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Protocol

Coronary artery disease treatment strategies and long-term renal function: rationale and design of the cardiorenal study

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ABSTRACT

Background: Treatment strategies for coronary artery disease (CAD), namely coronary artery bypass grafting (CABG), percutaneous coronary intervention (PCI) and optimized medical therapy (OMT), have well established cardiovascular outcomes, but their long-term effects on renal function remain underexplored. Patients with chronic kidney disease (CKD) are frequently underrepresented in large trials, and renal endpoints are usually treated as markers of cardiovascular risk rather than as outcomes in their own right. This article reports the rationale and design of a study evaluating the long-term renal impact of these strategies.
Methods: Single-centre, registry-based cohort study using the Medicine, Angioplasty or Surgery Study (MASS) registry, reported per the STROBE Statement. Eligible patients have stable multivessel CAD, preserved left ventricular function and annual serum creatinine over more than five years, and received OMT, CABG or PCI. The primary outcome is the longitudinal change in estimated glomerular filtration rate (eGFR) over five years; secondary outcomes are new-onset CKD, advanced CKD, renal replacement therapy and mortality. Renal-function trajectories will be modelled with generalized additive models for location, scale and shape (GAMLSS) including a random intercept per patient; time-to-event outcomes with Cox models adjusted for age, sex, diabetes, hypertension and baseline renal function. The cohort has been assembled and the vital-status update completed; outcome analyses are ongoing and will be reported separately.
Conclusions: By positioning renal function as a primary outcome, this study may generate evidence to integrate cardiovascular and renal risk into treatment selection for stable multivessel CAD.
Trial Registration: The study is registered at ClinicalTrials.gov (NCT07195747).

Keywords: Coronary artery disease, Chronic kidney disease, Myocardial revascularization, Glomerular filtration rate, Long-term outcomes, Study design

INTRODUCTION

The management of coronary artery disease (CAD) by coronary artery bypass grafting (CABG), percutaneous coronary intervention (PCI) or optimized medical therapy (OMT) has been extensively evaluated with a focus on cardiovascular outcomes. However, the long-term impact of these strategies on renal function remains insufficiently studied. The literature has largely addressed renal outcomes as secondary endpoints, interpreting renal

dysfunction as a mediator or marker of adverse cardiovascular events rather than as a clinically relevant outcome in its own right.[1-3] Cardiovascular procedures can directly affect renal function through contrast-induced nephropathy, systemic inflammation, intraoperative hypotension and haemodynamic stress, while the reciprocal influence of renal impairment on treatment outcomes remains less explored.

This gap is compounded by the frequent underrepresentation or exclusion of patients with CKD from major randomized trials in CAD, which limits the generalizability of findings and hinders a comprehensive understanding of cardiorenal interactions.[1,4] CKD is a well-established risk factor for adverse outcomes in CAD, particularly among patients with type 2 diabetes, and is associated with a poorer prognosis regardless of the therapeutic strategy employed.[5,6] A ten-year follow-up analysis demonstrated that diabetic kidney disease significantly influences both treatment selection and clinical outcomes, reinforcing the need for studies focusing on renal endpoints.[4,7]

The cardiorenal study was designed to address this gap by evaluating the long-term effects of surgical, percutaneous and medical treatment strategies for CAD on renal function. The primary objective is to assess changes in eGFR and the incidence of significant renal dysfunction over time. This article reports the rationale and design of the study; outcome analyses will be reported separately.

METHODS

Study design

This is a single-centre, registry-based cohort study conducted at the Instituto do Coracao (InCor), Hospital das Clinicas HCFMUSP, Universidade de Sao Paulo, Brazil, drawing on data from the ongoing MASS registry.[8] Patients are followed for a minimum of five years. The design and reporting follow the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement for observational studies.[9]

Population and eligibility

Participants were selected from the MASS registry, which includes individuals with angiographically confirmed CAD followed by a dedicated multidisciplinary team. Eligible patients had stable multivessel CAD and were candidates for any of the three conventional strategies (OMT, CABG or PCI). Stable CAD was defined as at least 70% stenosis in two or more major epicardial arteries with evidence of myocardial ischaemia by functional testing or stable angina (Canadian Cardiovascular Society class I-III).

Inclusion criteria were-multivessel CAD by angiography (two or more epicardial arteries with at least 70% stenosis); preserved left ventricular systolic function; treatment with OMT, CABG or PCI (drug-eluting or bare-metal stents); a baseline serum creatinine value at enrolment; and annual serum creatinine measurements for at least five years.

Exclusion criteria were-acute coronary syndrome at baseline; limited life expectancy due to non-cardiac comorbidities; inability to maintain regular follow-up; significant left main disease (stenosis above 50%); advanced CKD (eGFR below 30 mL/min/1.73 m^2); and end-stage renal disease requiring dialysis or prior kidney transplantation.

Therapeutic strategies

All patients received OMT according to contemporary guidelines for angina control and secondary prevention, including antiplatelet agents, beta-blockers, calcium-channel blockers, renin-angiotensin-aldosterone system inhibitors, diuretics, statins, nitrates and antiarrhythmic drugs as indicated, with individualized glycaemic control and dietary guidance. In the surgical group, complete revascularization was prioritized with preference for the internal thoracic artery, using cardioplegia under extracorporeal circulation or off-pump techniques, with renal-protective care and avoidance of prolonged hypotension to preserve renal perfusion. In the PCI group, elective procedures followed international guidelines with drug-eluting or bare-metal stents, dual antiplatelet therapy, continuous hydration and minimization of contrast volume using low- or iso-osmolar agents.

Data collection and follow-up

Baseline data included demographic characteristics, cardiovascular risk factors, comorbidities, angiographic findings and laboratory parameters, including serum creatinine. Patients were followed at scheduled annual visits by a multidisciplinary team. Serum creatinine was measured at baseline and annually using standardized enzymatic assays, and eGFR was calculated with the 2021 CKD Epidemiology Collaboration (CKD-EPI) creatinine-based equation, without a race coefficient.[10] Clinical events and hospitalizations were recorded annually in an electronic registry with ongoing quality control.

Outcomes

The primary outcome is the change in renal function over time, measured as the change in eGFR over five years. Secondary outcomes are: new-onset CKD (eGFR below 60 ml/min/1.73 m^2) in patients with previously normal renal function; progression to advanced CKD (eGFR below 30 ml/min/1.73 m^2); initiation of renal replacement therapy; all-cause mortality; cardiovascular mortality; and hospitalization for heart failure or other cardiovascular events.

Statistical analysis

Baseline characteristics will be summarized by treatment group. Continuous variables will be presented as mean and standard deviation or as median and interquartile range, and compared with the student t test or the Mann-Whitney U test; categorical variables will be presented as counts and percentages, and compared with the chi-square test or the Fisher exact test, as appropriate.

The longitudinal renal-function data comprise repeated measures correlated within patients, with marked between-patient heterogeneity, and therefore require a model that accounts for both features simultaneously.[11] The primary analysis models the longitudinal trajectory of eGFR, measured at baseline and annually up to five years, with a mixed GAMLSS including a random intercept per patient.[12] GAMLSS was preferred over classical linear mixed models because it models not only the conditional mean but also the dispersion, skewness and kurtosis of the response, thereby accommodating heavy-tailed distributions, and because it provides standardized worm-plot diagnostics of the quantile residuals. The patient-level random intercept is fitted with a ridge-type penalty whose smoothing parameter is calibrated by the Akaike information criterion (AIC).

For each patient and visit, the linear predictor for the conditional mean comprises treatment modality (OMT as reference, PCI, CABG), follow-up year, adjustment covariates (sex, age updated at each visit, hypertension, diabetes, left ventricular ejection fraction category, SYNTAX score category, smoking and baseline renal-function category), the treatment by covariate interactions, and the random patient intercept. Candidate response distributions (normal, gamma, Box-Cox-Cole-Green, Box-Cox-t and Student t) will be compared by AIC and by the Schwarz Bayesian criterion; the student t family is adopted, as it best accommodates the heavy tails expected in longitudinal renal data while remaining parsimonious. Covariates will be selected by manual backward elimination based on p values, with a significance level of 0.05, from the full specification.

To assess robustness to atypical measurements, potential outliers will be identified with the adjusted boxplot for skewed distributions, based on the medcouple statistic, stratified by year and treatment group, and the model will be refitted with and without flagged observations as a sensitivity analysis.[13] Flagged observations will not be excluded automatically: each will undergo individual clinical review against source documentation, whereby biologically plausible extreme values are retained, transcription errors are corrected, patients whose baseline renal function is incompatible with the inclusion criteria are excluded, and post-death time points are left blank without imputation.

Secondary time-to-event outcomes will be analysed with Kaplan-Meier estimates and Cox proportional-hazards models adjusted for the same covariates. Model adequacy will be assessed with worm plots, quantile residuals and term plots. A two-sided p value below 0.05 will be considered statistically significant. Analyses will be performed with R version 4.5 (R Foundation for Statistical Computing, Vienna, Austria), using the packages GAMLSS, robust base and tidy-verse.

Sample size

The study is based on a predefined cohort from the MASS registry. Although no a priori sample-size calculation was performed, the assembled cohort is considered adequate to detect clinically meaningful differences in renal outcomes between treatment groups in this exploratory analysis.

Study status

This article reports the rationale and design of the cardiorenal study; outcome data are not presented here, as no results are available at this stage. The cohort has been assembled from the MASS registry according to the criteria described above, and the vital-status update of all study patients was completed in March 2025. The database is currently in the verification phase. Baseline characteristics, renal-function trajectories and time-to-event analyses will be reported in a subsequent publication. The study is registered at ClinicalTrials.gov under the identifier NCT07195747.

DISCUSSION

This study offers a new perspective on the long-term impact of treatment strategies for stable multivessel CAD by focusing on renal-function trajectories, outcomes that are often underexplored in this setting. Using a well characterized cohort with rigorous longitudinal follow-up and standardized annual measurements, the analysis moves beyond the conventional endpoints of cardiovascular mortality and major adverse events, and positions renal function as an integrative and prognostically relevant marker of therapeutic impact.

Because this article reports the design of an ongoing study, no outcome data are available for interpretation; the following paragraphs therefore situate each planned parameter of the Cardiorenal Study against the evidence reported by previous investigations.

The exclusion of patients with renal impairment from cardiovascular trials is long standing and well documented, and it is the reason why the renal consequences of treatment strategies for stable CAD remain poorly defined.[1] Where advanced CKD has been studied prospectively, the emphasis has remained on cardiovascular endpoints: in ISCHEMIA-CKD, an initial invasive strategy did not reduce death or myocardial infarction compared with a conservative strategy in patients with an eGFR below 30 ml/min/1.73 m^2,

although the composite of death or initiation of dialysis was more frequent in the invasive arm, a signal that renal function may itself be modified by the treatment strategy.[14] The main ISCHEMIA trial, conducted in patients with preserved renal function, reported no reduction in ischaemic events with an invasive strategy but did not follow renal trajectories over time.[15] The Cardiorenal Study is positioned in the complementary space left by both trials: patients with preserved or only mildly impaired renal function at baseline, followed with standardized annual creatinine measurements, in whom incident renal decline is the outcome of interest rather than a covariate.

With respect to the comparison between revascularization strategies, previous work has consistently favoured surgical revascularization for cardiovascular endpoints in patients with CKD. Charytan et al reported a lower risk of myocardial infarction and repeat revascularization after CABG than after PCI in this population, and Baber et al. reached comparable conclusions among patients with diabetes and multivessel disease, with and without CKD.[2,6] Hannan et al likewise documented the influence of renal impairment on long-term outcomes across surgical, percutaneous and medical treatment.[7] These analyses, however, treated renal function as a baseline stratifying variable. Whether the same hierarchy holds when the endpoint is the trajectory of eGFR itself remains untested, and it is this reversal of the analytical perspective that the present study proposes.

Evidence from the MASS registry itself provides the most direct antecedent for the present design. Lopes et al. showed that mild chronic renal dysfunction already influences outcomes across the three treatment strategies in this cohort, and Batista et al demonstrated, over ten years of follow-up, that diabetic kidney disease affects both treatment selection and clinical outcomes.[3,4] Lima et al reported the long-term impact of CKD in diabetic patients treated surgically, percutaneously or medically.[5] These studies established that renal status matters in the MASS population, but each assessed renal function at a single point or as a dichotomous classification. The present protocol extends this line of work by modelling the full longitudinal trajectory of eGFR, which is the parameter for which no comparative data currently exist.

Several methodological considerations merit comment. The single-centre design and the non-randomized comparison of treatment groups for the renal endpoint may introduce selection and indication bias; multivariable adjustment and time-to-event modelling are planned to mitigate, though not eliminate, this limitation. The exclusion of patients with advanced CKD at baseline focuses the analysis on incident renal decline but limits generalizability to populations with established kidney disease. Because eGFR is derived from serum creatinine, standardized annual measurement and the 2021 CKD-EPI creatinine-based equation were adopted to improve consistency. Proteinuria and albuminuria were not systematically available across the full follow-up period and are therefore not included among the outcomes, which should be considered when interpreting the findings.

The choice of GAMLSS with a patient-level random intercept, rather than a classical linear mixed model, reflects the distributional characteristics anticipated in longitudinal renal data, and the pre-specified handling of atypical values by individual clinical review, rather than by automatic exclusion, is intended to preserve biologically plausible extreme values.

CONCLUSION

The cardiorenal study addresses an important evidence gap by positioning renal function as a primary outcome in the management of CAD. By focusing on long-term renal outcomes across surgical, percutaneous and medical strategies, it may provide new evidence to guide treatment selection in patients with stable multivessel CAD, integrating cardiovascular and renal risk into clinical decision-making. These features may aid clinical practice by providing additional criteria for individualized treatment selection in patients with preserved left ventricular function who are at risk of progressive renal dysfunction.

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Ethical approval: The study was approved by the Institutional Ethics Committee Comissao de Etica para Analise de Projetos de Pesquisa, CAPPesq) of the Hospital das Clinicas da Faculdade de Medicina da Universidade de Sao Paulo (CAAE 90089225.1.0000.0068).

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