgeons (1-5 OPCAB procedures) presented a high rate of conversion (12.9%), a lower number of grafts performed (2.60±0.88) and a higher rate of operative mortality (4.8%) compared to other OPCAB subgroups despite risk factors distribution was similar.

When OPCAB performed by 3 high volume OPCAB surgeons (>60) was compared to ONCAB by 95 "on-pump only" surgeons performing on-pump only we found similar 5-year overall mortality and MACCE rates.

Among 28 ONCAB cases performed by 3 high OPCAB volume surgeons (>60), we observed a high hospital mortality rate (7.1%). However, this subgroup presented a higher prevalence of important risk factors including LVEF <30% and increased creatinine compared to other ONCAB subgroups suggesting that these 3 surgeons selectively used on-pump for high risk cases.

Discussion

The main finding of the present post-hoc analysis of the ART showed that when compared to ONCAB, OPCAB was associated with comparable number of grafts performed, a reduced

operative morbidity and comparable 5-year mortality and incidence of MACCE. Conversion rate to on-pump was relatively low (2.3%) but was associated with a remarkable increase in hospital mortality and morbidity and poorer 5-year outcomes.

In the ART, over 50% of OPCAB procedures (668/1260) were performed by 3 surgeons only among 156 participating surgeons while 95 surgeons performed on-pump only. OPCAB performed by 3 high volume OPCAB surgeons was associated to hospital and 5-year mortality comparable to those observed after ONCAB performed by 95 "on-pump only" surgeons.

We found that OPCAB performed by "sporadic" OPCAB surgeons (between 1 and 5 OPCAB procedure) was associated with a marked increase in conversion rate (12.9%), a lower number of graft performed and increased hospital mortality (4.8%).

There is continued debate as to whether OPCAB may affect long-term outcomes due to a lower number of graft performed and subsequent effect of incomplete revascularization. Takagi et al. [2] pooled 5 randomized controlled trials and 17 adjusted observational studies that had reported long-term (≥5-year) all-cause mortality. In observational studies (102,820 patients) but not in randomized trials (1486 patients), OPCAB was associated with increased late mortality.

Criticisms for observational studies comparing OPCAB and ONCAB include a possible bias toward including higher-risk patients in the OPCAB group [13]. Furthermore, incomplete revascularization in retrospective studies may be a surrogate marker for higher burden of comorbidities and per se might not be particularly relevant on patients' outcome [14].

The CORONARY trial [6] is a large trial (n=4502 patients) designed to compare the two strategies. The final 5-year results showed similar outcomes with OPCAB and ONCAB. The difference between OPCAB and ONCAB in terms of number of grafts (3.0 vs. 3.2) and incidence of incomplete revascularization (11.8% vs. 10.0%) was only marginal. In the

CORONARY, each procedure was performed by a surgeon who had expertise in the specific type of surgery (completion of more than 100 cases of the specific technique either off-pump or on-pump). A limitation of the CORONARY is that only patients at higher risk were enrolled and this aspect might limit the generalizability of the study findings.

In contrary, in the ROOBY trial [7], which enrolled 2203 patients, OPCAB has been recently reported to be associated with increased 5-year mortality (15.2% in the OPCAB group versus 11.9% in the ONCAB group, relative risk, 1.28; 95% CI, 1.03 to 1.58; P=0.02). and MACCE rates (31.0% in the OPCAB group versus 27.1% in the ONCAB group (relative risk, 1.14; 95% CI, 1.00 to 1.30; P=0.046). This trial has also demonstrated that the patency rate of the off-pump arm was lower than that of the on-pump arm on 12-month angiography [15]. Such findings can be partially explained on the basis that the 53 participating surgeons enrolled on average only eight patients per year during the study period and had unacceptably high conversion rates to on-pump surgery (12%) and incomplete revascularization (18%). Moreover, in 60% of the cases, a resident was the primary surgeon again raising concerns about the relative inexperience translating into poor graft patency.

The present post-hoc analysis supports the equipoise between OPCAB and ONCAB in term of safety and efficacy. We found a trend towards a lower incidence of MI in the OPCAB group mainly related to early phase. It is well recognized that OPCAB is associated with a lower release of myocardial enzymes [16] but the clinical relevance of this observation remains unclear. Moreover, the definition of perioperative MI following myocardial revascularization remains controversial as well as its clinical implication [17].

In the ART, over 50% of OPCAB procedures were performed by 3 high volume OPCAB surgeons only and this can partially explain the present findings. When OPCAB was performed by “sporadic” off-pump surgeons, this was associated with a lower number of grafts, higher

297 conversion rate and higher hospital mortality. This observation supports the central role of
298 surgeon expertise in determining short and long-term results after off-pump.

299 The unique technical challenges of OPCAB fuel the perception that adoption of this myocardial
300 revascularization strategy may lead to poorer outcomes during each surgeon's "learning curve"
301 [18]. However, learning curve in off-pump CABG can be safely negotiated with appropriate
302 patient selection, individualized grafting strategy, peer-to-peer training of the entire team, and
303 graded clinical experience. Centers with established off-pump training programs have
304 consistently shown that OPCAB can be safely and successfully taught to trainees without
305 jeopardizing outcomes [19].

306 In the current era, increasing number of patients with high-risk profile is being referred for
307 surgical myocardial revascularization and off-pump represents an attractive strategy to reduce
308 operative morbidity especially in this subgroup as recently supported by a large meta-analysis
309 of RCTs [20]. Therefore, OPCAB should remain in the armamentarium of cardiac surgeons
310 (video 1). However, these superior outcomes in high-risk patients can only be achieved if off-
311 pump is offered to high- and low-risk patients alike and this further emphasizes the need for
312 recognition of off-pump as a subspecialty with structured training program.

313 The present analysis has intrinsic limitations. The main limitation is the retrospective analysis.
314 The propensity technique can adjust only for measurable and included variables, and we cannot
315 exclude a selection bias based on a nonmeasurable ‘‘eye-balling’’ including the quality of the
316 targets. We had no information on specific surgeon off-pump expertise and we used total
317 number of off-pump procedures performed in the ART as surrogate of off-pump expertise.
318 However, the validity of this approach was further limited by the large variability of number
319 of procedures performed per surgeon with a large proportion of surgeons performing less than
320 5 procedures (67 over 156 surgeons). Moreover, we had no information on reasons for

preferring off-pump over on-pump and vice-versa across surgeon subgroups. Therefore, subgroup analysis based on surgeon OPCAB volume should be considered only as descriptive and hypothesis generating. Despite the present analysis did not show a significant difference in terms of mortality between the two strategies, there is a marginal trend towards an excess of cardiovascular deaths in the OPCAB group (4.1% vs. 3.1%) and it can be argued that the present analysis is underpowered to demonstrate a significant difference between the two groups. However, this difference is irrelevant when all-cause mortality is considered (8.9% vs 8.3%). All-cause death is the most robust and unbiased index in cardiovascular research because no adjudication is required, thus avoiding inaccurate or biased documentation and inconsistency in endpoint definition.

In conclusion, the present post-hoc ART analysis, found no significant difference at 5 years between the OPCAB and ONCAB in the rate of death, nonfatal stroke, nonfatal myocardial infarction or in the rate of subsequent revascularization procedures. Our results indicate that both procedures are equally effective and safe at least over the medium term.

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Table 1. Baseline characteristics of patients undergoing OPCAB vs ONCAB

	OPCAB	ONCAB unmatched	SMD Pre-PSM	ONCAB matched	SMD Post PSM
n	1260	1700		1260	
Age (years) mean (sd)	64 (9)	64 (9)	1	64 (9)	1
Female n(%)	180 (14.3)	240 (14.1)	0	180 (14.3)	0
BMI mean (sd)	28.10 (4.10)	28.28 (3.87)	5	28.13 (3.87)	1
SBP (mmHg) mean (sd)	133 (19)	131 (17)	9	132.30 (18)	2
DBP (mmHg) mean (sd)	75 (11)	75 (11)	5	75.24 (11.32)	-1
Creatinine (mmol/l) mean (sd)	100 (23)	94 (21)	26	97.75 (21.58)	9
Treated Hypertension n(%)	943 (75)	1360 (80.0)	-12	950 (75.4)	-1
Treated Hyperlipaemia n(%)	1176 (93.3)	1601 (94.2)	-4	1178 (93.5)	-1
Diabetes n(%)			-6		1
No	980 (77.8)	1286 (75.6)		983 (78.0)	
Insulin dependent	70 (5.6)	93 (5.5)		67 (5.3)	
Non-insulin dependent	210 (16.7)	321 (18.9)		210 (16.7)	
Smoking n(%)			-14		-9
Current	180 (14.3)	242 (14.2)		149 (11.8)	
Ex-smoker	664 (52.7)	999 (58.8)		723 (57.4)	
Never	416 (33.0)	459 (27.0)		388 (30.8)	
COPD n(%)	29 (2.3)	43 (2.5)	-2	28 (2.2)	1
Asthma n(%)	63 (5.0)	65 (3.8)	6	59 (4.7)	2
PVD n(%)	90 (7.1)	120 (7.1)	0	81 (6.4)	3
TIA n(%)	40 (3.2)	60 (3.5)	-2	40 (3.2)	0
CVA n(%)	40 (3.2)	46 (2.7)	3	38 (3.0)	1
MI n(%)	510 (40.5)	726 (42.7)	- 5	513 (40.7)	-1
PCI n(%)	208 (16.5)	270 (15.9)	2	214 (17.0)	-1
Preop AF n(%)	19 (1.5)	24 (1.4)	1	16 (1.3)	2
preop LVEF (%)			5		2
≥50% (good)	950 (75.4)	1289 (75.8)		939 (74.5)	
31-49% (moderate)	268 (21.3)	389 (22.9)		303 (24.0)	
≤30% (poor)	42 (3.3)	22 (1.3)		18 (1.4)	
LMD n(%)	282 (22.4)	356 (20.9)	4	277 (22.0)	1
RA n(%)	240 (19.0)	381 (22.4)	-8	252 (20.0)	-2
SVG n(%)	936 (74.3)	1344 (79.1)	-11	956 (75.9)	-4
BITA n(%)	598 (47.5)	691 (40.6)	14	575 (45.6)	4

OPCAB: off-pump coronary artery bypass; ONCAB: on-pump coronary artery bypass; SMD: standardized mean difference; PSM: propensity score matching; SBP: systolic blood pressure; DPB: diastolic blood pressure; COPD: chronic obstructive pulmonary disease; PVD: peripheral vascular disease; TIA: transient ischemic attack; CVA: cerebrovascular accident; MI: myocardial infarction; PCI: percutaneous coronary intervention; AF: atrial fibrillation; LVEF: left ventricular ejection fraction; LMD: left main disease; RA: radial artery BITA: Bilateral internal thoracic arteries, SVG: saphenous vein graft

Table 2. Hospital outcomes of patients undergoing OPCAB vs ONCAB in the ART

	OPCAB	ONCAB unmatched	P-value* Pre-PSM	ONCAB matched	P-value‡ Post-PSM
n	1260	1700		1260	
Death n(%)	12 (1.0)	18 (1.1)	0.92	15 (1.2)	0.70
CVA n(%)	20 (1.6)	19 (1.1)	0.34	13 (1.0)	0.29
Periop MI n(%)	10 (0.8)	40 (2.4)	0.002	32 (2.5)	0.001
CK-MB 24h (U/L) mean (sd)	34 (179)	80 (125)	0.007	83 (139)	0.02
IABP insertion n(%)	58 (4.6)	59 (3.5)	0.14	46 (3.7)	0.27
Repeat Revascularization n(%)	8 (0.6)	7 (0.4)	0.56	7 (0.6)	1
POAF n(%)	279 (22.1)	451 (26.5)	0.007	333 (26.4)	0.01
Renal replacement therapy n(%)	72 (5.7)	79 (4.6)	0.22	64 (5.1)	0.54
AKI n(%)	225 (17.9)	290 (17.1)	0.61	221 (17.5)	0.88
Sternal wound complication n(%)	35 (2.8)	67 (3.9)	0.11	52 (4.1)	0.08
Reexploration for bleeding n(%)	40 (3.2)	62 (3.6)	0.55	51 (4.0)	0.29
RBC transfusion n(%)	165 (13.1)	280 (16.5)	0.01	207 (16.4)	0.02

OPCAB: off-pump coronary artery bypass; ONCAB: on-pump coronary artery bypass; PSM: propensity score matching; MI: myocardial infarction; CK-MB creatine kinase-MB; IABP: intra-aortic balloon pump; POAF: postoperative atrial fibrillation; AKI: acute kidney injury; RBC: red blood cell

*Chi test or t-test

‡ Mcnemar test or paired t-test

Table 3. 5-year outcomes of patients undergoing OPCAB vs ONCAB in the ART (expressed in number of events and cumulative incidence)

	OPCAB	ONCAB unmatched	ONCAB Matched	HR(95%CI) Post-PSM*	P-value Post-PSM*
n	1260	1700	1260		
Mortality n(%)	110(8.9)	134(8.0)	102(8.3)	1.14[0.86-1.52]	0.35
MACCE n(%)	175(14.3)	217(13.1)	169 (13.8)	1.05 [0.84-1.31]	0.65
CV death n(%)	51(4.1)	47(2.8)	39(3.1)	1.39[0.90-2.13]	0.13
MI n(%)	37(3.0)	61(3.6)	51(4.1)	0.66[0.43-1.02]	0.06
CVA n(%)	41(3.3)	42(2.5)	32(2.6)	1.32[0.83-2.11]	0.24
Revascularization n(%)	90(7.5)	108(6.4)	84(6.8)	1.09[0.80-1.49]	0.58

OPCAB: off-pump coronary artery bypass; ONCAB: on-pump coronary artery bypass; PSM: propensity score matching; MACCE: major cardiac and cerebrovascular event; CV: cardiovascular; MI: myocardial infarction; CVA: cerebrovascular accident

*Cox model stratified for matched pairs

Table 4. Outcomes in patients undergoing OPCAB converted vs non-converted to on-pump

	OPCAB converted to on-pump	OPCAB not converted	P-value
N	29	1231	
*In hospital outcomes**			
Death n(%)	3 (10.3)	9 (0.7)	<0.001
CVA n(%)	1 (3.4)	19 (1.5)	0.95
MI n(%)	0 (0.0)	10 (0.8)	1
CKMB at 24h (U/L) mean (sd)	182 (102)	31 (179)	0.15
IABP insertion n(%)	10 (34.5)	48 (3.9)	<0.001
Repeat Revascularization n(%)	1 (3.4)	7 (0.6)	0.46
POAF n(%)	15 (51.7)	264 (21.4)	<0.001
Renal replacement therapy n(%)	4 (13.8)	68 (5.5)	0.14
AKI n(%)	16 (55.2)	209 (17.0)	<0.001
Sternal wound complication n(%)	1 (3.4)	34 (2.8)	1
Re-exploration for bleeding n(%)	3 (10.3)	37 (3.0)	0.09
RBC transfusion n(%)	17 (58.6)	148 (12.0)	<0.001
5-year outcomes ǂ			
Mortality n(%)	4(13.8)	106(8.8)	0.3
MACCE n(%)	8(27.9)	167(14.0)	0.02
CV death n(%)	3(10)	48(4.0)	0.08
MI n(%)	2(6.9)	35(2.9)	0.18
CVA n(%)	1(3.4)	40(3.3)	0.92
Repeat Revascularization	4(13.8)	86(7.1)	0.12

OPCAB: off-pump coronary artery bypass; ONCAB: on-pump coronary artery bypass; PSM: propensity score matching; MI: myocardial infarction; IABP: intra-aortic balloon pump; POAF: postoperative atrial fibrillation; AKI: acute kidney injury; RBC: red blood cell; MACCE: major cardiac and cerebrovascular event; CV: cardiovascular; MI: myocardial infarction; CVA: cerebrovascular accident

* Chi test or t-test

ǂ Cox regression model

436 **Table 5.** Outcomes among OPCAB and matched ONCAB patients stratified for surgeon trial

437 OPCAB volume

	Matched ONCAB					OPCAB		
surgeon trial OPCAB volume quartiles	0	1-5	6-60	>60	0	1-5	6-60	>60
N of surgeons	95	33	25	3	95	33	25	3
N of patients	688	340	204	28	-	62	530	668
Hospital death n(%)	8 (1.2)	4 (1.2)	1 (0.5)	2 (7.1)	-	3 (4.8)	3 (0.6)	6 (0.9)
Conversion rate n(%)	-	-	-	-	-	8(12.9)	14(2.6%)	7 (1.0%)
N grafts mean(sd)	3.14 (0.77)	3.12 (0.78)	3.31 (0.72)	3.43 (0.57)	-	2.60 (0.88)	3.20 (0.85)	3.26 (0.87)
5-y Mortality n(%)	65(9.6)	22(6.7)	10(4.9)	5(17.9)	-	5(8.2)	40 (7.8)	65(9.9)
5-y MACCE n(%)	94(14.0)	44(13.4)	24(11.9)	7(25.7)	-	9(14.9)	52(10.2)	114(17.5)
5-y CV death n(%)	23(3.4)	8(2.4)	4(2.0)	28(14.3)	-	3(4.8)	15(2.9)	33(5.0)
5-y MI n(%)	23(3.4)	19(5.6)	8(3.9)	1(3.6)	-	3(4.8)	9(1.7)	25(3.8)
5-y CVA n(%)	16(2.4)	8(2.4)	6(3.0)	2(7.1)	-	2(3.3)	16(3.1)	23(3.5)
5-y Revascularization n(%)	52(7.7)	16(4.9)	14(6.9)	28(7.1)	-	3(5.0)	23(4.5)	64(9.7)

438 OPCAB: off-pump coronary artery bypass; ONCAB: on-pump coronary artery bypass; PSM:
439 propensity score matching; MACCE: major cardiac and cerebrovascular event; CV:
440 cardiovascular; MI: myocardial infarction; CVA: cerebrovascular accident
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Supplementary Table 1. OPCAB, ONCAB and total number of cases performed according to individual surgeon

Surgeon#	ONCAB	OPCAB	TOT
(unknown)	74	60	134
1	4	0	4
2	0	1	1
3	0	2	2
4	0	2	2
5	1	5	6
6	1	0	1
7	26	0	26
8	18	0	18
9	1	10	11
10	0	1	1
11	1	0	1
12	16	0	16
13	1	0	1
14	1	1	2
15	1	0	1
16	4	0	4
17	2	0	2
18	4	0	4
19	2	0	2
20	37	0	37
21	0	9	9
22	8	2	10
23	25	15	40
24	28	1	29
25	2	1	3
26	1	0	1
27	10	0	10
28	1	0	1
29	0	38	38
30	21	0	21
31	28	0	28
32	20	0	20
33	51	0	51
34	9	0	9
35	13	0	13
36	0	15	15
37	9	0	9
38	17	0	17
39	14	7	21
40	10	0	10

41	63	17	80
42	1	0	1
43	5	0	5
44	1	47	48
45	18	1	19
46	2	0	2
47	3	0	3
48	5	16	21
49	2	0	2
50	26	0	26
51	0	6	6
52	4	0	4
53	1	0	1
54	0	6	6
55	20	1	21
56	22	0	22
57	4	43	47
58	29	0	29
59	37	0	37
60	5	0	5
61	0	10	10
62	0	6	6
63	53	4	57
64	1	0	1
65	15	0	15
66	1	0	1
67	5	0	5
68	6	9	15
69	3	0	3
70	0	1	1
71	6	0	6
72	11	0	11
73	1	0	1
74	17	1	18
75	25	0	25
76	0	3	3
77	32	0	32
78	1	0	1
79	2	47	49
80	1	0	1
81	26	0	26
82	6	0	6
83	1	1	2
84	0	1	1
85	0	48	48

86	1	77	78
87	34	0	34
88	37	0	37
89	9	2	11
90	1	0	1
91	8	0	8
92	3	0	3
93	71	2	73
94	7	2	9
95	1	0	1
96	13	0	13
97	2	0	2
98	1	34	35
99	0	2	2
100	1	0	1
101	40	0	40
102	1	0	1
103	21	0	21
104	27	8	35
105	2	2	4
106	31	2	33
107	4	0	4
108	6	12	18
109	2	0	2
110	11	20	31
111	47	0	47
112	0	3	3
113	3	0	3
114	1	0	1
115	1	10	11
116	1	0	1
117	65	1	66
118	1	0	1
119	2	0	2
120	18	5	23
121	1	0	1
122	26	5	31
123	1	0	1
124	1	8	9
125	6	0	6
126	1	0	1
127	1	1	2
128	6	0	6
129	36	0	36
130	5	1	6

131	2	18	20
132	1	0	1
133	7	0	7
134	4	0	4
135	1	0	1
136	0	1	1
137	0	412	412
138	1	0	1
139	1	0	1
140	29	0	29
141	0	2	2
142	2	0	2
143	5	11	16
144	1	0	1
145	1	0	1
146	17	0	17
147	9	1	10
148	1	0	1
149	19	0	19
150	5	0	5
151	1	0	1
152	1	0	1
153	76	1	77
154	30	179	209
155	6	0	6
156	1	0	1

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Supplementary Table 2. Baseline characteristics in patients undergoing OPCAB converted vs non-converted to on-pump

	OPCAB not converted	OPCAB converted to on-pump	P*
n	1231	29	
Age (years) mean (sd)	63.59 (9.06)	64.40 (9.77)	0.634
Female n(%)	179 (14.5)	1 (3.4)	0.16
BMI mean (sd)	28.10 (4.11)	28.15 (3.99)	0.95
SBP (mmHg) mean (sd)	132.75 (19.11)	130.66 (17.94)	0.56
DBP (mmHg) mean (sd)	75.40 (11.07)	72.48 (11.85)	0.16
Creatinine (mmol/l) mean (sd)	99.68 (22.19)	107.76 (41.54)	0.06
Treated Hypertension n(%)	919 (74.7)	24 (82.8)	0.44
Treated Hyperlipaemia n(%)	1147 (93.2)	29 (100.0)	0.28
Diabetes n(%)			0.78
No	959 (77.9)	21 (72.4)	
Insulin dependent	68 (5.5)	2 (6.9)	
Non-insulin dependent	204 (16.6)	6 (20.7)	
Smoking n(%)			0.02
Current	173 (14.1)	7 (24.1)	
Ex-smoker	645 (52.4)	19 (65.5)	
Never	413 (33.5)	3 (10.3)	
COPD n(%)	29 (2.4)	0 (0.0)	0.83
Asthma n(%)	58 (4.7)	5 (17.2)	0.009
PVD n(%)	87 (7.1)	3 (10.3)	0.76
TIA n(%)	40 (3.2)	0 (0.0)	0.65
CVA n(%)	40 (3.2)	0 (0.0)	0.65
MI n(%)	493 (40.0)	17 (58.6)	0.07
PCI n(%)	199 (16.2)	9 (31.0)	0.06
Preop AF n(%)	18 (1.5)	1 (3.4)	0.92
preop LVEF (%)			0.37
≥50% (good)	927 (75.3)	23 (79.3)	
31-49% (moderate)	264 (21.4)	4 (13.8)	
≤30% (poor)	40 (3.2)	2 (6.9)	
LMD n(%)	276 (22.4)	6 (20.7)	1
RA n(%)	231 (18.8)	9 (31.0)	0.15
SVG n(%)	916 (74.4)	20 (69.0)	0.65
BITA n(%)	582 (47.3)	16 (55.2)	0.51

OPCAB: off-pump coronary artery bypass; SBP: systolic blood pressure; DPB: diastolic blood pressure; COPD: chronic obstructive pulmonary disease; PVD: peripheral vascular disease; TIA: transient ischemic attack; CVA: cerebrovascular accident; MI: myocardial infarction; PCI: percutaneous coronary intervention; AF: atrial fibrillation; LVEF: left ventricular ejection fraction; LMD: left main disease; RA: radial artery BITA: Bilateral internal thoracic arteries, SVG: saphenous vein graft

*Chi test or t-test

Supplementary Table 3. Baseline characteristics of OPCAB and matched ONCAB patients stratified for surgeon trial OPCAB volume

	Matched ONCAB					OPCAB			
surgeon trial OPCAB volume quartiles	0	1-5	6-60	>60		0	1-5	6-60	>60
N of surgeons	95	33	25	3		95	33	25	3
N of patients	688	340	204	28		-	62	530	668
Age (years) mean (sd)	64(9)	62(9)	6(9)	66(9)		-	64(8)	62(8)	65(9)
Female n(%)	93 (13.5)	55 (16.2)	28 (13.7)	4 (14.3)		-	7 (11.3)	55 (10.4)	118 (17.7)
BMI mean (sd)	28(4)	28(4)	28(4)	29(4)		-	27(4)	28 (4)	28(4)
SBP (mmHg) mean (sd)	133 (17)	132 (17)	133 (21)	134 (15)		-	132 (17)	131 (19)	134 (20)
DBP (mmHg) mean (sd)	75.50 (11.51)	74.91 (10.99)	75.22 (11.02)	72.72 (13.01)		-	75.11 (8.85)	76.51 (10.96)	74.42 (11.30)
Creatinine (mmol/l) mean (sd)	98 (23)	95 (20)	101 (19)	111 (17)		-	94 (31)	96 (22)	104 (22)
Treated Hypertension n(%)	508 (73.8)	272 (80.0)	146 (71.6)	24 (85.7)		-	53 (85.5)	389 (73.4)	501 (75.0)
Treated Hyperlipaemia n(%)	629 (91.4)	323 (95.0)	201 (98.5)	25 (89.3)		-	59 (95.2)	516 (97.4)	601 (90.0)
Diabetes n(%)						-			
No	540 (78.5)	257 (75.6)	163 (79.9)	23 (82.1)		-	49 (79.0)	415 (78.3)	516 (77.2)
Insulin dependent	28 (4.1)	24 (7.1)	13 (6.4)	2 (7.1)		-	2 (3.2)	25 (4.7)	43 (6.4)
Non-insulin dependent	120 (17.4)	59 (17.4)	28 (13.7)	3 (10.7)		-	11 (17.7)	90 (17.0)	109 (16.3)
Smoking n(%)						-			
Current	78 (11.3)	50 (14.7)	18 (8.8)	3 (10.7)		-	8 (12.9)	85 (16.0)	87 (13.0)
Ex-smoker	384 (55.8)	196 (57.6)	131 (64.2)	12 (42.9)		-	37 (59.7)	264 (49.8)	363 (54.3)
Never	226 (32.8)	94 (27.6)	55 (27.0)	13 (46.4)		-	17 (27.4)	181 (34.2)	218 (32.6)
COPD n(%)	14 (2.0)	6 (1.8)	8 (3.9)	0 (0.0)		-	1 (1.6)	11 (2.1)	17 (2.5)
Asthma n(%)	35 (5.1)	11 (3.2)	11 (5.4)	2 (7.1)		-	2 (3.2)	24 (4.5)	37 (5.5)
PVD n(%)	45 (6.5)	20 (5.9)	14 (6.9)	2 (7.1)		-	2 (3.2)	29 (5.5)	59 (8.8)

TIA n(%)	18 (2.6)	10 (2.9)	11 (5.4)	1 (3.6)		-	1 (1.6)	19 (3.6)	20 (3.0)
CVA n(%)	28 (4.1)	7 (2.1)	3 (1.5)	0 (0.0)		-	1 (1.6)	11 (2.1)	28 (4.2)
MI n(%)	272 (39.5)	148 (43.5)	81 (39.7)	12 (42.9)		-	28 (45.2)	226 (42.6)	256 (38.3)
PCI n(%)	102 (14.8)	63 (18.5)	46 (22.5)	3 (10.7)		-	17 (27.4)	135 (25.5)	56 (8.4)
Preop AF n(%)	8 (1.2)	3 (0.9)	5 (2.5)	0 (0.0)		-	0 (0.0)	7 (1.3)	12 (1.8)
preop LVEF (%)						-			
≥50% (good)	516 (75.0)	253 (74.4)	153 (75.0)	17 (60.7)		-	52 (83.9)	405 (76.4)	493 (73.8)
31-49% (moderate)	162 (23.5)	85 (25.0)	48 (23.5)	8 (28.6)		-	10 (16.1)	112 (21.1)	146 (21.9)
≤30% (poor)	10 (1.5)	2 (0.6)	3 (1.5)	3 (10.7)		-	0 (0.0)	13 (2.5)	29 (4.3)
LMD n(%)	149 (21.7)	85 (25.0)	34 (16.7)	9 (32.1)		-	6 (9.7)	101 (19.1)	175 (26.2)
RA n(%)	137 (19.9)	84 (24.7)	27 (13.2)	4 (14.3)		-	9 (14.5)	90 (17.0)	141 (21.1)
SVG n(%)	524 (76.2)	232 (68.2)	175 (85.8)	25 (89.3)		-	38 (61.3)	400 (75.5)	498 (74.6)
BITA n(%)	308 (44.8)	171 (50.3)	85 (41.7)	11 (39.3)		-	23 (37.1)	252 (47.5)	323 (48.4)

OPCAB: off-pump coronary artery bypass; ONCAB: on-pump coronary artery bypass; SBP: systolic blood pressure; DPB: diastolic blood pressure; COPD: chronic obstructive pulmonary disease; PVD: peripheral vascular disease; TIA: transient ischemic attack; CVA: cerebrovascular accident; MI: myocardial infarction; PCI: percutaneous coronary intervention; AF: atrial fibrillation; LVEF: left ventricular ejection fraction; LMD: left main disease; RA: radial artery BITA: Bilateral internal thoracic arteries, SVG: saphenous vein graft

Figure Legend

Central picture: 5-year cumulative incidence for mortality in the matched OPCAB and ONCAB groups. (OPCAB: off-pump coronary artery bypass; ONCAB: on-pump coronary artery bypass)

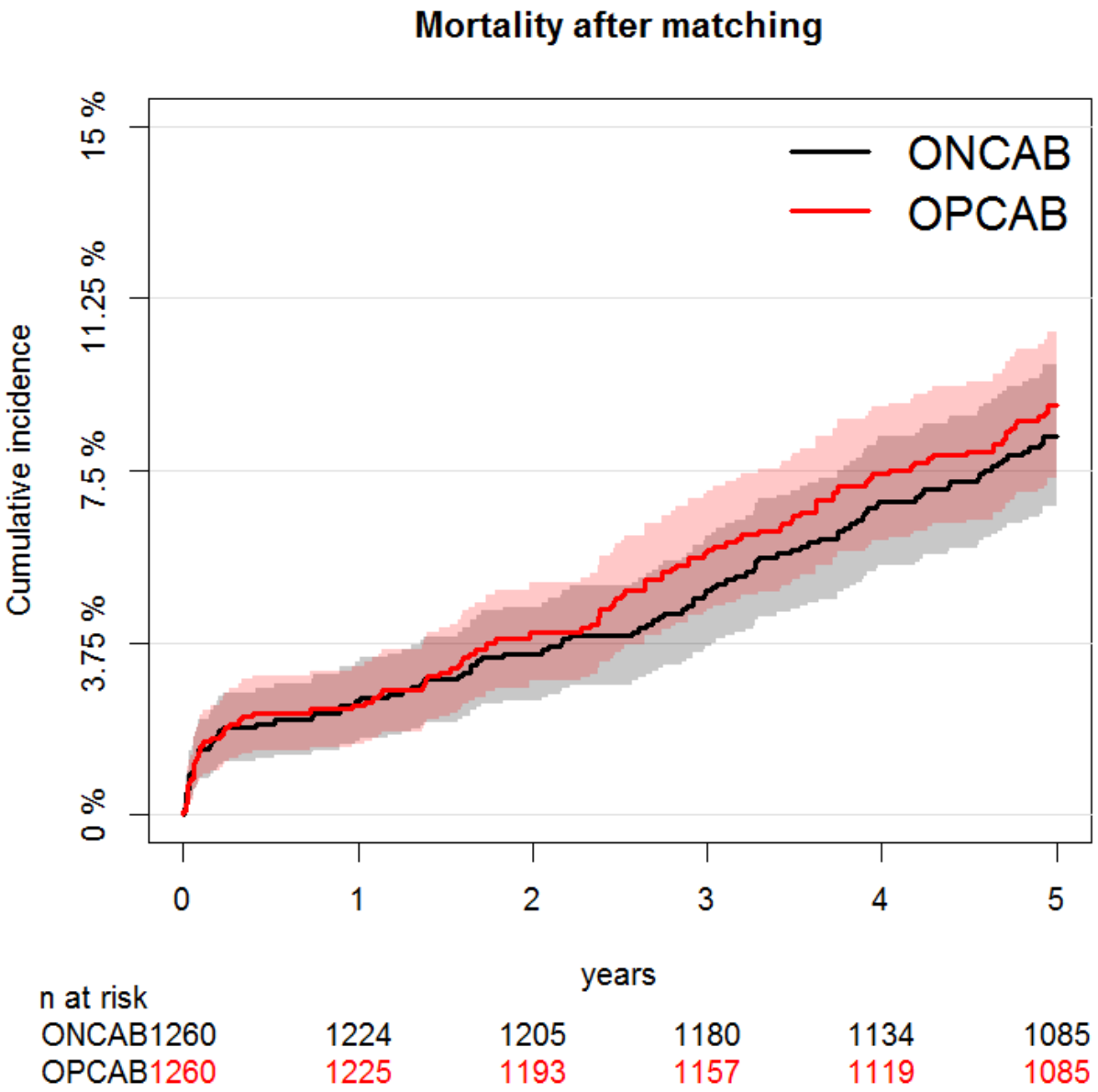


Figure 1. Study flow chart for patient inclusion/exclusion (OPCAB: off-pump coronary artery bypass; ONCAB: on-pump coronary artery bypass)

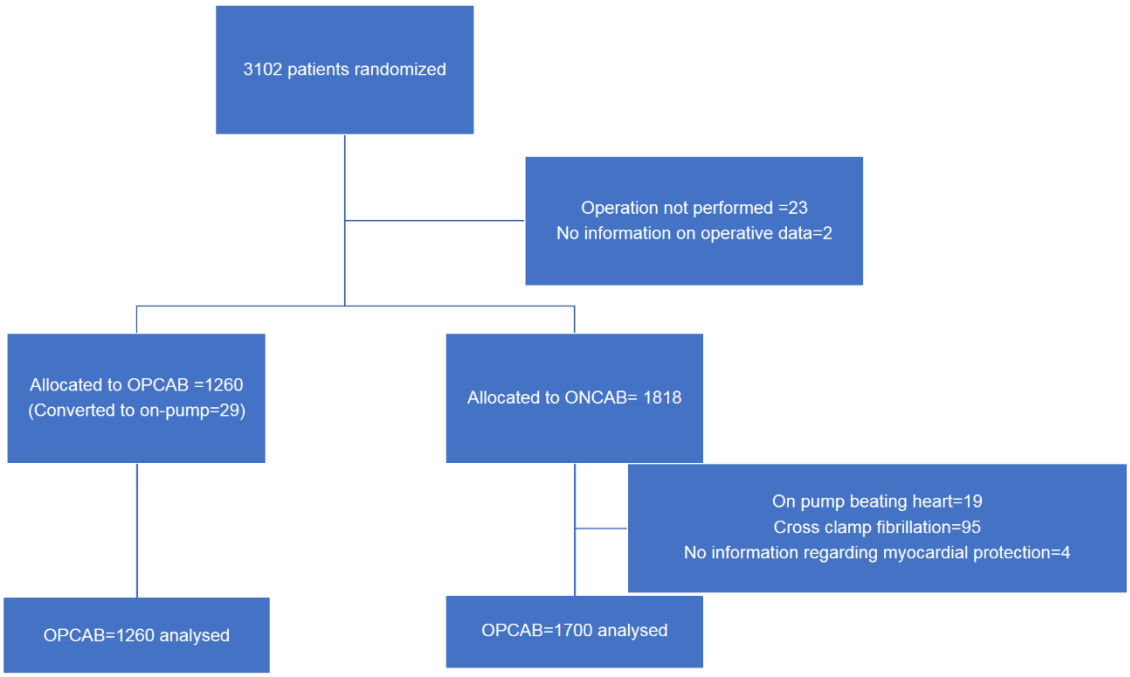


Figure 2. 5-year cumulative incidence for mortality and major adverse cardiac and cerebrovascular events (MACCE) in the matched OPCAB and ONCAB groups. (OPCAB: off-pump coronary artery bypass; ONCAB: on-pump coronary artery bypass)

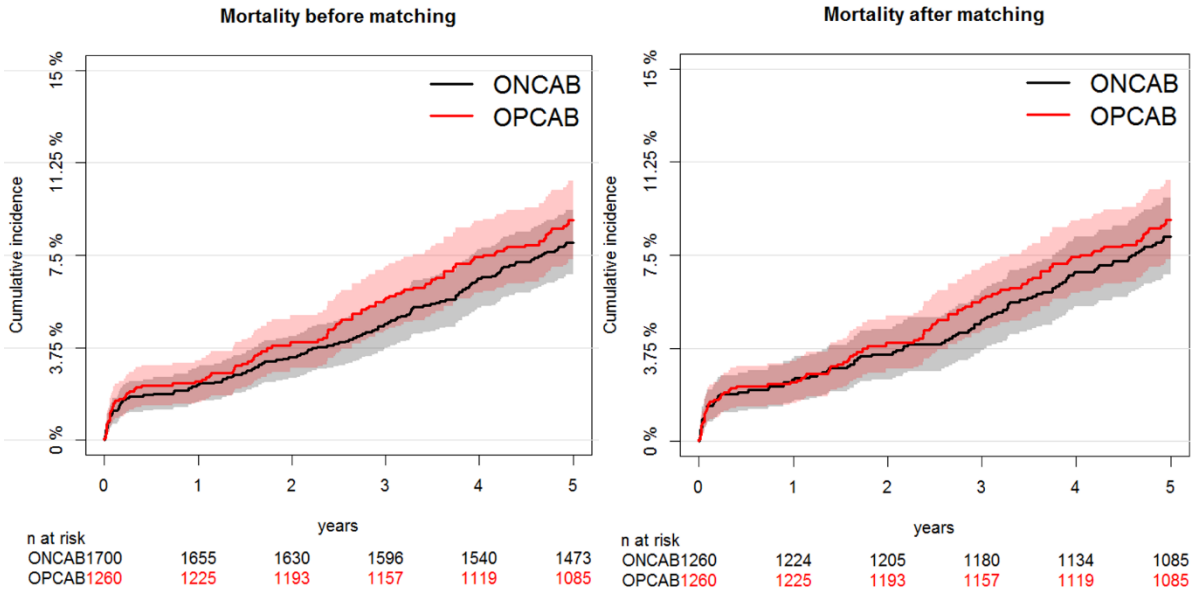
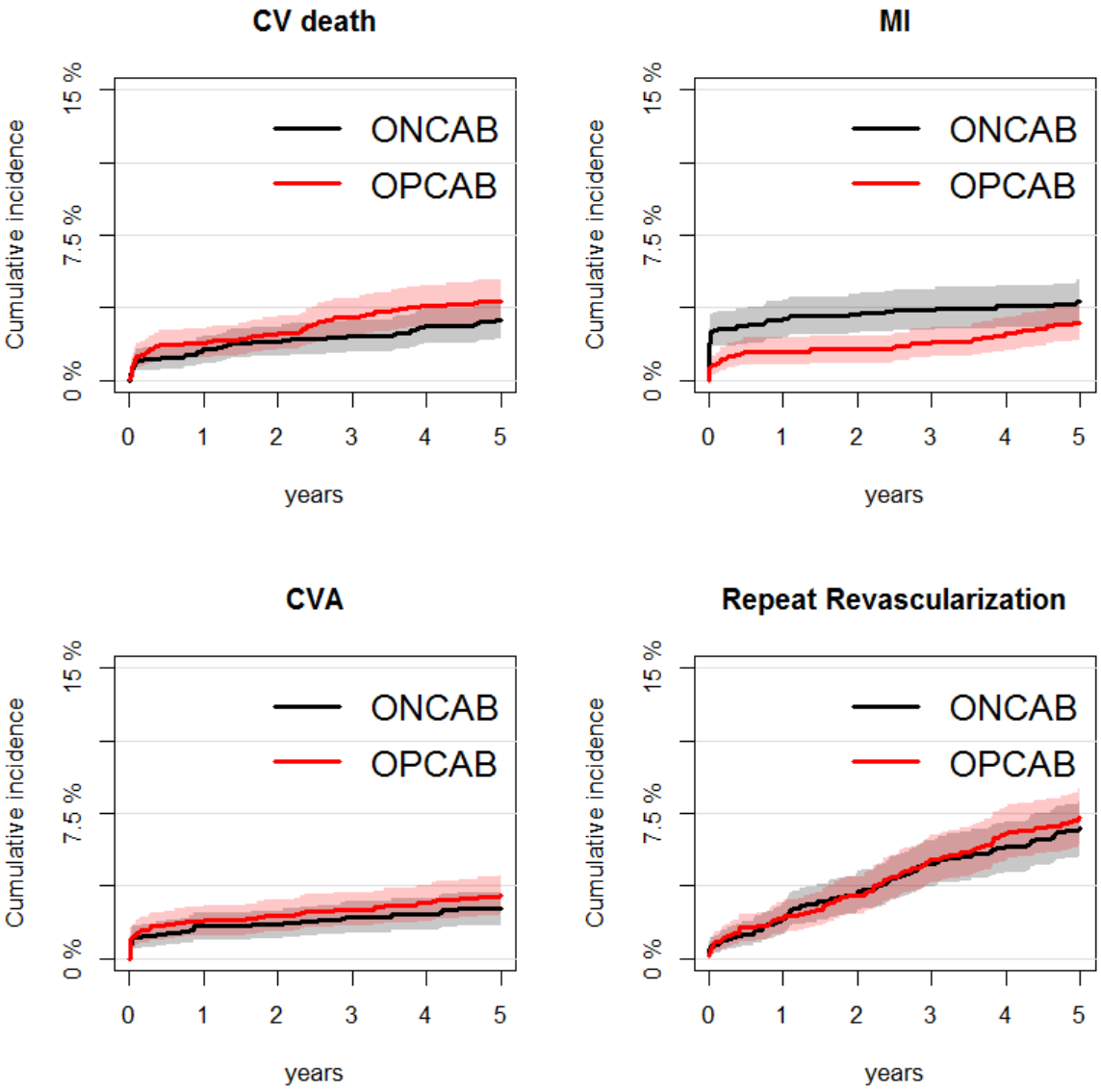
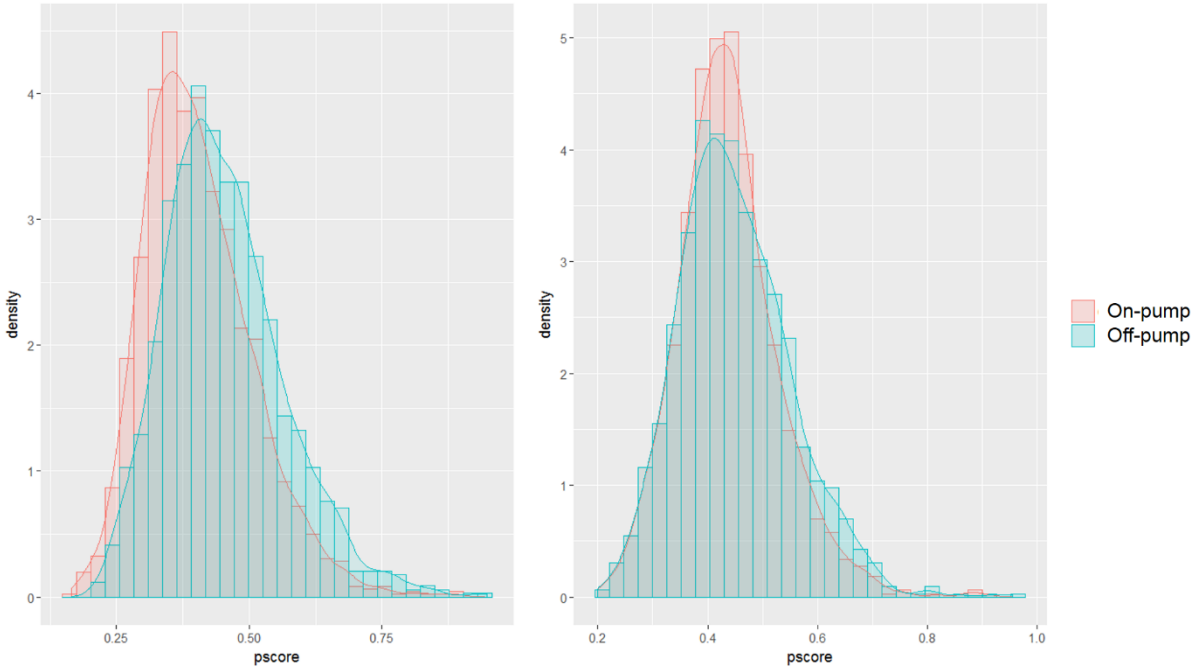


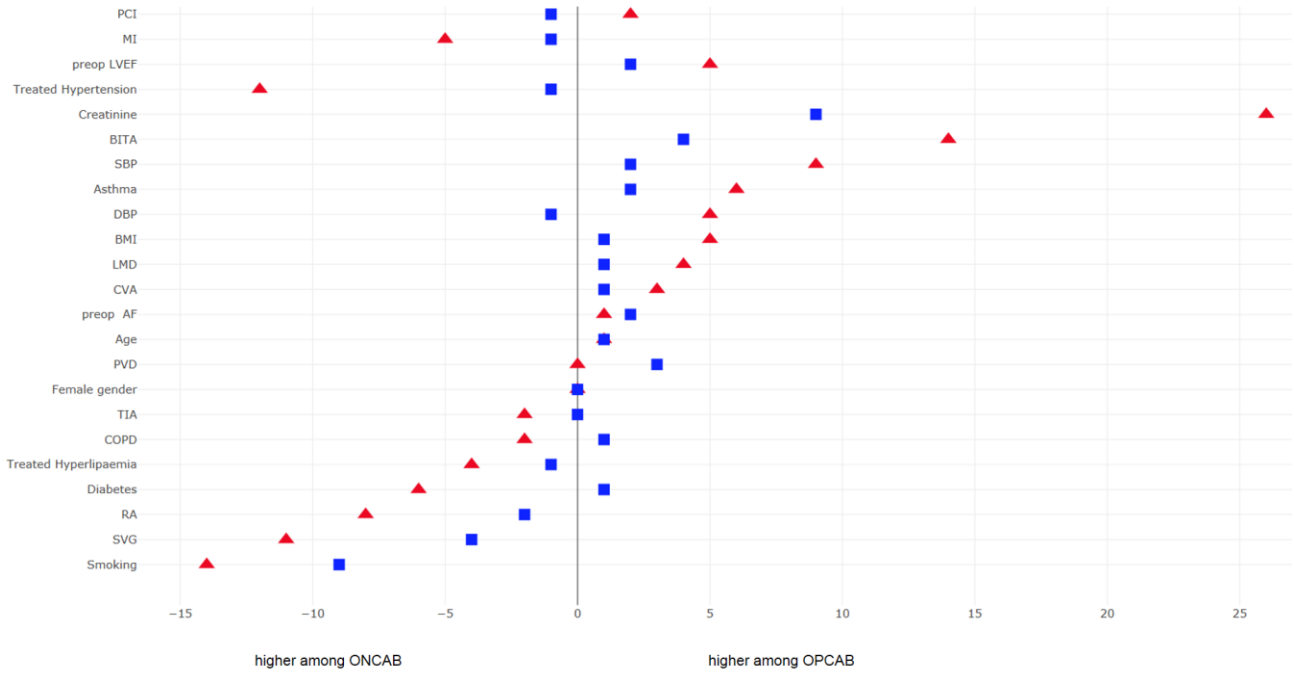
Figure 3. 5-year cardiovascular(CV)-death, myocardial infarction (MI), cerebrovascular accident (CVA) and revascularization cumulative incidence in the OPCAB and ONCAB groups. (OPCAB: off-pump coronary artery bypass; ONCAB: on-pump coronary artery bypass)



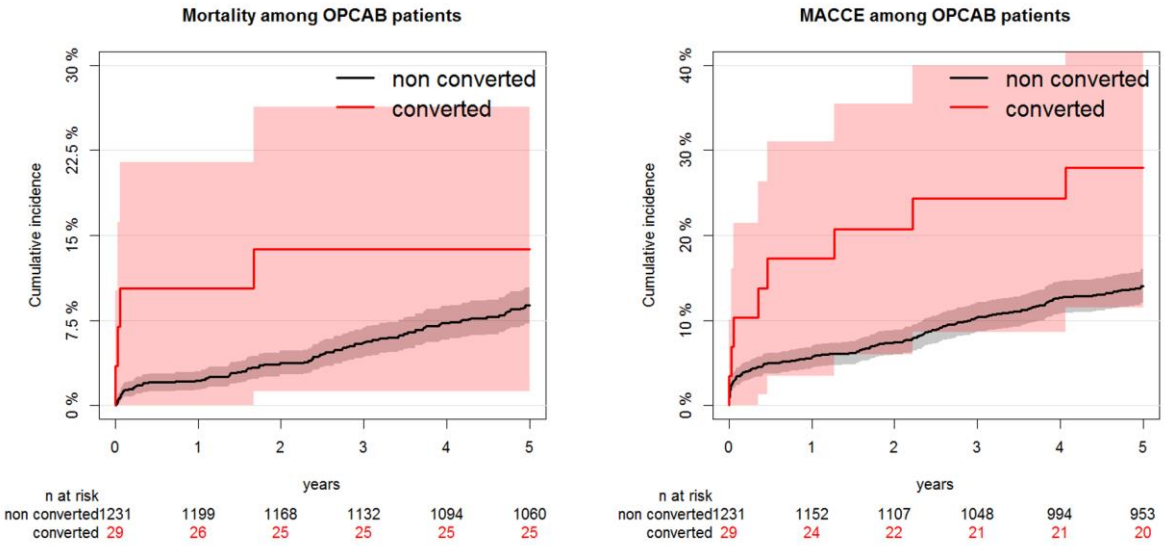
Supplementary Figure 1. Propensity score density before and after matching



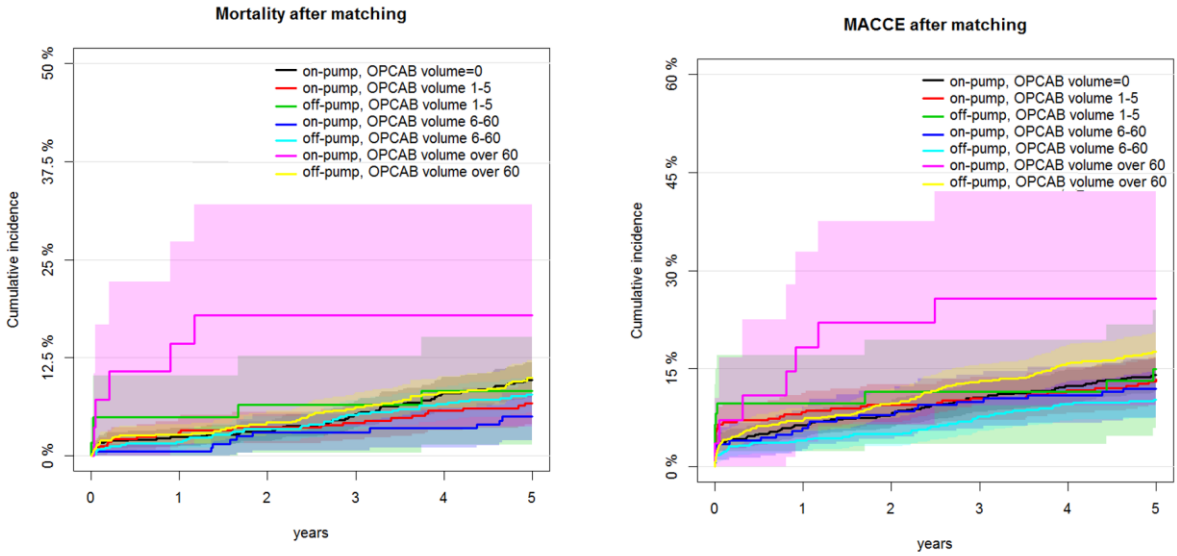
Supplementary Figure 2. Changes in standardized mean difference for baseline characteristics between OPCAB and ONCAB before (red) and after matching (blue). (OPCAB: off-pump coronary artery bypass; SBP: systolic blood pressure; DPB: diastolic blood pressure; COPD: chronic obstructive pulmonary disease; PVD: peripheral vascular disease; TIA: transient ischemic attack; CVA: cerebrovascular accident; MI: myocardial infarction; PCI: percutaneous coronary intervention; AF: atrial fibrillation; LVEF: left ventricular ejection fraction; LMD: left main disease; RA: radial artery BITA: Bilateral internal thoracic arteries, SVG: saphenous vein graft)



Supplementary Figure 3. 5-year cumulative incidence for mortality and major adverse cardiac and cerebrovascular events (MACCE) in the OPCAB group according to the incidence of conversion to on-pump. (OPCAB: off-pump coronary artery bypass)



Supplementary Figure 4. 5-year cumulative incidence for mortality and major adverse cardiac and cerebrovascular events (MACCE) in the OPCAB and ONCAB groups according to surgeon trial OPCAB volume (0=performing on-pump only; 1-5 low OPCAB volume; 6-60: moderate volume; >60 high volume) (OPCAB: off-pump coronary artery bypass; ONCAB: on-pump coronary artery bypass)



Video 1. Off-pump coronary artery bypass grafting at Bristol Heart Institute