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ORIGINAL ARTICLE

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Comparison between off-pump and on-pump coronary artery bypass grafting in patients with severe lesions at the circumflex artery territory: 5-year follow-up of the MASS III trial

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Abstract

OBJECTIVES: The technical difficulty in the revascularization of the circumflex artery territory with off-pump surgery may compromise the outcome of this method in clinical follow-up. We aimed to evaluate cardiac events in patients with stable coronary artery disease and severe obstruction of the circumflex system, undergoing coronary artery bypass grafting (CABG) with or without cardiopulmonary bypass.

METHODS: MASS III was a single-centre study that evaluated 308 patients with multivessel coronary artery disease randomized to on-pump (153) or off-pump (155) CABG. Of this total, 260 (84.4%) patients had, on coronary angiography, at least one 70% obstruction in the circumflex territory (141 on-pump and 119 off-pump). The combined outcome was death, myocardial infarction, target vessel revascularization (angioplasty or surgery) or hospitalization for cardiac causes. Variables with possible associations ($P < 0.1$) were included in the multivariate analysis.

RESULTS: The two groups were well matched for demographics and clinical and angiographic characteristics. After 5 years of follow-up, off-pump CABG had higher combined events than on-pump had: 25 (21%) vs 17 (12%), hazard ratio 1.88, 95% confidence interval 1.02–3.48, $P = 0.041$. In the multivariate model with the inclusion of the following variables: age ($P = 0.09$) and complete revascularization ($P = 0.68$), off-pump surgery remained as a predictor of combined events in 5 years, $P = 0.03$.

CONCLUSIONS: In patients with multivessel coronary artery disease and severe lesions in the circumflex territory, off-pump coronary artery bypass surgery resulted in a higher incidence of cardiac events at 5-year follow-up.

Clinical trial registration number: ISRCTN59539154 (http://www.controlled-trials.com).

Keywords: Coronary artery disease • Coronary artery bypass grafts • Cardiopulmonary bypass • CPB

INTRODUCTION

Currently, there is an intense debate in cardiac surgery concerning which strategy of coronary artery bypass grafting (CABG), with (on-pump) or without (off-pump) the use of cardiopulmonary bypass, is superior. Several clinical trials have failed to demonstrate any additional benefit in long-term cardiovascular outcomes with off-pump CABG compared with standard on-pump surgery [1–3].

Grafting of the circumflex artery (CXA) and its major branches remains the major technical limitation of the off-pump technique, since revascularization of the CXA territory with a beating heart may result in haemodynamic instability, because it requires lifting and rotating the heart [4–8]. Therefore, there is some evidence that off-pump surgery increases the incidence of poor graft quality and incomplete revascularization, which may compromise the long-term clinical outcomes in select patients [9–11].

This report is a *post hoc* analysis from the third Medicine, Angioplasty or Surgery Study (MASS III) trial [3]. MASS III was a randomized clinical trial that evaluated postoperative outcomes and long-term clinical events in patients with multivessel coronary artery disease, and preserved ventricular function, undergoing on-pump and off-pump CABG. The main finding of the MASS III trial was that either revascularization strategy provides similar rates of all-cause mortality and major cardiovascular events at 5 years. This current investigation aims to evaluate cardiac events in patients with coronary artery disease and necessary involvement

of CXA territory in patients undergoing CABG with or without cardiopulmonary bypass.

PATIENTS AND METHODS

Study design and treatment

Protocol details have been published previously [12]. In brief, patients with angiographically documented proximal multivessel coronary stenosis >70% by visual assessment, stable angina and preserved ventricular function were considered for inclusion. Patients were enrolled and randomized if the surgeons agreed that revascularization could be achieved by either strategy. All angiograms were reviewed, and a surgical plan was documented before randomization. Patients were eligible if they were referred for isolated coronary bypass surgery for the first time, and an off-pump procedure was deemed technically feasible. In this *post hoc* analysis, we included only patients with at least a 70% obstruction in the CXA or its major side branches (≥1.5 mm in diameter) at the time of randomization. Complete revascularization was analysed according to the anatomical revascularization definition. Thus, all lesions occupying >50% diameter stenosis with a vessel diameter of ≥1.50 mm were scored as potentially amenable to treatment. Patients were excluded if they required emergency or concomitant major surgery, unstable angina requiring emergency revascularization, ventricular aneurysm requiring repair, left ventricular ejection fraction of <40%, previous stroke, peripheral vascular disease or chronic renal insufficiency with an estimated creatinine clearance of <60 ml/min. Patients were also excluded if they were unable to provide written informed consent. The study was carried out according to the principles of the Declaration of Helsinki. The ethics committee and the institutional review board approved the study protocol. All subjects gave informed consent.

Trial operators were required to perform optimum coronary revascularization in accordance with current best practices. The procedure was performed by surgeons experienced in both on-pump and off-pump bypass surgery. Anastomosis quality control with Doppler was made intraoperatively at the discretion of the surgeon. Stabilization devices were used during off-pump surgery to allow the safe construction of the anastomosis of the graft with the recipient artery. All patients should have been taking acetylsalicylic acid (ASA) 100–300 mg/day before CABG without it needing to be discontinued. The first dose of ASA postoperatively was provided within the first 6 h.

Qualification of surgeons

Each operation was performed by a surgeon with more than 20 years of experience and having completed more than 100 procedures per year in both techniques.

Study end-points

The primary composite end-point was death from any cause or hospitalization for cardiac causes within 5 years, non-fatal myocardial infarction between 30 days and 5 years or refractory angina requiring additional revascularization between 30 days and 5 years. Hospitalization for cardiac causes was defined as heart failure or unstable angina requiring hospitalization.

Follow-up

Adverse and other clinical events were tracked from randomization. Patients were assessed with follow-up visits every 6 months at the Heart Institute.

Statistical analysis

All data were analysed on an intention-to-treat principle beginning immediately after randomization. The risk of an event after on-pump surgery was compared with that after off-pump surgery, and the results are presented as the absolute difference with the corresponding 95% confidence intervals (CIs). Values are expressed as mean (±SD). Dichotomous data were compared by the χ^2 statistic or Fisher's exact test. Continuous variables that were not distributed normally, as evaluated through the Kolmogorov–Smirnov test, were compared by the Mann–Whitney *U*-test. Continuous variables with a normal distribution were compared using the Student's *t*-test. All reported probability values are two-sided. Event-free survival was graphically compared by using Kaplan–Meier curves. Event rates were compared with the use of the log-rank test of time to the first event after randomization. Relative risks are expressed as hazard ratios with associated CIs and were derived using the Cox proportional hazards model. A probability value of $P < 0.05$ was considered statistically significant. Multivariable analysis with Cox proportional hazards model was used, including variables with a possible association ($P < 0.1$) or biological plausibility with the combined end-point. These analyses were performed with SPSS, version 17.0 (SPSS, Inc.).

RESULTS

Between March 2001 and March 2006, 308 patients with stable coronary artery disease were assigned to CABG: 153 to on-pump surgery and 155 to off-pump surgery. Of those, 260 (84.4%) patients had at baseline coronary angiography demonstrating at least one obstruction >70% by visual assessment of CXA territory. Of those, 119 patients were referred for off-pump CABG and 141

Table 1: Baseline characteristics

	On-pump CABG (*n* = 141)	Off-pump CABG (*n* = 119)	*P*-value
Age (years)	59 (±8.0)	61 (±8.0)	0.19
Male gender (%)	110 (78)	83 (69.7)	0.15
Diabetes (%)	52 (36.9)	53 (44.5)	0.25
Hypertension (%)	96 (68.1)	86 (72.3)	0.50
Current smokers (%)	40 (28.4)	25 (21.0)	0.74
Previous MI (%)	66 (46.8)	56 (47.1)	1.0
Angina (%)	127 (90.1)	108 (90.8)	0.51
Angina CCS III–IV (%)	22 (17.3)	21 (19.6)	0.63
Ejection fraction (%)	64.2 (±8.9)	66.4 (±6.5)	0.31
Cholesterol (mg/dl)	213 (±44.9)	216 (±44.9)	0.69
LDL-c (mg/dl)	135 (±39)	136 (±36)	0.68
HDL-c (mg/dl)	40 (±9.4)	40 (±8.9)	0.73
Triglycerides (mg/dl)	185 (±112)	196 (±112)	0.45
3-Vessel CAD (%)	124 (87.9)	102 (85.7)	0.71

CABG: coronary artery bypass graft; MI: myocardial infarction; CCS: Canadian Cardiovascular Society; CAD: coronary artery disease; LDL-c: low-density lipoprotein cholesterol; HDL-c: high-density lipoprotein cholesterol.

for on-pump CABG. The demographic, clinical and angiographic characteristics are summarized in Table 1. There was no crossover between study groups, and no patients were lost to follow-up. The median follow-up was 5 years.

There was no significant difference between groups in postoperative myocardial infarction and stroke (Table 2). No hospital mortalities and no acute renal failures requiring haemodialysis occurred. Complete revascularization was more often achieved with on-pump CABG than with off-pump: 81 (57.4%) vs 48 (40.3%) $P = 0.006$, respectively. The amount of grafts used was also greater in the on-pump group: 3.0 (±0.65) vs 2.6 (±0.57) $P = 0.0001$. On the univariate analysis, after 5 years of follow-up, off-pump CABG had higher combined events than on-pump had: 25 (21%) vs 17 (12%), hazard ratio 1.88, 95% CI 1.02–3.48, $P = 0.041$ (Table 3, Fig. 1).

Besides the type of revascularization performed, the only variable that showed a possible association with the combined end-point was age ($P = 0.09$), which was included in the multivariate model. Also included in the multivariate model was the achievement of complete revascularization because of its biological plausibility ($P = 0.68$). After the multivariate analysis, off-pump CABG remained a significant and independent variable associated with the combined end-point ($P = 0.03$) (Table 4).

DISCUSSION

In this *post hoc* analysis of the MASS III trial, the study population had characteristics similar to those of the original trial. More than a third of patients were diabetic and there was a high prevalence of angina symptoms and 3-vessel coronary artery disease on angiography. There was an overall low rate of complete revascularization in both groups. This result is probably due to the strict anatomical definition of complete revascularization used in our study, unlike recent trials where the completeness of revascularization was determined by the number of grafts performed when compared with the number planned, or was assessed by the surgeon at the time of surgery [1, 2]. As seen in other studies, the achievement of complete revascularization and the number of grafts performed were more common with on-pump surgery [1, 2, 13, 14]. Particularly in this study, the universal presence of coronary obstruction in the CXA system may have affected the ability to achieve complete revascularization in the off-pump group and probably contributed to the smaller number of grafts performed. In recent studies, the circumflex territory was incompletely revascularized in a greater proportion of off-pump than on-pump patients and that accounted for the difference in the rates of complete revascularization [15, 16].

In this population of patients with coronary artery disease, performing coronary artery bypass surgery without cardiopulmonary bypass conferred a worse prognosis in combined events at 5 years. This finding could not be explained by the lower rate of complete revascularization in this group of patients, as it was

Table 2: Hospital complications

	On-pump CABG, *n* (%)	Off-pump CABG, *n* (%)	*P*-value
Postoperative myocardial infarction[a]	14 (9.9)	6 (5.0)	0.16
Stroke[b]	4 (2.8)	1 (0.8)	0.38
Operative death	0	0	–
Haemodialysis	0	0	–

[a]Postoperative myocardial infarction was considered if elevation of creatine kinase MB or troponin was five times or more the 99th percentile.
[b]Stroke was defined as a focal brain injury that persisted for >24 h.
CABG: coronary artery bypass graft.

Table 3: Combined events at 5 years

	On-pump CABG, *n* (%)	Off-pump CABG, *n* (%)	*P*-value
Hospitalization for cardiac causes[a]	8 (5.8)	16 (13.7)	0.05
New revascularization	7 (5.0)	6 (5.0)	1.0
Myocardial infarction	6 (4.3)	7 (6.0)	0.58
Death	6 (4.3)	9 (7.6)	0.29
Combined events	17 (12)	25 (21)	0.041

[a]Hospitalizations for cardiac causes were due to unstable angina or heart failure.
CABG: coronary artery bypass graft.

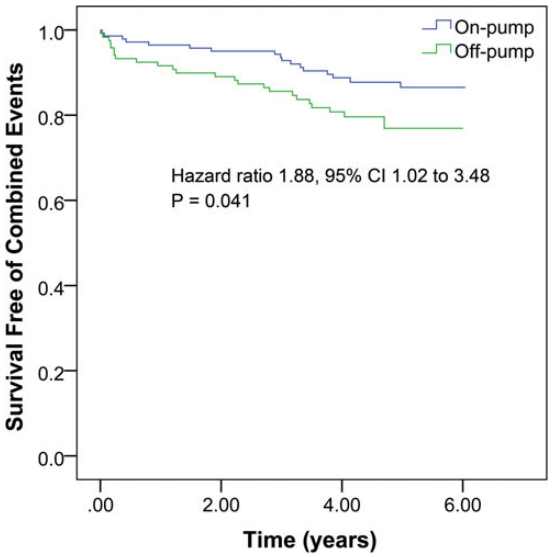

Figure 1: Kaplan–Meier estimates of survival free of combined events after surgery. 95% CI: 95% confidence interval.

Table 4: Multivariate predictors of combined end-point at 5 years

	Odds ratio	95% Confidence interval	*P*-value
Age	1.03	0.99–1.07	0.09
Complete revascularization	1.30	0.70–2.41	0.41
Off-pump CABG	1.97	1.06–3.70	0.03

CABG: coronary artery bypass graft.

independently associated with the study end-point. Furthermore, in this study, the completeness of revascularization had no impact on long-term clinical outcomes. Although it has been suggested that incomplete revascularization is inferior to complete revascularization, some studies have provided conflicting results [11, 17]. Recent data suggest that long-term survival was not adversely affected in patients with multivessel coronary artery disease who received reasonable incomplete revascularization in other than the left anterior descending territories [18–20]. One reason why complete revascularization in this study did not provide long-term clinical benefit is that we performed revascularization based on the definition at that time of anatomical complete revascularization. This definition has been replaced more recently by complete functional revascularization where only arteries with obstructions with proven haemodynamic compromise underwent intervention. Another reason for no benefit is the lack of power of the study to evaluate this specific issue (Type II error). One possible explanation for the higher incidence of long-term clinical events in patients undergoing off-pump CABG would be the worse graft patency in this group [21]. In the Rooby trial, graft patency was significantly worse with off-pump CABG, which negatively affected 1-year event rates [16]. Graft quality might be decreased because of the technical difficulty of revascularization of that territory, particularly in patients with severe lesions in the CXA system.

The strength of this study lies in the long-term follow-up of a specific population with coronary artery disease and preserved ventricular function with no loss to follow-up. Furthermore, given the important therapeutic decisions in coronary artery disease, this study may help in selecting the best revascularization strategy in clinical practice. There are some limitations. First, only clinical outcomes were assessed on this trial; graft patency was not assessed during the follow-up. There were no measured end-points that look specifically for events (myocardial infarction or new revascularizations) at the circumflex territory. This is a single-institution study with a small sample size that is subject to Type II error. Finally, this *post hoc* analysis was not pre-specified in the original design of the MASS III trial and therefore subject to the biases inherent in this analysis.

CONCLUSIONS

In patients with multivessel coronary artery disease and severe, non-protected lesions in the circumflex territory, off-pump coronary bypass surgery resulted in a higher incidence of cardiac events at 5-year follow-up.

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