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Comparison between off- and on-pump coronary artery bypass grafting: long-term results of a real-world registry[†]

Francesco Nicolini[a,*], Daniela Fortuna[b], Giovanni Andrea Contini[c], Davide Pacini[d], Davide Gabbieri[e], Claudio Zussa[f], Rossana De Palma[b], Antonella Vezzani[c] and Tiziano Gherli[a] on behalf of the RERIC (Registro dell'Emilia Romagna degli Interventi Cardiochirurgici) Investigators

[a] Cardiac Surgery Unit, Department of Clinical and Experimental Medicine, University of Parma, Parma, Italy
[b] Regional Agency for Health and Social Care, Emilia-Romagna Region, Bologna, Italy
[c] Cardiac Surgery Unit, Surgery Department, Parma Hospital, Parma, Italy
[d] Cardio-Thoracic-Vascular Department, University Hospital S.Orsola-Malpighi, Bologna, Italy
[e] Department of Clinical Cardiology and Thoraco Vascular Surgery, Hesperia Hospital, Modena, Italy
[f] Department of Cardiology and Cardiac Surgery, Villa Maria Cecilia Hospital, Lugo (Ravenna), Spain

* Corresponding author. Heart Surgery Unit, Department of Clinical and Experimental Medicine, University of Parma, Via A. Gramsci 14, 43126 Parma, Italy. Tel: +39-0521-703270; fax: +39-0521-293196; e-mail: francesco.nicolini@unipr.it (F. Nicolini).

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Abstract

OBJECTIVES: The aim of this study was to compare 5-year rates of overall death, cardiac-related death, myocardial infarction, repeat revascularization, stroke and new occurrence of postoperative renal failure in a large cohort of patients with coronary disease, treated with on- or off-pump coronary artery bypass grafting (CABG).

METHODS: Two propensity score-matched cohorts, each of 560 patients, undergoing isolated surgical coronary revascularization at the regional public and private centres of Emilia-Romagna region (Italy) over the period 1 January 2003 – 31 December 2013, were used to compare long-term outcomes of on-pump CABG (6711 patients) and off-pump CABG (597 patients).

RESULTS: The matched on-pump group received significantly more bypass grafts than the matched off-pump group (2.4 ± 1.1 vs 1.6 ± 0.9, $P < 0.0001$). The on-pump group reported statistically significant lower cardiac-related mortality. There was a trend towards higher overall mortality and the need for repeat revascularization procedures in the off-pump group. No difference was found for myocardial infarction, stroke or new occurrence of postoperative renal failure between groups in the follow-up. The multivariate analysis of significant predictors of mortality in the overall population confirmed that the off-pump revascularization strategy was an independent predictor of death at long-term follow-up. On-pump CABG reported significantly better results in terms of mortality in the subgroups of patients with a depressed left ventricular ejection fraction and in patients with three-vessel disease.

CONCLUSIONS: In patients undergoing elective isolated CABG, on-pump strategy conferred a long-term survival advantage compared with off-pump strategy, particularly for patients with more extensive coronary disease. No benefits were found in terms of reduction of postoperative morbidity with the off-pump strategy. On-pump surgery should be the preferred revascularization technique, and off-pump surgery reserved for patients for whom the perioperative risk of cardiopulmonary bypass is greater than the risk of a less complete coronary revascularization.

Keywords: Cardiac surgery • Coronary artery bypass grafting • Off-pump

INTRODUCTION

Numerous studies have been conducted in order to compare the outcomes of on- and off-pump coronary artery bypass grafting (CABG). The results remain a matter of debate in that some studies reported favourable outcomes associated with off-pump CABG [1–5], but other studies have not confirmed this benefit [6–13]. Recently, large-scale, prospective randomized trials have shown trends towards reduced early risks after surgery with off-pump CABG, although these early benefits have not been significantly confirmed in longer-term follow-up [14–16]. Moreover, off-pump CABG has reported worse outcomes in terms of graft patency and greater need for coronary reintervention in comparison with conventional on-pump CABG up to 1 year after surgery [16, 17]. To date, results of randomized trials remain limited to within 1 year of follow-up [14, 15, 17].

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Only few long-term direct comparisons of off- and on-pump CABG in the subgroup of patients potentially eligible to both myocardial revascularization strategies reported robust long-term mortality and morbidity data [5, 8, 10, 13]. As it is widely believed that the benefits of CABG most likely appear throughout a long-term period, the two operative strategies for myocardial revascularization need to be compared using long-term follow-up data.

Therefore, the primary end-point of this multicentre registry study was to compare 5-year rates of overall mortality, cardiac-related mortality, myocardial infarction, repeat revascularization, stroke and postoperative renal failure in a large cohort of patients affected by coronary artery disease and who had undergone off- and on-pump CABG. The secondary aim was to evaluate significant risk factors for mortality in this cohort of patients and to identify the subgroups of patients who reported worse outcomes after off-pump CABG.

MATERIALS AND METHODS

Data source

Emilia-Romagna (ER) is an Italian region with ~4 million inhabitants where six hospitals (two public University Hospitals and four private Hospitals) perform cardiac surgery. Since 2002, the Agency for Health and Social Care of ER region has maintained the Registro dell'Emilia Romagna degli Interventi Cardiochirurgici (RERIC) Registry, a prospective regional database collecting pre-, intra- and postoperative data from all the patients undergoing cardiac surgical procedures in the region. The rationale and methodology of RERIC have been published previously [18, 19].

A selection of variables jointly agreed by the six Cardiac Surgery Departments was extrapolated from the database of the Italian Society for Cardiac Surgery (SICCH). The Regional Agency for Health and Social Care ensures data quality/completeness control. Information on the occurrence of follow-up mortality and morbidity is obtained by linking the RERIC to the ER regional mortality registry and the regional hospital admission database. These registries were based on current clinical practice; so, the authorities required only ordinary written informed consent to perform percutaneous coronary intervention or CABG, which was obtained from all patients. The protocol of the study is in accordance with the Declaration of Helsinki.

Study population

From 1 January 2003 to 31 December 2013, data of all the patients undergone CABG were collected in the RERIC Registry. Exclusion criteria were as follows: associated valve surgery procedures, supra-aortic vessels disease requiring surgery, emergency/urgency, anatomical contraindications to aortic cross-clamping like severe aortic wall atherosclerosis or porcelain aorta. After these exclusions, the resulting 9382 patients were subjected to isolated and elective CABG. Additional exclusion criteria were patients not resident in ER (administrative follow-up not feasible) and the presence of incomplete information about baseline and procedural characteristics (Fig. 1). The remaining 7308 patients, 6711 operated with on-pump CABG and 597 patients who received off-pump CABG, were followed through December 2014.

Procedures

Decisions about the type of treatment were taken according to the local practices and there were no standard regional protocols. The choice of CABG technique has been previously described [18]. Follow-up angiography was not performed routinely in either group of patients.

Outcomes

All-cause death included overall mortality occurring during the index hospital admission or thereafter. Cardiac death was defined as any death due to a cardiac cause [e.g. myocardial infarction (MI), low-output failure and fatal arrhythmia], procedure-related deaths and death of an unknown cause. Acute MI was defined as any hospital admission occurring after the index procedure with a principal diagnosis of MI. Stroke included complications at the index admission and further hospital admissions with stroke as the principal diagnosis. Repeat revascularization was defined as any percutaneous coronary reintervention during follow-up, taking care of a luminal stenosis occurring in the same coronary vessel treated at the index procedure, or treating other native vessel stenosis not previously approached. Postoperative renal failure was defined as any hospital admission occurring after the index procedure with a principal diagnosis of renal failure, excluding from the analysis all the patients with a preoperative creatinine level of ≥2.0 mg/dl.

Statistical analysis

Prevalence of risk factors and demographic and clinical features of the patients in both groups were compared by the χ^2 test and Fisher's exact test.

Propensity score (PS) matching was used to reduce the effect of treatment-selection bias. PS, that is the probability of treatment assignment conditional on observed baseline characteristics, was estimated by multivariate logistic regression analysis with a binary-dependent variable representing off- versus on-pump. Variables included in the PS model were all baseline covariates that, as

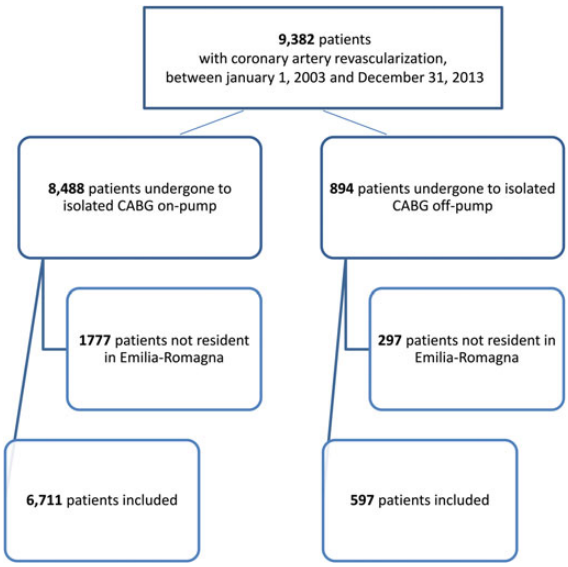


Figure 1: Selection criteria. CABG: coronary artery bypass grafting.

resulting from a preliminary univariate analysis, affected both treatment assignment and the outcomes (the true confounders of the treatment outcomes relationship) and outcomes (potential confounders). So, the PS model developed was a full non-parsimonious model that included the following variables: age, gender, obesity, critical preoperative state, unstable angina, left ventricular ejection fraction, previous myocardial infarction, active endocarditis, preoperative serum creatinine, diabetes, systolic pulmonary artery pressure, chronic pulmonary disease, functional classification (NYHA), extracardiac arteriopathy, neurological dysfunction disease, previous cardiac surgery, number of diseased vessels and EuroSCORE.

We used matched-paired analysis; we computed the logit of the PS, then we used a greedy-matching algorithm to implement nearest-neighbour, one to one, caliper matching without replacement, with common support. The size of the caliper was 0.25 SD of the logit of the estimated PS. The degree to which matching on the PS created a sample that balanced measured covariates between the two treatment group was assessed by computing the standardized differences for each covariate.

The standardized difference is the absolute difference in sample means divided by an estimate of the pooled standard deviation of the covariate. It represents the difference in means between the two groups in unit of standard deviation. A standardized difference of greater than 10 represents meaningful imbalance in a given covariate between treatment groups.

We evaluated the interactions between the variables (as the preoperative serum creatinine $\geq$2 mg/dl and two EuroSCORE's categories) that were unbalanced between the two treatments in the matched sample (standardized differences >10%), and the other variables included in the model. None of them achieved a statistical significance lower than 0.1, so the final PS model did not include any interaction terms.

Kaplan–Meier estimates were used to plot the rates of the long-term adverse events, and the differences between risk curves were assessed using the Klein–Moeschberger test for matched pairs.

Long-term outcomes between patients undergoing the two procedures were compared with Cox regression, using a robust sandwich covariance matrix estimate to account for the intracluster dependence. At first, we included in the model all baseline covariates and we selected the covariates significant by the stepwise selection process, until no (additional) effects met the 0.05 level for entry into the model.

To compare the long-term mortality in subgroups, a PS-matched sample was calculated for each subgroup, and Cox proportional hazard models with robust standard errors were performed to estimate the hazard ratio of off- versus on-pump.

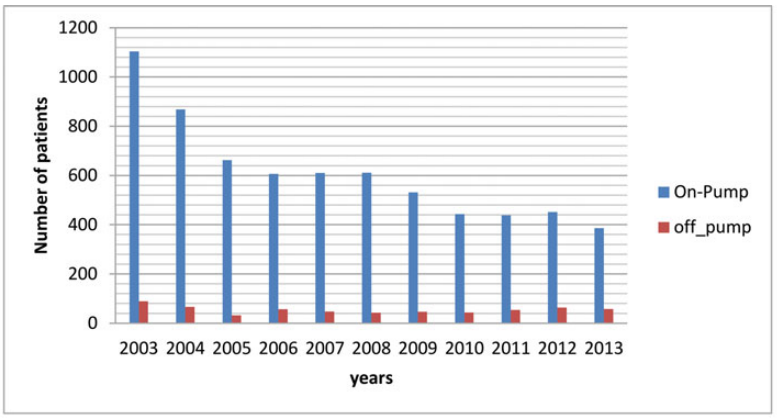
All the analyses were performed with SAS version 9.3.

RESULTS

A constant reduction in the number of overall isolated elective CABG was observed in our registry between 2003 and 2013. During this study period, off-pump CABG surgery in our region represented an average of 8.2% of the total CABG procedures performed (ranging from 4.9 to 14.4% among the six participating centres), showing a slight and steady increase over the years (8% in 2003 and 15% in 2013; Fig. 2).

The entire study cohort showed patient risk profiles significantly different in the two groups (Table 1). Patients who underwent off-pump were older, had a higher prevalence of depressed left ventricular ejection fraction, extracardiac arteriopathy, chronic renal failure and chronic obstructive pulmonary disease and previous coronary surgical and percutaneous procedures. On the other hand, the on-pump group had more patients with previous MI and presented with a more complex and severe coronary artery disease. Three-vessel disease was diagnosed in 53.8% of patients operated on on-pump CABG and in 16.8% of those who underwent off-pump CABG ($P < 0.0001$).

The entire on-pump group received 3.1 ± 1.1 bypass grafts, compared with 1.7 ± 1.0 in the off-pump group ($P < 0.0001$). The median duration of follow-up in the entire study cohort was 54.7 ± 12.4 months in the on-pump subgroup and 50.7 ± 15.1 months in the off-pump subgroup.



	Year											
	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	Total
On-Pump	1104	868	662	606	610	611	531	443	438	452	386	6711
off_pump	89	66	32	57	47	42	46	43	54	63	58	597
Total	1193	934	694	663	657	653	577	486	492	515	444	7308

Figure 2: Coronary artery bypass grafting trend over the years in the Emilia-Romagna region (Italy).

Table 1: Baseline and propensity score-adjusted characteristics of the patients according to treatment

Patients' characteristics	% On-pump (*N* = 6711)		% Off-pump (*N* = 597)		*P*-value	% On-pump (*N* = 560)		% Off-pump (*N* = 560)		Standardized differences	Mc Nemar's test *P*-value
	n	%	*n*	%		*n*	%	*n*	%		
≤70 years	3973	59.2	266	44.6	<0.0001	265	47.3	260	46.4	−0.018	0.6598
70–80 years	2654	39.5	300	50.3	<0.0001	273	48.8	272	48.6	−0.004	0.9324
>80 years	331	4.9	57	9.5	<0.0001	47	8.4	52	9.3	0.031	0.5637
Female	1218	18.1	114	19.1	0.5661	102	18.2	109	19.5	0.032	0.4817
BMI ≥30: obesity	1421	21.2	120	20.1	0.5377	115	20.5	113	20.2	−0.009	0.843
Unstable angina	546	8.1	36	6.0	0.0686	23	4.1	34	6.1	0.089	0.1308
LVEF ≤30%	167	2.5	24	4.0	0.0246	17	3	22	3.9	0.049	0.4111
LVEF 30–50%	1668	24.9	186	31.2	0.0007	162	28.9	165	29.5	0.012	0.7833
Previous myocardial infarction	2061	30.7	160	26.8	0.0465	136	24.3	153	27.3	0.069	0.1375
Serum creatinine ≥2 mg/dl	162	2.4	26	4.4	0.0041	11	2	21	3.8	0.107	0.0588
Diabetes	2073	30.9	196	32.8	0.3259	177	31.6	179	32	0.008	0.8597
Systolic PA pressure >60 mmHg	8	0.1	0	0.0	0.3986	1	0.2	0	0	−0.06	0.8597
Chronic pulmonary disease	351	5.2	55	9.2	<0.0001	41	7.3	48	8.6	0.046	0.3621
NYHA III–IV	721	10.7	61	10.2	0.6904	47	8.4	56	10	0.056	0.2715
Extracardiac arteriopathy	1514	22.6	188	31.5	<0.0001	155	27.7	166	29.6	0.043	0.3402
Neurological dysfunction disease	124	1.8	16	2.7	0.1551	10	1.8	15	2.7	0.06	0.2752
Previous cardiac surgery	115	1.7	38	6.4	<0.0001	25	4.5	28	5	0.025	0.6473
Single-vessel disease	487	7.3	254	42.5	<0.0001	215	38.4	217	38.8	0.007	0.7518
Double-vessel disease	2612	38.9	243	40.7	0.3924	250	44.6	243	43.4	−0.025	0.3778
Triple-vessel disease	3612	53.8	100	16.8	<0.0001	95	17	100	17.9	0.024	0.2971
Previous PCI	1012	15.1	134	22.4	<0.0001	119	21.3	111	19.8	−0.035	0.4689
Previous CABG	92	1.4	29	4.9	<0.0001	18	3.2	21	3.8	0.029	0.59
Previous valve intervention	7	0.1	2	0.3	0.1235	1	0.2	1	0.2	0	1
EuroSCORE: 0–4	3603	53.7	223	37.4	<0.0001	266	47.5	222	39.6	−0.159	0.0015
EuroSCORE: 5–6	1458	21.7	132	22.1	0.827	118	21.1	124	22.1	0.026	0.6473
EuroSCORE: 7–9	943	14.1	135	22.6	<0.0001	109	19.5	123	22	0.062	0.2743
EuroSCORE: ≥10	206	3.1	55	9.2	<0.0001	23	4.1	44	7.9	0.159	0.0082

BMI: body mass index; LVEF: left ventricular ejection fraction; NYHA: New York Health Association; PCI: percutaneous coronary intervention; CABG: coronary artery bypass grafting; PA: pulmonary artery.

Matching on estimated PS made available a matched cohort of 1120 patients, 560 for each group, with similar demographic, clinical and angiographic risk profiles (Table 1). In the matched cohort, the mean follow-up was 54.4 ± 12.8 months in the on-pump group and 50.6 ± 15 months in the off-pump group. The matched on-pump group received significantly more bypass grafts than the matched off-pump group (2.4 ± 1.1 vs 1.6 ± 0.9, $P < 0.0001$).

Kaplan–Meier risk curves for the matched population at 5 years were reported. The on-pump group reported a lower cumulative rate of all-cause death at the limits of statistical significance (Fig. 3A). Cardiac-related mortality resulted significantly higher in off-pump patients at 5 years (Fig. 3B). The off-pump CABG group confirmed greater need for repeat revascularization procedures, although without any statistical significance (Fig. 4A). No difference was found for MI (Fig. 4B), stroke (Fig. 5A) or new occurrence of postoperative renal failure between groups in the follow-up (Fig. 5B).

Table 2 summarizes multivariate analysis of significant predictors of mortality in the overall population. It is significant that the off-pump revascularization strategy was an independent predictor of death at long-term follow-up.

Table 3 presents the hazard ratios for death for off- versus on-pump CABG in subgroups of patients. On-pump CABG reported significantly better results in terms of mortality in patients with a depressed left ventricular ejection fraction (LVEF) and in patients with three-vessel disease.

DISCUSSION

The main findings of this study are as follows: at 5 years, the on-pump CABG group reported a lower cumulative rate of all-cause death, although at the limits of statistical significance; the benefit of on-pump CABG was clear in significantly reducing the rate of cardiac death in a PS-matched population; the off-pump CABG group confirmed a greater need for repeat revascularization procedures, although without any statistical significance; the off-pump CABG did not show any advantage in postoperative morbidity in comparison with the on-pump CABG, because no differences were found for MI, stroke and new occurrence of postoperative renal failure between groups in the follow-up.

Moreover, the multivariate analysis of significant predictors of mortality in the overall population confirmed that the off-pump revascularization strategy was an independent predictor of death at long-term follow-up. On-pump CABG reported significantly better results in terms of mortality only in the subgroups of patients with a depressed LVEF and with three-vessel disease. However, differences in mortality rates in the majority of subgroups of patients stratified by baseline and operative variables might be not significant because the sample size was underpowered to appraise statistically significant differences.

The potential advantages attributed to off-pump coronary revascularization are related to the avoidance of extracorporeal

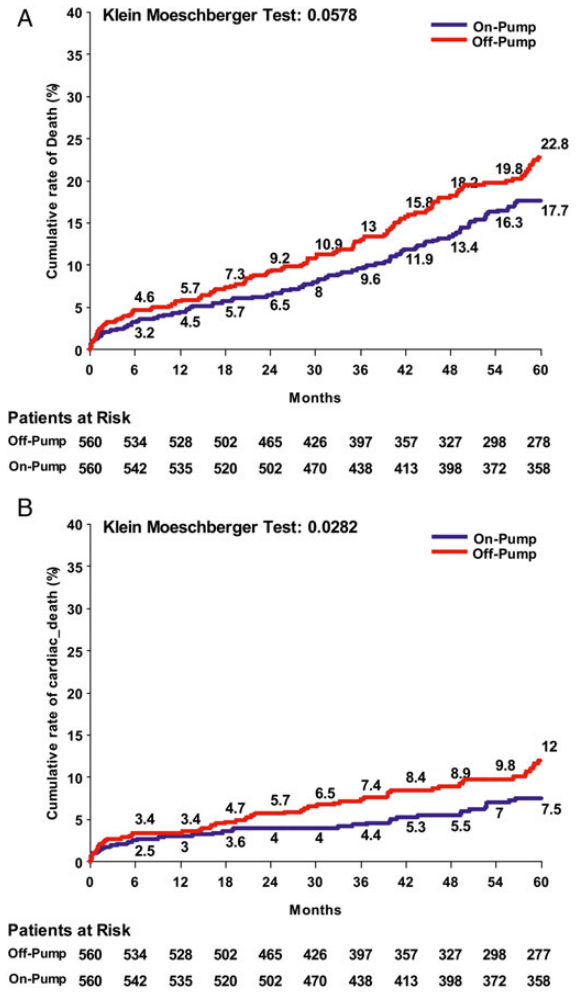


Figure 3: Kaplan–Meier risk curves between on-pump CABG and off-pump CABG: (**A**) cumulative rate of all-cause death and (**B**) cardiac-related mortality. CABG: coronary artery bypass grafting.

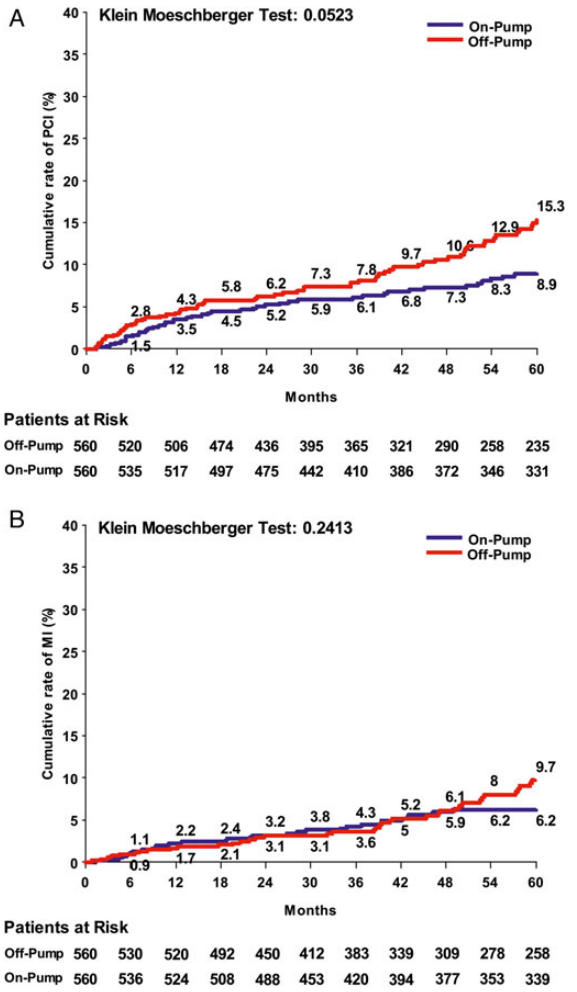


Figure 4: Kaplan–Meier risk curves between on-pump CABG and off-pump CABG: (**A**) repeat revascularization rate and (**B**) myocardial infarction rate. CABG: coronary artery bypass grafting; PCI: percutaneous coronary intervention; MI: myocardial infarction.

circulation and aortic cross-clamping during CABG, with consequent reduction in the risks of embolic stroke induced by invasive aortic manipulation, surgical bleeding, coagulopathy and renal dysfunction [20, 21]. Nevertheless, the efficacy of off-pump CABG has recently been questioned. In a recent meta-analysis, Takagi and colleagues [22] found a significant 7% increase in all-cause long-term (≥5 years) mortality for off-pump surgery compared with on-pump surgery. Five randomized, controlled trials and 17 adjusted observational studies met the eligibility criteria and were considered relevant. These 22 studies included a total of 104 306 patients. Although the subanalysis of the five randomized, controlled trials (1486 patients) demonstrated a statistically not significant 14% increase in long-term mortality risk in the off-pump group, the subanalysis of the 17 adjusted observational studies (102 820 patients) showed a statistically significant 7% ($P = 0.0004$) increase in long-term mortality risk in the off-pump group. It is noticeable that fewer bypass grafts and more incomplete revascularization were reported in the off-pump strategy.

Recently, three large multicentre randomized, controlled trials have compared outcomes of on- and off-pump revascularization. The 1-year results of largest international CORONARY (CABG Off or On Pump Revascularization Study) trial [14] showed no significant differences between the two groups in terms of death, non-fatal stroke, non-fatal MI or renal failure. The key points of this trial were that it enrolled a very large study group (4752 patients) in order to have sufficient power to support the outcome analysis, and that, to avoid potential biases, a strict criterion was applied to include only skilled and experienced surgeons. Also, the second largest randomized trial, the German Off-Pump Coronary Artery Bypass Grafting in Elderly Patients [15], enrolled 2370 patients, operated on by recognized experts in the performance of either off- or on-pump CABG. At 1 year, the trial showed no significant differences between off- and on-pump CABG with regard to death, stroke, MI, repeat revascularization or new renal replacement therapy. The future results of long-term outcomes of these large-scale expertise-based, randomized trials, enrolling high-risk or elderly patients, will be important to provide a robust judgement for the controversy regarding the superiority of one strategy over the other. On the shorter time scale, the ROOBY (Veterans Affairs Randomized On/Off Bypass) trial [7] enrolled 2203 patients undergoing CABG from 18 Veteran Administration medical centres in the USA. The trial confirmed that 30-day adverse composite outcome and short-term morbidities were similar between the two arms. However, 1-year adverse composite outcome consisting of all-cause death, non-fatal MI and repeat revascularization from the time of surgery to 1 year was 47% higher with

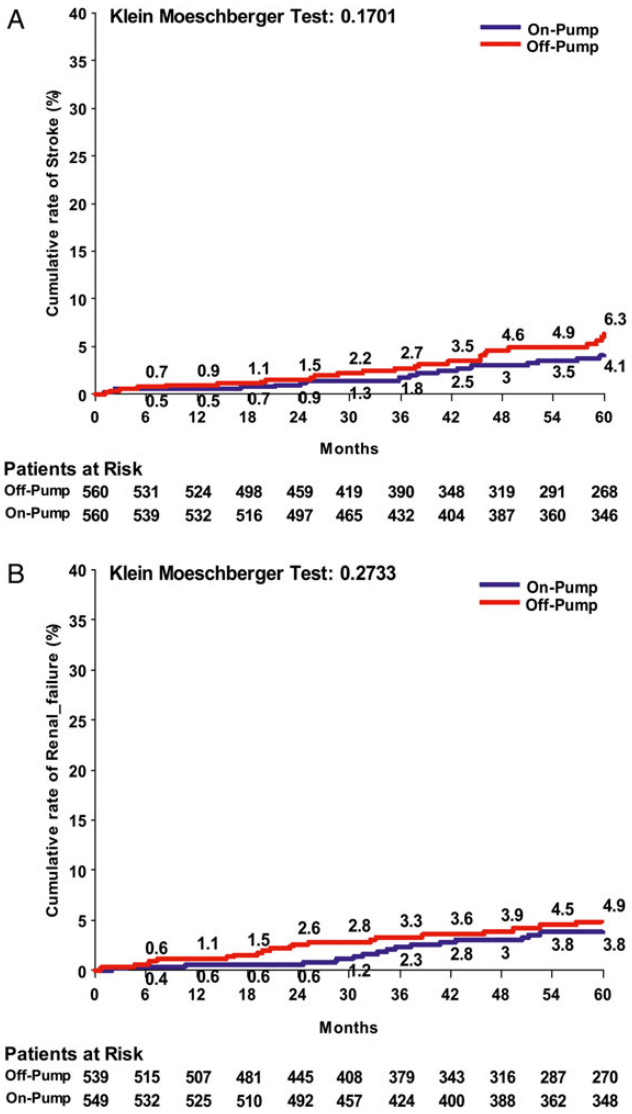


Figure 5: Kaplan–Meier risk curves between on-pump CABG and off-pump CABG: (**A**) stroke rate and (**B**) new occurrence of postoperative renal failure. CABG: coronary artery bypass grafting.

off-pump CABG (14.6 vs 9.9%; $P < 0.001$). Interestingly, graft patency and effective revascularization at 1 year were significantly better with conventional on-pump CABG. Patients with less effective revascularization were likely to have higher rates of adverse events such as a non-fatal MI or repeat revascularization [16]. The randomized, controlled DOORS (Danish On-Pump versus Off-Pump Randomized Study) study confirmed these findings reporting inferior graft patency in patients undergoing off-pump surgery. This multicentre trial included 900 patients older than 70 years undergoing either on- or off-pump CABG. Although only 481 patients (56% of survivors) underwent angiography at 6 months, the on-pump group reported 86% of grafts patency compared with 79% of the off-pump group ($P = 0.01$), particularly related to a higher frequency of stenotic or occluded vein, radial artery and right internal thoracic artery grafts in the off-pump group in the circumflex and right coronary territories.

All these studies have demonstrated no benefit in terms of early decrease in mortality, stroke, MI or renal failure requiring dialysis with off-pump CABG in spite of surgeons' experience, enrolment of patients at higher risk and advances in off-pump surgery management. Moreover, it can be the case that the higher 1-year mortality in patients undergoing off-pump strategy is related directly to lower graft patency and completeness of revascularization obtained with off-pump CABG.

The present study is one of the few large-scale clinical retrospective studies comparing the long-term outcomes of off- versus on-pump CABG. Our findings were similar to those reported by Bakaeen *et al.* [12] who found no significant differences in the earlier survival outcome up to 3 years, but reported a significant increase in the risk-adjusted mortality in the off-pump CABG group at 5 and 10 years. Recent long-term survival results following on- versus off-pump CABG of a large institutional Korean database were published in 2014 [13]. Despite similar early mortality between off- and on-pump CABG, on-pump CABG conferred a superior survival benefit over off-pump CABG in the long term. It is significant that these results were obtained from a large population operated on at one of the centres which has been the most favourable in the world to performing off-pump CABG, and that the authors made rigorous statistical adjustments after considering the 'surgeon expertise level' and the 'year of operation' of the study period in order to obtain robust conclusions.

Table 2: Multivariate analysis of significant predictors of mortality in the overall population

Parameter	Hazard ratio	95% Hazard ratio Confidence limits		*P*-value
		LCI	UCI	
Off-pump CABG	1.2	1.0	1.6	0.061
Age: 70–80 years	2.6	2.1	3.4	<0.0001
Age: >80 years	4.0	2.8	5.7	<0.0001
BMI ≥30 : obesity	1.3	1.0	1.8	0.042
Chronic pulmonary disease	1.7	1.2	2.3	0.002
Extracardiac arteriopathy	1.3	1.0	1.7	0.028
Serum creatinine ≥2 mg/dl	4.5	2.9	7.0	<0.0001
LVEF ≤30%	2.5	1.5	4.1	<0.0001
LVEF 30–50%	1.8	1.4	2.3	<0.0001
Previous MI	1.3	1.0	1.7	0.024
Diabetes	1.5	1.2	1.9	0.001

CABG: coronary artery bypass grafting; BMI: body mass index; LVEF: left ventricular ejection fraction; MI: myocardial infarction; LCI: lower confidence interval; UCI: upper confidence interval.

Table 3: Subgroup analyses: hazard ratios of death at 5 years

Subgroups	No. of patients	HR (off-pump versus on-pump)	LCI	UCI	*P*-value
≤70 years	506	1.2	0.6	2.1	0.610
70–80 years	556	1.1	0.8	1.6	0.474
>80 years	88	1.3	0.6	2.9	0.525
Female	222	1.4	0.8	2.3	0.219
BMI ≥30 : obesity	222	1.9	1.0	3.5	0.040
Logistic EuroSCORE >15%	88	1.7	0.9	3.3	0.123
Unstable angina	54	2.3	0.8	6.6	0.124
LVEF ≤30%	28	4.0	1.1	14.1	0.034
LVEF 30–50%	340	1.0	0.6	1.4	0.804
Previous myocardial infarction	296	1.1	0.7	1.6	0.772
Serum creatinine ≥2 mg/dl	24	4.5	1.9	10.8	0.001
Diabetes	356	1.4	0.9	2.1	0.122
Chronic pulmonary disease	86	0.7	0.4	1.4	0.343
NYHA III–IV	100	1.1	0.5	2.3	0.826
Extracardiac arteriopathy	322	1.2	0.8	1.7	0.376
Neurological dysfunction disease	16	2.5	0.3	23.4	0.433
Previous cardiac surgery	42	1.0	0.4	2.9	0.960
Single-vessel disease	436	1.3	0.8	1.9	0.255
Double-vessel disease	486	1.3	0.8	2.0	0.242
Triple-vessel disease	200	2.0	1.0	3.8	0.036
Previous off-pump	226	0.9	0.5	1.8	0.803
Previous CABG	26	0.6	0.2	1.9	0.357
EuroSCORE: 0–4	446	1.0	0.5	2.2	0.968
EuroSCORE: 5–6	250	0.9	0.5	1.6	0.728
EuroSCORE: 7–9	244	1.2	0.7	1.9	0.469
EuroSCORE: ≥10	64	3.7	1.7	8.1	0.001

BMI: body mass index; LVEF: left ventricular ejection fraction; NYHA: New York Health Association; CABG: coronary artery bypass grafting; HR: hazards ratio; LCI: lower confidence interval; UCI: upper confidence interval.

Our results also confirmed that off-pump CABG patients received fewer grafts and that a higher proportion of on-pump CABG patients were more completely revascularized. These findings, similar to previous reports [7, 13], could explain the greater need for repeat revascularization procedures, and the lower long-term survival rate reported in the off-pump group.

It has been suggested that high-risk patients, such as patients with severe atherosclerotic aorta or peripheral arterial disease, show a significant reduction in stroke rate after off-pump CABG [23]. On the other hand, a number of randomized studies comparing off-pump CABG with the conventional on-pump CABG procedures have not confirmed an advantage with off-pump CABG regarding stroke [7, 14, 15]. Our study found no differences between strategies in terms of stroke in the follow-up. Moreover, our results like those obtained from other large-scale clinical trials confirm that the benefits of avoiding extracorporeal circulation with off-pump CABG are lost at long-term follow-up.

It has been speculated that CABG without extracorporeal circulation might influence the incidence and magnitude of acute renal failure [20]. However, our study reported similar rates of hospital admission due to the new occurrence of renal failure in the follow-up between groups, confirming the findings of other trials [14, 15] that off-pump CABG is not associated with decreased rates or reduced severity of acute renal failure.

The limitations of a retrospective registry study should be noted. In our patient population, only 8.2% of the total CABG procedures were performed off-pump. Although all the senior surgeons who participated in our study were experts in the both techniques of coronary revascularization, the decision of whether to perform off- or on-pump CABG was strongly affected by personal preferences. Training programmes were conducted in the two public University Hospitals participating in the study, but the trainees were designated as first surgeon only in case of on-pump surgery. Finally, the design of our database did not allow for tracking the name of the first surgeon for each procedure.

Although we tried to rigorously adjust selection bias using PS-based analysis, unmeasured confounders and hidden biases might have affected our results. The decision to perform off- versus on-pump CABG was strongly affected by the surgeons' preferences, as well as by several other important baseline demographic and clinical profiles present in the entire study cohort. Off-pump surgery was most frequently indicated in older patients, with a higher prevalence of depressed left ventricular ejection fraction, extracardiac arteriopathy, chronic renal failure and chronic obstructive pulmonary disease, and previous coronary surgical and percutaneous procedures. On the other hand, surgeons significantly preferred to perform surgery with on-pump strategy in case of patients with previous MI, and with a more complex and severe coronary artery disease. Therefore, the PS analysis could as a result be imperfect, and we could not completely adjust for hidden selection biases. Moreover, only clinical outcomes were assessed in this study and graft patency was not assessed during the follow-up.

Emergency crossover from off- to on-pump CABG is known to increase the risks of early mortality and morbidity. The original design of our database did not allow for tracking surgical conversions or their specific causes, reporting only the technique finally adopted by the surgeon to perform the operation. Owing to the lack of these data, we are unable to report and analyse intraoperative conversion from off- to on-pump CABG. The comparison of

the two CABG strategies in the present study is thus to be interpreted as an 'as treated' analysis.

Finally, our database did not allow us to define and classify acute renal failure according to two recent definition systems for acute kidney injury. In Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease (RIFLE), the diagnosis is based on well-described changes over a 1-week period, the Acute Kidney Injury Network (AKIN) requires only changes within a designated 48-h period [24], whereas our database shows the value of preoperative creatinine level and the highest one achieved by the patient during the postoperative hospital stay, regardless of a specific period of observation time after surgery.

CONCLUSIONS

This is a very large registry series of patients with long-term follow-up. At 5 years, off-pump coronary surgery results in fewer bypass grafts, and consistent trends towards higher long-term mortality than on-pump surgery, without any advantage in terms of morbidity. Off-pump revascularization was an independent predictor of death at long-term follow-up. The mid-term and long-term outcomes of CORONARY and GOPCABE randomized trials have yet to appear, but in the meantime our findings strongly suggest that on-pump surgery should remain the preferred revascularization technique, particularly in patients affected by severe and diffuse coronary disease. The recent ESC/EACTS guidelines stated that off-pump CABG should be considered for subgroups of high-risk patients in high-volume off-pump institutions (Class of recommendation IIa, level of evidence B) [25]. Accordingly, in centres with no extensive experience of off-pump coronary surgery, the technique should be reserved for patients with severe contraindications to extracorporeal circulation, such as those with extensive aortic atherosclerosis, for whom it is reasonable to tolerate a less complete revascularization.

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