Cost-effectiveness of on-pump and off-pump coronary artery bypass grafting for patients with coronary artery disease: Results from the MASS III trial

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A B S T R A C T

Background: Recent trials have reported similar clinical outcomes between on-pump and off-pump coronary artery bypass graft (CABG). However, long-term cost-effectiveness of these strategies is unknown.

Methods: A prespecified economic study was performed based on the MASS III trial. Costs were estimated for all patients based on observed healthcare resource usage over a 5-year follow-up. Health state utilities were evaluated with the SF-6D questionnaire. Cost-effectiveness was assessed as cost per quality-adjusted life-year (QALY) gained using a Markov model. Probabilistic sensitivity analysis with the Monte-Carlo simulation and cost-effectiveness acceptability curve were used to address uncertainty.

Results: Quality of life improved significantly in both groups during follow-up compared with baseline. At 5 years, when comparing on-pump and off-pump CABG groups, no differences were found in cumulative life-years (4.851 and 4.766 years, \( P = .319 \)) and QALY gained (4.150 and 4.105 QALYs, \( P = .332 \)). Mean cost in US dollars per patient during the trial did not differ significantly between the on-pump and off-pump groups ($5890.29 and $5674.75, respectively, \( P = .409 \)). Over a lifetime horizon, the incremental cost-effectiveness ratio of on-pump versus off-pump CABG was $12,576 per QALY gained, which is above the suggested cost-effectiveness threshold range (from $3210 to 10,122). In the sensitivity analysis, the probability that on-pump CABG is cost-effective compared to off-pump surgery for a willingness-to-pay threshold of $3212 per QALY gained was <1%. For the $10,122 per QALY threshold, the same probability was 35%.

Conclusion: This decision-analytic model suggests that on-pump CABG is not cost-effective when compared to off-pump CABG from a public health system perspective.

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1. Introduction

Health expenditures represent a considerable burden in budgetary policy decision-making [1] and cardiovascular disease expenses are an important contributor [2]. These costs can be explained by the rising number of invasive procedures, especially on-pump coronary artery bypass graft surgery (CABG). This procedure is one of the most common interventions provided by healthcare systems [3]. An alternative technique, off-pump surgery, has emerged to minimize the adverse effects of on-pump surgery. Nevertheless, the cost-effectiveness of these strategies continues to be debated.
The in-hospital cost-analysis of the MASS III (Medicine, Angioplasty and Surgery Study III) trial [4] showed that off-pump compared with on-pump CABG was associated with higher costs, but the post-procedure hospital stay costs were significantly greater in the on-pump CABG group. On the other hand, the ROOBY (Randomized On/Off Bypass) trial [5] found no differences in costs and quality of life in patients with multivessel coronary artery disease who underwent on-pump and off-pump CABG at 1-year follow-up, excluding late conversions. Recently, the CORONARY (CABG Off or On Pump Revascularization Study) trial [6] also found no differences between on-pump and off-pump CABG in terms of costs and no significant between-group differences in quality of life at 5-year follow-up. However, methodological limitations are associated with these economic analyses.

The aim of this study was to assess the long-term economic outcomes and quality of life of these 2 surgical strategies by applying a Markov model.

2. Methods

2.1. Study design, patients, and setting

MASS III was a randomized controlled trial conducted at a single public hospital in Brazil to assess the safety and cost-effectiveness of on-pump versus off-pump CABG. The design and results of MASS III have been previously reported [7]. The present study was a prespecified analysis of the MASS III trial. Briefly, patients with multivessel coronary artery disease (CAD) who had no prior CABG and were deemed suitable for either on-pump or off-pump CABG were enrolled and randomly assigned on a 1:1 basis to either technique. Patients were enrolled and randomized if the surgeons agreed that revascularization could be attained by either strategy. Patients were excluded if they required emergency or concomitant major surgery, unstable angina requiring emergency revascularization, ventricular aneurysm requiring repair, or left ventricular ejection fraction <40%.

In-person assessments were performed 1 month post-procedure, every 3 months in the first year post-randomization, and every 6 months thereafter. The ethics committee of our institution approved the study protocol, and all patients provided informed consent.

2.2. Resource utilization data

For each patient, cardiovascular healthcare resource use associated with the index hospitalization and follow-up hospitalizations were recorded prospectively. Resource utilization included (1) initial CABG procedure, length of intensive care unit (ICU) stay, and ward settings until discharge; (2) complications in the postoperative period, from the time of the ICU until hospital discharge; (3) medications during follow-up; (4) subsequent hospitalizations (including subsequent CABG or percutaneous coronary intervention (PCI)); (5) outpatient visits; and (6) laboratory examinations and cardiovascular tests during follow-up. Detailed resource use was recorded for each initial and any subsequent revascularization procedures.

2.3. Costs

Unit costs for all resources used by trial patients were obtained from national databases [8]. Because the cost analysis was conducted from the Brazilian public healthcare system perspective, it included only direct medical costs for cardiovascular hospitalizations, medications, new coronary procedures (PCI or CABG), and outpatient care. All costs computed over 5-year follow-up were adjusted for the change in the year 2017 by the local Consumer Price Index [9]. The figures were then converted into US dollars (USD) using the December 2017 currency conversion rate [10].

Costs of cardiovascular interventions and their complications as well as outpatient visits and cardiovascular tests were estimated with average reimbursement rates obtained from the public healthcare system [8]. All medications were assigned a cost based on the health price database of the Ministry of Healthcare wholesale price for enalapril (for angiotensin-converting enzyme inhibitors), aspirin, clopidogrel, amiodarone (for antiarrhythmic drugs), warfarin (for anticoagulant drugs), atorvastatin (for statins), atenolol (for beta-blockers), amlodipine (for calcium channel blockers), digoxin (for cardiac glycosides), hydrochlorothiazide (for diuretics), isoroorbic acid mononitrate (for nitrates), metformin and glibenclamide (for oral hypoglycemic agents), and NPH insulin (for insulin).

2.4. Quality of life

Quality of life was assessed directly from patients at baseline and at 6, 12, 24, and 60 months post-procedure with the SF-36 health status instrument [11] and converted to SF-6D health utility weights with the use of an algorithm developed from the Brazilian population [12]. Quality-adjusted life-years (QALYs) were calculated by multiplying the duration of time spent in a health state by utility, a measure of health status scaled from 0 (death) to 1 (perfect health).

2.5. Statistical analysis

For the purposes of the economic analysis, patients were categorized according to their assigned treatment. Descriptive data are reported as frequencies. Continuous variables with normal distribution are expressed as mean ± standard deviation, and the variables with non-normal distribution are expressed as median and interquartile range (IQR). Discrete variables were compared using Fisher’s exact-test. Those continuous variables with normal distribution were compared using the Student t-test, and those with non-normal distribution were compared using the Wilcoxon rank-sum test. Cost data are reported as both mean and median values. Quality-adjusted life expectancy during the trial period was estimated for each patient at the time-weighted average of his or her utility value, using the midpoint between assessments as the transition between health states. For the calculation of quality-adjusted life-years (QALYs), missing utility values for patients known to have been alive at follow-up time points were estimated using multiple imputation, with baseline patient characteristics, previous utility values, and previous in-trial clinical events informing the imputation. The comparison between the 2 operative techniques was assessed in prespecified subgroups defined by the presence or absence of previous acute myocardial infarction, diabetes mellitus, complete or incomplete revascularization, number of diseased vessels, sex, age, and ischemia in previous tests. The value of P < .05 was considered statistically significant. These analyses were performed using SPSS version 20.0 (SPSS, Inc.).

2.6. Cost-effectiveness analysis

The cost-effectiveness analysis was based on projections of costs and quality-adjusted life expectancy beyond the 5-year trial follow-up using modeling techniques. The primary outcome is the cost per QALY gained. All costs and effects are presented in disaggregated and aggregated form and the incremental cost-effectiveness ratio (ICER). The ICER is expressed as the ratio of the difference in costs between 2 strategies to the difference in effectiveness: (cost of on-pump CABG – cost of off-pump CABG) / (QALY of on-pump CABG – QALY of off-pump CABG).Projections of post-trial costs and QALY were obtained from a Markov disease-simulation model. In the Markov model, each surviving patient was assumed to face annual risk of death, with estimates of this risk based on age-, sex-, and race-matched risks of death obtained from Brazilian life tables, calibrated to the observed 5-year mortality for the MASS III trial population [13]. The Markov model was constructed with 4 health states: asymptomatic (state 1), stable angina (state 2), postoperative myocardial infarction (state 3), and death (state 4; Fig. 1). The 3 major events that can lead to transition from state 1 to state 4 are myocardial infarction, angina, and revascularization. Only the first occurrence of any of these events was included in the model. We assumed that patients experiencing an event were either stable or dead at the following cycle; patients could also die directly from any state, without the listed events. The cycle length used was 1 year and the analysis considered a lifetime horizon and half-cycle correction was applied [14]. An annual discount rate of 5% was applied to costs and outcomes, according to recommendations of the Methodological Guidelines Studies of Economic Evaluation of Technologies in Health of the Brazilian Ministry of Health [15]. A brief explanation about modeling, the Markov Model, as well as a glossary containing the most frequently used terms in health utility analysis may be found in the Online supplement.

2.7. Sensitivity analysis

The effect of assumptions and single parameters on the main results was examined by using multiple univariate sensitivity analyses, and a multivariate sensitivity analysis was performed to vary the maximum and minimum values considered of main interest. Probabilistic sensitivity analysis was used to assess overall parameter uncertainty in the model. Point estimates for each parameter were replaced by values sampled from statistical distributions, and the ICER was recalculated using the new resampled values by the Monte Carlo simulation. Utilities parameters followed a distribution and costs y distribution (Online Supplement Table S1). This process was repeated 10,000 times to estimate uncertainty and to predict the likelihood that on-pump CABG would be cost-effective at different cost-effectiveness thresholds. We adopted the cost-effectiveness threshold suggested by the University of York with the range for Brazil between $3210 and 10,122 [16]. A cost-effectiveness acceptability curve was generated to show the proportion of cost-effective simulations over a range of willingness-to-pay thresholds. All analyses of data from the trial period, and the analyses of cost-effectiveness based on the combined trial data and lifetime projections, were performed using TreeAge Pro 2015 (TreeAge Software Inc. Williamstown, MA).

3. Results

3.1. Patient enrollment and clinical outcomes

A total of 153 and 155 patients were randomized to either on-pump CABG or off-pump CABG, respectively. All patients were included in the economic analysis (Online Supplement Fig. S1). Baseline characteristics for patients are summarized in Online Supplement Table S2. No patient was lost to follow-up and only 1.6% of the patients had any incomplete or missing data. No significant difference was observed for the composite
primary end point of death, stroke, additional revascularization or myocardial infarction (16.2% in the on-pump group and 23.2% in the off-pump group, \(P = .21\)) at 5-year follow-up.

3.2. Initial resource utilization and treatment costs

Among patients assigned to off-pump CABG, 3 underwent initial on-pump CABG. The on-pump group had more grafts than the off-pump group (2.97/patient vs. 2.49/patient, \(P < .001\)). There was a higher rate of incomplete myocardial revascularization in patients undergoing off-pump CABG (57.5% vs. 47.1%, \(P = .052\)). The time in the intensive care unit (19.5 ± 17.8 vs. 43 ± 17 h, \(P < .001\)) and the total length of hospital stay (6 ± 2 vs. 9 ± 2 days, \(P < .001\)) were significantly lower in patients who underwent off-pump CABG. Moreover, intraoperative red blood cell transfusion was statistically lower in the off-pump than in the on-pump group (31.0% vs. 61.0%, \(P < .001\)).

Although the operating room time of off-pump surgery was considerably shorter than the time for on-pump surgery (240 ± 65 vs. 300 ± 87.5 min, \(P < .001\)), the index procedure costs were significantly lower for on-pump CABG ($3084.95 vs. $2964.31, \(P < .001\)).

Clinical events, resource use, periprocedural data, and costs during the index hospitalization are summarized in Online Supplement Table S3.

CABG costs per patient associated with the post-procedure hospital stay (including physician fees) were significantly greater in the on-pump CABG group ($486.10 vs. $270.36, \(P < .001\)). As a result, total index hospitalization costs per patient were slightly higher in the on-pump CABG group ($3450.42 vs. $3355.31, \(P = .293\)).

3.3. Follow-up resource utilization and costs

The annual rates of additional revascularization, diagnostic catheterization, and hospitalization were similar between on-pump and off-pump CABG. Costs for medical consultation, diagnostic cardiovascular tests, and medications were also similar between the 2 groups (Online Supplement Table S4). The cumulative 5-year cost was $215.34 higher per patient with on-pump CABG (Fig. 2).

3.4. Quality of life, utility weights and QALYs

For the eight domains of health-related quality of life measured by the SF-36, Online Supplement Fig. S2 shows the mean scores by treatment group at randomization (baseline) and at six months, one year, two years, and five years of follow-up. Both groups showed substantial improvements over the six months in most aspects of quality of life, especially in physical role functioning, emotional functioning and mental health, although we did not observe differences between the groups during follow-up. Utility weights as assessed by the SF-6D are summarized in Online Supplement Table S5. Overall, utility weights improved substantially for both treatment groups over the course of the trial. However, utility weights remained similar for both groups over the trial (Online Supplement Fig. S3). By the end of the 5-year follow-up period, life-years gained (4.851 vs. 4.766 years) and quality-adjusted life expectancy (4.150 vs. 4.105 QALYs) were also similar between on-pump and off-pump CABG, respectively (Online Supplement Table S6).
3.5. Subgroup analysis

Results from prespecified subgroup analysis are presented in Online Supplement Table S7. Despite the greater uncertainty associated with reduced sample sizes, these results were generally consistent with our primary analysis. Our analysis demonstrated that there was no difference among all the subgroups with the exception of cumulative QALY in the patient subgroup stratified by age.

3.6. Cost-effectiveness analysis

The in-trial results were used to project economic outcomes beyond the trial. On-pump CABG was associated with lifetime incremental costs of $1710 (95% CI, $1670.77 to $1767.18) together with an increase in overall quality-adjusted life expectancy of 0.136 QALYs (95% CI 0.135 to 0.137). The resulting ICER for on-pump compared with off-pump CABG was $12,576 per QALY gained (95% CI -$12,692 to $82,852).

3.7. Sensitivity analysis

A tornado diagram of the univariate sensitivity analyses shows the effect on the estimated ICER if one model assumption is altered while other assumptions remain at base case values (Online Supplement Fig. S4). Our analysis was robust to clinically plausible alternative scenarios, and univariate sensitivity analysis identified the 3 most influential parameters on cost-effectiveness: the health utility of asymptomatic patients in the off-pump group, the health utility of asymptomatic patients in the on-pump group, and the cost of PCI in the on-pump group.

The probabilistic sensitivity analysis was performed with 10,000 Monte Carlo simulations. The spread of simulated points is shown in Fig. 3 and the acceptability curve in Fig. 4. The sensitivity analysis indicates that, when considering a willingness-to-pay threshold of $10,122 per QALY gained, on-pump has a probability of 35% to be cost-effective versus off-pump CABG. With a threshold of $3210, this probability is <1%. We conclude that the model is robust to uncertainty.

4. Discussion

This study is the first long-term prospective economic analysis of on-pump versus off-pump CABG for treatment of multivessel CAD. On basis of results obtained alongside the MASS III trial, we found that hospital costs of off-pump group were higher than on-pump group due to need to maintain the cardiopulmonary bypass machine in the operating room with the perfusionist team and the use of “Octopus” tissue stabilizer, used in the off-pump CABG to stabilize and minimize movement of selected areas of the heart with pulsations. However, at 5 years after CABG, cumulative costs per patient were $5674.75 in the off-pump group and $5890.29 in the on-pump group (P = .409). The subgroup analysis showed that treatment results were not greatly changed by clinical characteristics at baseline. Interestingly, the greatest long-term costs in both treatment groups resulted from the medication.

When we performed a formal cost-effectiveness analysis using a decision-analytic model that was on the basis of the trial data, we found that on-pump CABG was not associated with much larger gains in quality-adjusted life expectancy compared to off-pump CABG (0.136 QALYs), whereas projected costs remained about $1710/patient higher with on-pump CABG. We estimated that the lifetime ICER for on-pump versus off-pump CABG was $12,576/QALY gained. According to University of York, ICERs <$3120/QALY gained suggest high-value, ICERs between $3120 and $10,122/QALY gained suggest intermediate-value, and ICERs >$10,122/QALY gained suggest low-value treatment strategies for Brazil [16].

The overall results were relatively robust in sensitivity analyses. Specifically, in a probabilistic sensitivity analysis in which all model parameters were varied simultaneously, the results of our patient-level economic study suggest that on-pump CABG provides low value relative to off-pump CABG for patients with multivessel CAD. In our analysis, using a willingness-to-pay threshold of $10,122 per QALY gained, the probability of on-pump surgery to be cost-effective, when compared to off-pump surgery, is 35%. With a threshold of $3210 per QALY gained, this probability is <1%.

These findings suggest that for patients undergoing CABG who are similar to those enrolled in the MASS III trial, off-pump CABG is likely to be reasonably cost-effective compared with on-pump CABG within the context of public healthcare system.
4.1. Comparison with previous studies

The cost-effectiveness of off-pump versus on-pump CABG for CAD has been studied previously [5,6]. However, these studies contrast with the cost-effectiveness analysis of the MASS III trial. First, both studies did not develop a long-term decision-analytic model of cost-effectiveness. Second, the economic analysis of the ROOBY trial had only 1-year follow-up. This is important because differences in clinical events between patients treated with on-pump and off-pump may not be detected in the first year of surgery. Therefore, any cost analysis restricting the time horizon to 1 year can result in an incomplete assessment of the cost-effectiveness of the surgery. Finally, the CORONARY study did not include the costs of CABG supplies (cardiopulmonary bypass circuits), and quality of life and neurocognitive tests were optional for both the patients and the investigators at the study sites, which resulted in a rate of questionnaires applied to the sample of only 60%.

Our study provides several important advantages over these previous studies. First, by prospectively collecting resource use and cost data alongside a randomized clinical trial, our study required few assumptions regarding the actual cost of the alternative revascularization procedures. Moreover, our trial includes rigorous methods to minimize...
bias (randomization, explicit study protocols, complete follow-up, analysis based on the intention-to-treat principle, and adequate health economic assessment tool). Recruitment of a single center sample in the case of cost-effectiveness studies, allows a more homogeneous collection and analysis of the data and results. The other strength of our model is the probabilistic approach and the use of clinical effectiveness data from a comprehensive randomized clinical trial.

4.2. Study limitations

The results of our study should be considered in light of several limitations. First, the MASS III trial was conducted at a single center, only patients from the Brazil were included in the primary economic analysis, which limits its external validity to patients in other healthcare systems that have different patterns of care and cost structures. However, because these are comparative groups, we believe that small inconsistencies cancel out. Second, given the size of the MASS III trial, it is possible that outliers more strongly influence results and clinical outcomes compared with a larger study. On the other hand, CORONARY and ROOBY trials did not show any difference in MACE and costs between the two surgical treatment strategies. Third, our economic analysis was performed from the perspective of the public healthcare system. Therefore, it only considered direct healthcare costs. Costs such as out of hospital costs and productivity losses for patients and their caregivers were not included, but are unlikely to have a significant impact on our results because clinical results were similar. Despite these limitations, the results of the present sensitivity analysis were robust.

5. Conclusions

This current analysis from a Brazilian public healthcare system perspective suggests that, despite providing higher rates of complete revascularization, on-pump CABG is not cost-effective when compared against off-pump CABG. The economic outcomes in MASS III were consistent with the clinical outcomes, which show that off-pump CABG is as safe and effective as on-pump CABG. This report provides important information for public health, optimizing healthcare spending and sparing expenses.

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Conflicts of interest

The authors report no relationships that could be construed as a conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2018.08.044.

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