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Original Research Article

Cardiovascular events related to the treated coronary artery after surgical or percutaneous revascularization in patients with stable multivessel coronary artery disease: long-term comparison with medical treatment

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ABSTRACT

Background: Myocardial revascularization via coronary artery bypass grafting (CABG) or percutaneous coronary intervention (PCI) is central for complex coronary artery disease (CAD). However, post-procedural adverse cardiovascular events remain challenging. Traditional efficacy assessments use composite endpoints, such as major adverse cardiovascular events (MACE), which include events unrelated to the treated artery, potentially compromising the evaluation of the intervention's true clinical impact. Objectives were to compare adverse cardiovascular events-nonfatal myocardial infarction and cardiac death-directly attributable to the artery treated by CABG or PCI, versus patients with similar CAD managed exclusively with medical therapy.
Methods: This comparative study includes patients with stable multivessel CAD undergoing CABG, PCI, or medical therapy alone. Only clinical events anatomically linked to the treated artery (or the target vessel in the medical therapy cohort) will be analyzed. This methodology aims to deliver a precise evaluation of the technical and clinical efficacy of each revascularization strategy.
Results: Data collection and statistical analysis are ongoing. The upcoming results will detail and compare the precise incidences of vessel-related myocardial infarction and cardiac death across the three therapeutic groups.
Conclusions: By prioritizing vessel-specific outcomes over traditional composite endpoints, this study addresses existing methodological limitations. It offers an accurate assessment of PCI and CABG efficacy in real-world clinical practice, aiming to guide individualized, evidence-based therapeutic decisions for stable CAD management.

Keywords: Coronary artery disease, CABG, PCI, Cardiovascular events

INTRODUCTION

Myocardial revascularization, executed either via CABG or PCI, represents a cornerstone therapeutic strategy in the contemporary management of complex CAD, notably for individuals presenting with extensive multi-vessel lesions or ischemic symptoms refractory to optimal medical therapy.[1] Despite substantial technological and pharmacological advancements over recent decades, the longitudinal incidence of post-procedural adverse

cardiovascular events continues to impose a pronounced clinical and socioeconomic burden.[2] Consequently, identifying precise methodologies to evaluate comparative treatment efficacy remains an ongoing focus of modern cardiovascular research.[3] Historically, clinical trials have heavily relied on broad composite endpoints, universally termed MACE or major adverse cardiac and cerebrovascular events (MACCE), encompassing clinical targets such as cardiovascular mortality, non-fatal myocardial infarction, stroke, and repeat revascularization.[4] Although composite endpoints are statistically advantageous for magnifying study power and minimizing required sample sizes, they inherently group together diverse pathophysiological events that may not directly reflect the technical success or failure of the treated artery.[5] For instance, a stroke might stem from a carotid thromboembolic mechanism, and all-cause mortality frequently includes non-cardiac aetiologies, thereby diluting and potentially confounding the true therapeutic impact of the local coronary intervention.[6] Thus, analysing clinical outcomes strictly localized and anatomically attributable to the treated vessel-such as target-vessel myocardial infarction or cardiac death linked to the treated territory-presents a fundamentally more robust and reliable marker of clinical and technical success.[7] Milestone historical trials, such as the coronary artery surgery study (CASS), alongside earlier percutaneous evaluations like the second randomized intervention treatment of angina (RITA-2) trial, established initial comparative benchmarks between medical, surgical, and percutaneous pathways; however, their primary analytical endpoints focused on overall mortality and undifferentiated systemic events. Subsequent landmark contemporary protocols, including the SYNTAX trial, utilized composite MACCE scores to contrast PCI and CABG, while the heavily debated ISCHEMIA trial3 expanded event criteria to incorporate hospitalizations for unstable angina and heart failure.[8-10]

While these trials advanced clinical guidelines, their aggregate event clusters frequently obscured individual vessel-level dynamics, heavily confounding procedure-specific efficacy with systemic disease progression in untreated native segments. To bridge this critical methodological gap, the present study proposes a localized evaluation framework, focusing specifically on non-fatal myocardial infarction and cardiac death directly attributable to the target anatomical vessels managed via PCI and CABG.

These procedural cohorts are robustly compared against a tightly matched control group of patients with stable multi-vessel CAD managed exclusively through guideline-directed medical therapy. By filtering out non-vessel-specific systemic events, this approach aims to achieve unprecedented precision in isolating procedure-specific risk factors, elucidating localized failure mechanisms, and providing high-fidelity clinical data capable of steering more individualized, precision-based decision-making in multi-vessel CAD management.

Objectives

Objectives were to evaluate the occurrence of cardiovascular events-specifically non-fatal myocardial infarction and death-related to the artery treated by surgical revascularization or angioplasty. The outcomes of these patients will be compared to those of individuals with CAD in the same clinical conditions but treated exclusively with drug therapy.

METHODS

Study design

This comprehensive study was initiated in January 2012 and completed in December 2019. Throughout this five-and-a-half-year period, the research focused on collecting extensive data, conducting rigorous analyses, and tracking long-term trends to achieve its primary objectives.

Study setting and period

This is a single-center, retrospective cohort study based on data from the mass (medicine, angioplasty, or surgery study) study group, based in the outpatient clinics of the Heart Institute of the Hospital das Clínicas of the University of São Paulo School of Medicine (InCor-HCFMUSP). The MASS database includes patients with CAD and documented myocardial ischemia, indicated for surgical, percutaneous, or medical treatment, participating in randomized or observational research protocols. This study was approved by the institutional review board (Approval opinion No. 8.094.301; CAAE No. 92421225.4.0000.0068).

Sample selection criteria

Patients with angina pectoris and multivessel CAD, defined as stenosis >70% of the lumen in at least two major coronary arteries, confirmed by coronary angiography, were included. The presence of myocardial ischemia was documented by exercise stress testing or myocardial perfusion scintigraphy (physical or pharmacological stress). Angina was graded according to the Canadian cardiovascular society (CCS) classification.

Inclusion criteria

Patients with multivessel CAD and myocardial ischemia documented by functional tests were considered eligible, provided there was a clinical indication for percutaneous, surgical, or exclusively pharmacological treatment were included from study.

Exclusion criteria

Patients with limited life expectancy, impossibility of long-term clinical follow-up, use of implantable cardiac devices, severe left ventricular dysfunction (ejection

fraction <55%), acute coronary syndrome in the last 6 months, percutaneous revascularization in the previous 12 months, significant valvular disease, chronic kidney disease (creatinine ≥2.0 mg/dL), active rheumatologic diseases, sepsis, pulmonary thromboembolism or deep vein thrombosis in the last 6 months, and malignant neoplasms under active treatment were excluded.

Definitions

CAD was defined as stenosis >70% of the lumen of the main epicardial vessels. Left ventricular function was considered preserved when the left ventricular ejection fraction (LVEF) was ≥55%, as estimated by echocardiography or other appropriate method.

Treatment protocols

All patients received optimized drug therapy according to current guidelines for angina control and secondary prevention of cardiovascular events. Medications included aspirin, P2Y12 receptor blockers, beta-blockers, calcium channel blockers, ACE inhibitors, diuretics, spironolactone, statins, nitrates, and antiarrhythmics, as indicated. Glycemic control was individualized with oral agents or insulin. A low-fat diet with restriction of simple carbohydrates was also recommended.

In surgical group, complete revascularization was sought, with preference for the internal thoracic artery. Surgeries followed standardized techniques, using mild hypothermia and cardioplegia with cardiopulmonary bypass/alternatively, an off-pump technique, depending on clinical assessment. In angioplasty group, patients underwent elective PCI, indicated according to international guidelines for the treatment of CAD. All procedures were performed using standard techniques, using radial or femoral access, appropriate guide catheters, balloon predilation when necessary, and implantation of drug-eluting or bare-metal stents at the operator's discretion. During procedure, patients received dual antiplatelet therapy and anticoagulation according to institutional protocols. Clinical, angiographic, and laboratory data were collected prospectively, and clinical outcomes were monitored in outpatient follow-up.

Follow-up

Patients were followed up biannually in outpatient clinic visits for an average period of 5 years. At each visit, a detailed clinical evaluation was performed, and laboratory and functional tests requested for glycemic and lipid control and cardiac performance assessment.

Outcomes

Surgical treatment

The primary study outcomes were: nonfatal acute myocardial infarction (AMI) related to the treated artery and cardiac death attributed to the treated artery. AMI was defined according to international guidelines: presence of compatible chest pain, elevation of biomarkers of myocardial necrosis, and/or appearance of new Q waves in at least two contiguous leads on the electrocardiogram. The treated artery was identified by angiographic review. If angiographic study was not possible, the attribution of death related to the treated artery was based on clinical, echocardiographic (identification of segmental dysfunction in the corresponding territory), or angiographic data. Non-cardiac deaths were recorded but not considered in the primary outcomes and were analyzed separately.

Percutaneous treatment

Myocardial infarction was identified similarly to that observed in surgical treatment, and the treated artery was identified by angiographic review, and the diagnosis followed the same international guidelines. Death related to the treated artery was identified similarly to the surgical group. If angiographic study was not possible, the identified vessel was attributed based on clinical, echocardiographic (compromise of the wall corresponding to the treated vascular territory), or angiographic evidence.

Medical treatment

Myocardial infarction was identified using the same criteria as in the previous groups, as was death related to the diseased vessel previously identified by angiographic studies. Since there was no intervention, the events (infarction and death) were attributed to the artery previously identified as diseased by the initial angiographic examination, assuming that the events were related to the diseased vessel.

Sample size calculation

This retrospective analysis included a cohort of over 1,500 patients, representing a significant sample size and lending methodological robustness to the study. This size allows for greater statistical power for detecting significant differences, in addition to reducing the likelihood of Type II errors. Although this is a retrospective design, the sample size contributes to the representativeness of the results and strengthens the interpretation of the observed associations between clinical variables and cardiac events.

Ethical approval

All patients provided written informed consent at the time of inclusion in the MASS database, in accordance with the principles of the declaration of Helsinki. The protocol for this study was approved by the institution's research ethics committee under Nº CAAE-92421225.4.0000.0068 and number of technical decisions-8.094.301.

Statistical analysis

Statistical analyses will be performed to compare the occurrence of cardiovascular events directly related to the treated artery between groups of patients undergoing PCI, CABG, or exclusive clinical treatment. Categorical variables will be described as absolute frequencies and percentages, and compared between groups using the chi-square test or Fisher's exact test, where appropriate. Continuous variables will be assessed for normality using the Shapiro-Wilk test and described as mean and standard deviation or median and interquartile range, depending on the distribution. For comparison between groups, the ANOVA or Kruskal-Wallis test will be used, as applicable. Event-free survival (myocardial infarction related to the treated artery and cardiac death) will be analyzed using the Kaplan-Meier method, with comparison between groups using the log-rank test. Univariate and multivariate Cox regression models were used to identify independent predictors of outcomes, calculating the hazard ratio (HR) and respective 95% confidence intervals. The variables included in the multivariate model were selected based on statistical significance in the univariate analysis ($p<0.10$) and/or recognized clinical relevance. Significance level adopted was 5% ($p<0.05$). Statistical analyses will be performed with IBM SPSS Statistics version 24.0 (IBM Corp., Armonk, NY, USA) and R (R Foundation for Statistical Computing, Vienna, Austria) version 3.5.2/higher.

RESULTS

Patient enrollment has been completed, and the stages of database consistency checks, clinical event adjudication, and statistical analyses are currently underway. The final results will report the incidence of non-fatal AMI and cardiac death attributable exclusively to the treated coronary artery (or the corresponding target artery in the clinical treatment group), enabling a direct comparison between CABG, PCI, and optimal medical therapy. The definitive findings will be released in due course following the completion of analyses and publication of the study. Participant demographics and clinical characteristics are presented in Table 1.

Table 1: Clinical, laboratory, and angiographic characteristics of patients according to the initial therapeutic strategy.

Variables	CABG, n=572 (%)	PCI, n=549 (%)	OMT, n=574 (%)	P value			
				P value (global)	CABG/ PCI	CABG/ OMT	PCI/ OMT
Age (in years)	62 [55-68]	60 [53.7-66]	61 [54-67]	0.004	0.003	0.129	0.340
BMI (kg/m²)	27.1 [24.9-30.1]	27.3 [24.6-29.9]	27.5 [24.9-30.3]	0.567	0.984	0.662	0.602
Gender-Male	397 (69.4)	363 (66.1)	383 (66.7)	0.455	0.265	0.362	0.879
Hypertension	469 (82.0)	462 (84.2)	453 (78.9)	0.074	0.376	0.216	0.029
Diabetes	294 (51.4)	289 (52.6)	334 (58.2)	0.049	0.721	0.024	0.070
TC (mg/dL)	196 [160-236]	196 [158-230]	192 [160-225]	0.359	0.997	0.408	0.458
LDL (mg/dL)	121 [90-152]	118 [91-149]	111 [90-150]	0.636	0.997	0.662	0.720
HDL (mg/dL)	38 [33.8-44]	37 [32-44]	38 [32-45.8]	0.068	0.153	0.925	0.084
TG (mg/dL)	150.5 [108-209]	153 [111-219]	144 [103-203]	0.068	0.591	0.359	0.057
Glucose (mg/dL)	112 [97-149]	112 [98-144]	115 [99-151]	0.155	0.975	0.188	0.259
HbA1c (%)	6.10 [5.70-7.20]	6.20 [5.70-7.50]	6.70 [6.00-7.70]	0.004	0.258	0.003	0.201
Creatinine (mg/dL)	1.02 [0.90-1.20]	1.00 [0.90-1.20]	1.00 [0.90-1.20]	0.179	0.231	0.260	0.994
Angina grade							
1	60 (10.5)	62 (11.3)	124 (21.6)	<0.001	<0.001	<0.001	<0.001
2	367 (64.2)	234 (42.6)	314 (54.7)				
3	121 (21.2)	173 (31.5)	127 (22.1)				
4	24 (4.2)	80 (14.6)	9 (1.6)				
AMI previous	242 (42.3)	246 (44.8)	222 (38.7)	0.111	0.433	0.233	0.043
LVEF	62 [56-68]	62 [56-68]	61 [55-68]	0.400	0.621	0.876	0.402
Number of diseased vessels							
1	0 (0.0)	4 (0.7)	1 (0.2)	<0.001	<0.001	0.209	<0.001
2	135 (23.6)	221 (40.3)	154 (26.8)				
3	437 (76.4)	324 (59.0)	419 (73.0)				
AD	547 (95.6)	515 (93.8)	557 (97.0)	0.032	0.218	0.266	0.014
LCX	494 (86.4)	437 (79.6)	492 (85.7)	0.003	0.003	0.817	0.009
RCA	518 (90.6)	450 (82.0)	513 (89.4)	<0.001	<0.001	0.569	<0.001
AMI previous	55 (9.6)	61 (11.1)	69 (12.0)	0.42	0.469	0.224	0.702

*Data are presented as number (%) or median [interquartile range]. Comparisons were performed using the chi-square test for categorical variables and the Kruskal-Wallis test for continuous variables. Abbreviations: BMI: body mass index; CABG: coronary artery bypass grafting; HDL: high-density lipoprotein; LAD: left anterior descending coronary artery; LCx: left circumflex coronary artery; LDL: low-density lipoprotein; LVEF: left ventricular ejection fraction; MI: myocardial infarction; OMT: optimal medical therapy; PCI: percutaneous coronary intervention; RCA: right coronary artery.

DISCUSSION

CAD persists globally as a leading driver of cardiovascular morbidity and mortality, necessitating highly refined therapeutic approaches. While myocardial revascularization through CABG or PCI remains vital for symptomatic multi-vessel disease management, selecting the ideal approach continues to be heavily debated due to late-stage adverse events. The overarching limitation of traditional cardiovascular literature lies in its historical reliance on broad composite outcomes, such as MACE or MACCE. These traditional composite targets tend to artificially inflate statistical power while simultaneously pooling clinically disparate events, several of which bear no causal relationship to the intervention or the revascularized vessel pathology itself.

The comparative structural insights generated by classic and contemporary trials, from CASS and RITA-2 to SYNTAX and ISCHEMIA, underscore a persistent clinical trend: prioritizing aggregate endpoints at the expense of localized vessel-specific analysis.[3,8,9,11] By treating all-cause death, stroke, or remote-vessel infarctions with identical weight alongside target-vessel failure, traditional methodologies have often introduced systemic bias, masking the localized technical superiority of one revascularization mode over another.[12] The absolute necessity to decouple remote atherosclerotic progression from direct procedural failure is essential for a highly accurate clinical assessment.[13] The clinical and academic justification for this study centers on addressing these exact methodological shortcomings. By restricting the primary investigative focus to hard endpoints (non-fatal myocardial infarction and cardiac death) directly attributable to the specific revascularized artery-or the primary target vessel in the medical therapy control cohort-this study minimizes systemic noise and diagnostic confounding. This highly targeted strategy allows for a truer measurement of the long-term mechanical and biological durability of surgical versus percutaneous techniques against a backdrop of standard medical therapy. Consequently, these findings are uniquely positioned to eliminate historical clinical biases, clarify the precise therapeutic yield of mechanical interventions, and establish a more reliable, evidence-based framework to guide personalized heart team choices in multi-vessel CAD management.

Limitations

The observational design prevents causal inference and does not exclude residual confounding, even after multivariable adjustment. Non-randomized allocation may have been influenced by clinical factors, anatomical complexity, or unmeasured variables.

CONCLUSION

By prioritizing specific outcomes related to the treated vessel, this study seeks to overcome the methodological limitations of traditional composite outcomes, offering a more accurate assessment of the effectiveness of PCI and CABG in clinical practice. The findings are expected to contribute to more individualized and effective therapeutic decisions in the management of stable CAD.

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