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Effect of chronic kidney disease in ischemic cardiomyopathy

Long-term follow-up - REVISION-DM2 trial

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Abstract

A strong association exists between chronic kidney disease (CKD) and coronary artery disease (CAD). The role of CKD in the long-term prognosis of CAD patients with versus those without CKD is unknown. This study investigated whether CKD affects ventricular function.

From January 2009 to January 2010, 918 consecutive patients were selected from an outpatient database. Patients had undergone percutaneous, surgical, or clinical treatment and were followed until May 2015.

In patients with preserved renal function (n = 405), 73 events (18%) occurred, but 108 events (21.1%) occurred among those with CKD (n = 513) ($P < .001$). Regarding left ventricular ejection fraction (LVEF) <50%, we found 84 events (21.5%) in CKD patients and 12 (11.8%) in those with preserved renal function ($P < .001$). The presence of LVEF <50% brought about a modification effect. Death occurred in 22 (5.4%) patients with preserved renal function and in 73 (14.2%) with CKD ($P < .001$). In subjects with LVEF <50%, 66 deaths (16.9%) occurred in CKD patients and 7 (6.9%) in those with preserved renal function ($P = .001$). No differences were found in CKD strata regarding events or overall death among those with preserved LVEF. In a multivariate model, creatinine clearance remained an independent predictor of death ($P < .001$).

We found no deleterious effects of CKD in patients with CAD when ventricular function was preserved. However, there was a worse prognosis in patients with CKD and ventricular dysfunction.

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Abbreviations: CABG = coronary artery bypass graft, CAD = coronary artery disease, CCS = Canadian Cardiovascular Society, CI = confidence intervals, CKD = chronic kidney disease, DM = Diabetes mellitus, eGFR = estimated glomerular filtration rate, HR = hazard ratio, IQR = interquartile range, LVEF = left ventricular ejection fraction, MACE = major adverse cardiovascular events, MT = medical therapy, PCI = percutaneous coronary intervention, SD = standard deviation.

Keywords: chronic kidney disease, congestive heart failure

1. Introduction

Chronic kidney disease (CKD) arises as a worldwide disease, affecting patients of different ages or ethnicities becoming an independent cardiovascular risk factor.[1] Several studies suggested that mild-to-moderate elevations in serum creatinine levels are associated with increased rates of death from any cause and also, from cardiovascular causes.

However, whether CKD independently increases the risk of any type of cardiovascular disease has not been established.[2] Furthermore, it is observed that previous studies have been limited by the inclusion of relatively small samples of persons with kidney disease, as well as the use of binary groups of estimated kidney function. Additionally, the use of the serum creatinine level alone instead of GFR decreases the weight of information.

Composed of multiple adverse pathophysiological causes leading to the increased morbidity and mortality in CKD in general,[3] an association with traditional risk factors configures an additional cause for worse outcome of CKD patients.[4] Moreover, Diabetes mellitus (DM) and CKD are independently associated with substantially increased cardiovascular risk.[5] In this direction, diabetic patients, as well as patients with CKD, are more likely to present complications following major adverse

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cardiovascular events (MACE).[6] In this scenario, the relationship between CKD, DM or both, on ischemic cardiomyopathy is still debated, once CKD patients are not included in most trials. Our aim was investigating the relationship between CKD and ischemic cardiomyopathy in a cohort of patients with coronary artery disease (CAD).

2. Methods

The database from the MASS Registry and REVISION-DM Registry, at the Heart Institute of the University of São Paulo includes patients with CAD and ischemic cardiomyopathy. The inclusion of these patients allows them to be accommodated in different therapeutic options. From this database, samples were available for randomized trials as well as "real-world" treatment assessments for follow-up. In this scenario, the present study included, for follow-up, patients with different types of treatment received and with different degrees of coronary disease and ventricular impairment. The present study included, for follow-up, patients with different types of treatment received and with different degrees of coronary and ventricular function. With this inclusion, it was possible to correlate degrees of ventricular and renal function as well as coronary heart disease and diabetes.

Present study was approved by the Ethics Committee of the Heart Institute of the University of São Paulo Medical School and was carried out according to Declaration of Helsinki.

2.1. Recruiting patients for registration

Study records were designed to include patients with stable CAD and documented myocardial ischemia for use in many trials. Thus, these patients formed a large database generating multiple analyzes. Patients with stable multi-arterial coronary disease who had various therapeutic options available for CAD were considered for this study: medical treatment (MT), coronary artery bypass graft (CABG), or percutaneous coronary intervention (PCI). Myocardial ischemia was documented through a stress test or myocardial scintigraphy. Angina pectoris, when present, was graded according to Canadian Cardiovascular Society (CCS) classes II or III. For inclusion in this study, ventricular function was assessed by transthoracic echocardiography and left ventricular ejection fraction (LVEF) using the Simpson method. LVEF was considered preserved when values were $\geq$55% and dysfunction values were $\leq$30%. This analysis included patients with stable CAD, and optimized medical therapy alone, CABG, or PCI. Patients with limited life expectancy or incapacity for long-term outpatient follow-up were not included. In addition, we did not include patients with artificial cardiac devices or cardiac transplant patients. For the diagnosis of DM, the guidelines of the American Diabetes Association were used.[7]

CKD was defined as estimated glomerular filtration rate (eGFR) $<60\,mL/min/1.73\,m^2$, which was calculated using both the Cockroft-Gault and MDRD equations. Renal replacement therapy, hemodialysis, and peritoneal dialysis were not included.

The clinical treatment indicated for patients was medical therapy for the relief of angina symptoms and heart failure. For secondary prevention of cardiovascular events, therapeutic targets were used as recommended by the specific guidelines. The medications used included nitrates, acetylsalicylic acid, beta-blockers, calcium channel blockers, diuretics, spironolactone, angiotensin-converting enzyme inhibitors, statins, or a combination of these drugs. A diet low in saturated fats and carbohydrates was recommended. Insulin and oral hypoglycemic agents were prescribed for better control of hyperglycemia. For patients undergoing PCI, bare-metal or drug-eluting stents were used at the physician's discretion. The interventional cardiologist was encouraged to perform complete revascularization. Angioplasty was performed according to the institutional protocols where acetylsalicylic acid and/or clopidogrel were prescribed before the procedure. Treatment with platelet anti-aggregation after angioplasty followed the guidelines of national and international societies. For the patients who underwent the surgical intervention, a complete and anatomic revascularization was planned. The use of the internal mammary artery, as a graft, was strongly recommended. The surgical procedure also complied with standardized techniques with the application of mild hypothermia and blood cardioplegia in patients operated on during extracorporeal circulation. Surgery without the extracorporeal circulation was performed according to medical criteria.

2.2. Follow-up

The patients were followed regularly in consultations every 4 months involving a rigorous clinical evaluation. Clinical events were recorded and dated from patient inclusion in the study. Laboratory tests to monitor therapeutic, lipid, and glycemic goals were requested semiannually. Echocardiography and subsidiary examinations to evaluate cardiac function were requested according to clinical indication.

2.3. Outcomes

Events considered were overall mortality, nonfatal myocardial infarction, stroke, and additional revascularization procedures. The diagnosis of myocardial infarction was established when chest pain, new "Q" waves in 2 or more contiguous leads on the ECG, and elevated biomarkers of myocardial necrosis were present. Heart failure was diagnosed according to the presence of symptoms of dyspnea, pulmonary rales, tissue hypoperfusion, and peripheral edema.

2.4. Statistical analysis

Baseline data are summarized as (%), mean $\pm$ standard deviation (SD), or median interquartile range (IQR), according to the distribution. Demographic and clinical variables, as well as the treatment applied, are included in the analysis. Other variables were also tested for significance, including LVEF, metabolic profile, arterial pattern, and smoking status. Results are described as relative risks (HR; hazard ratio) with 95% confidence intervals (CI). Mean levels of continuous variables were compared by 1-way ANOVA, followed by the Tukey multiple-comparisons test. The chi-square test was used to compare qualitative variables in groups. The Fisher exact test was used for categorical variables. The Wilcoxon scores were used for categorical variables with an ordinal scale. Discrete variables are expressed as counts and percentages.

Event rates were estimated using the Kaplan–Meier method, and differences among groups were assessed by means of the log-rank test. Potential independent predictors of outcomes were identified by univariate analyses for each renal function stratum by Cox proportional hazards analysis. Demographic and clinical variables were included in this analysis. Other variables were also tested for significance, including LVEF, treatment arm, metabolic profile, arterial pattern, smoking status, and renal function. To construct the multivariable model, we first examined univariate

Cox models, and variables that were at least marginally associated with the combined endpoint ($P < .10$) were included in a model in which stepwise selection was used for predictor selection at each step. Additional candidate variables were included in the multivariable model if there were significant treatment by predictor interactions ($P \leq .05$). The assumption of proportional hazards was verified for every model using time-dependent Cox models with time as a continuous variable.

The effect of LVEF according to the presence of any degree of CKD was estimated using a contrast of main effects and interaction effects without further covariate adjustment. The statistical significance of differences in the effect of LVEF and the presence of CKD on each endpoint was evaluated using the full population and a multiplicative interaction term. In the same way, interaction between therapeutic strategy with ventricular dysfunction and CKD status on outcomes were investigated.

All tests were 2-tailed, and values of $P < .05$ were considered statistically significant. All statistical analyses were performed with the statistical package SPSS 21.0 (SPSS Inc, Chicago, IL).

3. Results

3.1. Characteristics of the patients and treatment assignments

From January 2009 and May 2010, 2160 patients with CAD were selected. Of these, 918 patients were included in the study. They were included sequentially, prospectively, and followed quarterly until May 2015. The vital status of all included patients was ascertained in May 2015. For patients still alive, the minimum length of follow-up was 5 years, and the maximum was 6 years (average 5.3 years). According to ventricular function and eGFR, 4 groups were selected (Fig. 1).

Of the 918 patients included in the study, 426 (46.4%) had preserved LVEF and 492 (53.6%) had ventricular dysfunction. Of those with preserved ventricular function, 303 had preserved glomerular filtration and 123 had CKD. Of those with ventricular dysfunction, 102 had preserved renal function and 390 CKD.

Baseline characteristics of patients with CKD and preserved renal function are depicted in Table 1. That is, patients were similar with respect to age, sex, employment status, past or present tobacco use, and hypertension. Severity of angina was similar in patients with preserved ventricular function, and heart failure was similar in patients with ventricular dysfunction. Patients were also similar in terms of proportional number of vessel disease and treatment previously received. All patients received optimal medical regimens per predefined guidelines.

3.2. Follow-up outcomes

The overall major adverse cardiac and cerebrovascular events at the 5-year follow-up per ventricular function are shown in Table 2. No patients from any study groups were lost to follow-up.

3.3. Event rates

The rates of major adverse cardiac events (MACE), namely the combined incidence of overall mortality, nonfatal MI, stroke, or refractory angina that required revascularization, were significantly different among patients in the groups in the 5-year follow-up. Among patients with preserved renal function (n = 405), we observed 73 events (18%), and among those with CKD (n = 513) we observed 108 events (21.1%) (log-rank $P < .001$; HR: 1.71 95%IC: 1.26–2.31; $P < .001$) (Fig. 2).

Analyzing patients with and without CKD among subjects with LVEF <50%, we found 84 events (21.5%) in CKD patients and 12 (11.8%) in those with preserved renal function (log-rank $P < .001$; HR: 3.06 95%IC 1.66–5.64, $P < .001$) (Fig. 3). Among

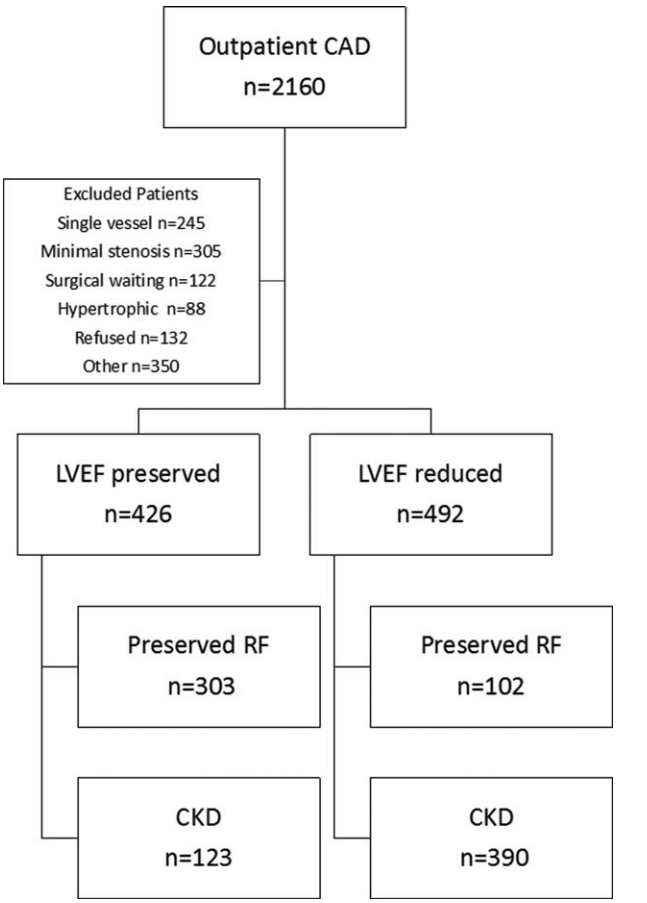

Figure 1. Flowchart with patient selection.

Table 1

Demographic, clinical, laboratory, and angiographic characteristics.

Patients	Preserved RF (n = 405)	CKD (n = 513)	*P value*
Demographic profile			
Age (years)	66 ± 9.7	67 ± 9.9	.008
Male (%)	62.5	76.2	<.001
Smokers or ex-smokers (%)	69.1	64.3	.13
Medical history %			
Previous infarction	66.6	81.5	<.001
Hypertension	65.7	79.6	<.001
DM	44.7	58.1	<.001
Laboratory (mg/dL)			
Creatinine clearance (mL/min)	79.7 ± 18	42.7 ± 12	<.001
Angiographic data (%)			
Multivessel disease	70.6	63.5	.16
Left artery disease	92.1	84.8	.001
Ejection fraction (average)	48 ± 12	34 ± 12	<.001

CKD = chronic kidney disease, DM = Diabetes mellitus, RF = renal function.

Table 2

Major adverse cardiac events at 5-year follow-up.

Patients (%)	LVEF <50% CKD	LVEF <50% Preserved RF	*P*	Preserved LVEF CKD	Preserved LVEF Preserved RF	*P*
MACE	84 (21.5)	12 (11.8)	<.001	24 (19.5)	61 (20.1)	.900
Overall Mortality	66 (16.9)	7 (6.9)	.001	7 (5.7)	15 (5)	.688

LVEF = left ventricular ejection fraction, MACE = major adverse cardiac events, RF = renal function.

patients with preserved LVEF, event rate was 19.5% and 20.1%, respectively, for subjects with CKD and preserved renal function (log-rank $P = .900$; HR: 1.03 95%IC: 0.64–1.65; $P = .901$) (Fig. 3). There was an effect modification by the presence of LVEF <50% ($P_{interaction} = .004$) (Fig. 4).

Regarding treatment strategies, among those with LVEF <50% event rates for patients assigned to PCI, CABG, and MT were 18.4%, 17.1%, and 24.6%, respectively ($P = .122$). In subjects with preserved LVEF event rates were 21.6% for those in PCI, 18.4% in CABG, and 20.4% in MT group ($P = .709$). Treatment strategy did not modify the effect of LVEF on MACE ($P_{interaction} = .191$). Among patients with CKD, event rates were 19.7%, 17.3%, and 27.5% for PCI, CABG, and MT, respectively ($P = .06$). In those with preserved renal function event rates were 19.8% for those in PCI, 18.1% in CABG, and 16.4% in MT group ($P = .876$). Treatment strategy did not modify the effect of CKD on MACE ($P_{interaction} = .134$).

3.4. Overall mortality

Among patients with preserved renal function, we observed 22 deaths (5.4%), and among those with CKD 73 deaths (14.2%) (log-rank $P < .001$; HR: 3.66 95%IC: 2.26–5.92; $P < .001$) (Fig. 2).

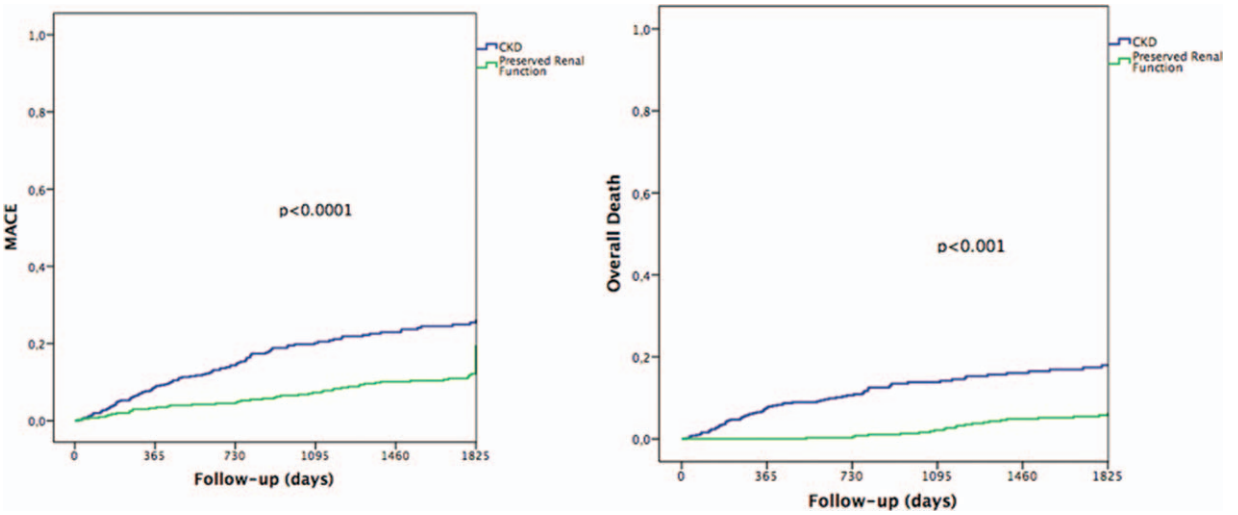

Figure 2. Kaplan–Meier with event and overall death rates of patients with preserved renal function and CKD.

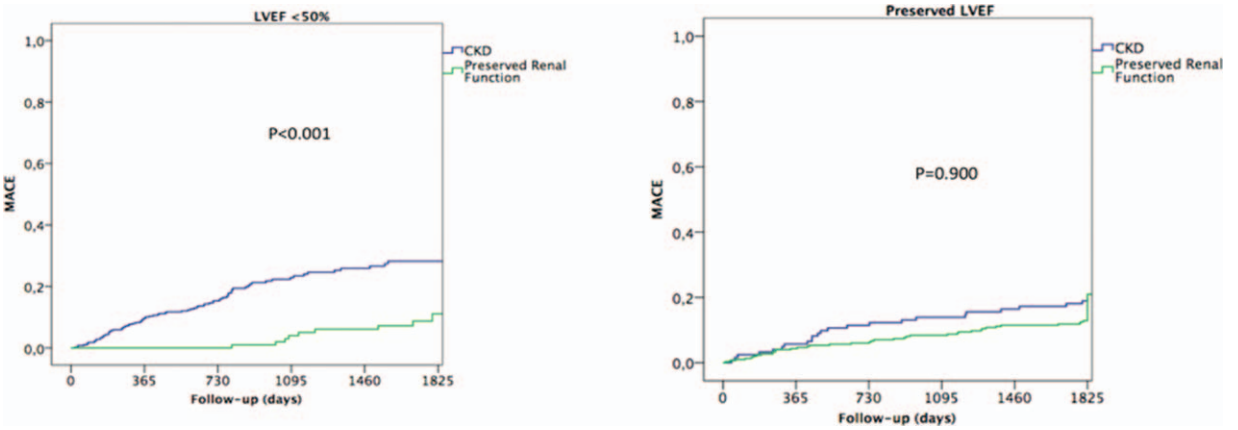

Figure 3. Kaplan–Meier with event rates of patients with preserved renal function and CKD in preserved and reduced LVEF groups.

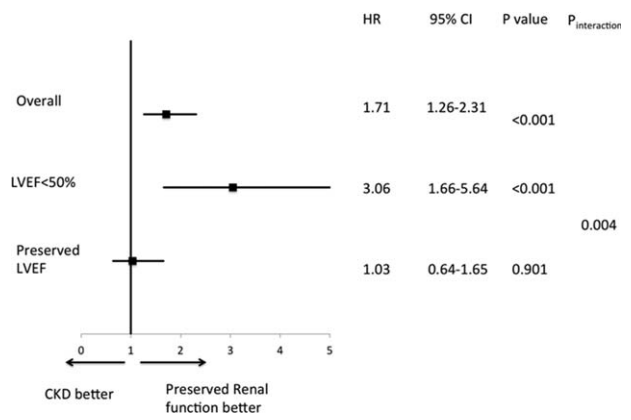

Figure 4. Cox-proportional hazards for MACE in preserved renal function versus CKD in specific subgroups.

In subjects with LVEF <50%, 66 deaths occurred (16.9%) in CKD patients and 7 (6.9%) in those with preserved renal function (log-rank $P=.001$; HR: 3.65 95%IC 1.66–8.02, $P=.001$) (Fig. 5). Among patients with preserved LVEF, the death rate was 5.7% and 5% for subjects with CKD and preserved renal function, respectively, (log-rank $P=.688$; HR: 1.20 95%IC: 0.49–12.94; $P=.688$) (Fig. 5). Once more, we found an effect modification by the presence of LVEF <50% ($P_{interaction}=.044$).

In relation to treatment strategies, among those with LVEF <50% death rates for PCI, CABG, and MT groups were 13.6%, 12.3%, and 20.1%, respectively ($P=.079$). In subjects with preserved LVEF death rates were 0.9% for those in PCI, 6.7% in CABG, and 5.2% in MT group ($P=.068$). Once again, treatment strategy did not modify the effect of LVEF on mortality ($P_{interaction}=.371$). Among patients with CKD, death rates were 11.8%, 12%, and 19.6% for PCI, CABG, and MT, respectively ($P=.078$). In patients with preserved renal function death rates were 2.7% for those in PCI, 7.2% in CABG, and 5.5% in MT group ($P=.307$). Here again, treatment strategy did not modify the effect of CKD on mortality ($p_{interaction}=.849$).

3.5. Multivariate analysis

A multivariate model was used to identify independent predictors of death in our cohort. Creatinine clearance remained an independent predictor of death (HR 0.97 95% IC 0.96–0.98, $P<.001$). In addition to creatinine clearance, covariates independently related to death were age, sex, DM, and LVEF (Table 3).

Table 3

Variables associated with death in a multivariable analysis.

Variable	HR	95% IC	P
Clearance (per each 1mL/min)	0.97	0.96–0.98	<.001
Age (per year)	1.03	1.01–1.06	<.001
Female sex	0.56	0.33–0.95	.033
Hypertension	0.78	0.44–1.39	.408
Diabetes	2.49	1.52–4.06	<.001
LVEF (per 1%)	0.018	0.002–0.158	<.001
CABG (vs OMT)	0.85	0.64–1.13	.172
Percutaneous coronary luminal (vs OMT)	0.79	0.57–1.10	.272

CABG = coronary artery bypass graft, LVEF = left ventricular ejection fraction.

4. Discussion

The results of the present study reveal that CKD is associated with a poorer prognosis compared with the prognosis in patients with preserved renal function with a significant interaction with ventricular function. Then, in the presence of left ventricular dysfunction, renal failure is related to the higher incidence of MACE and overall death, but among those with preserved left ventricular function, a difference in cardiac events was observed among patients with different renal function strata.

It is well known that left ventricular dysfunction, diabetes, and CKD are related to higher cardiac events in patients with CAD irrespective of the treatment used, whether interventional or medical treatment. We do not clearly understand how these factors interact with each other because most trials do not include patients together with these conditions, or report results with interaction of CKD and reduced LVEF in clinical events.

In a cohort of diabetic subjects with multivessel CAD from the MASS database,[8] comparison of treatment strategies in different strata of renal function found no difference in mortality rates among different levels of glomerular filtration levels in a 5-year follow-up. However, the presence of CKD was associated with higher mortality even in this specific population irrespective of treatment strategy. Different from our present analysis, this

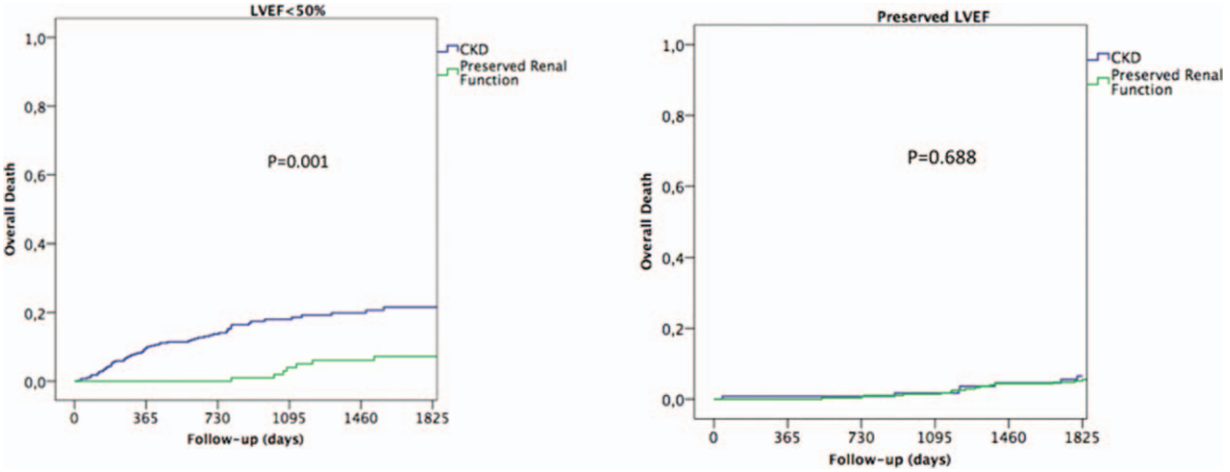

Figure 5. Kaplan–Meier with overall death rates of patients with preserved renal function and CKD in preserved and reduced LVEF groups.

cohort included only patients with preserved LVEF, which did not allow evaluation of the interaction between LVEF and renal function in that sample.

Baber et al[9] investigating the impact of CKD (defined as GFR <60 mL/min) among diabetic patients randomized to CABG or drug eluting stents (DES) in the FREEDOM trial found 5-year estimated mortality rates of 19% and 26.4% for CABG and PCI, respectively ($P = .40$) among patients with CKD. CKD was associated with higher rates of death and major adverse cardiac and cerebrovascular events compared with non-CKD subjects. Once more, CKD status did not influence the outcomes according to treatment used.

Results of the STICH Trial[10] in relation to ventricular dysfunction, regardless of the glomerular filtration rate, revealed an annual mortality rate of 8%, whereas in the clinical arm of the CASS Trial[11] mortality was 11%. The annual mortality in our study reached 10.5% in non-CKD and 18.4% in CKD patients with ventricular dysfunction. This result reveals the importance of glomerular filtration in the mortality of patients with ventricular dysfunction. The possible relationship between CKD and ischemic cardiomyopathy still needs to be proven. Recent studies have shown both abnormally high plasma levels of lipid peroxidation products such as malondialdehyde in CKD patients with CHF and a correlation of these levels with disease severity.[12,13] Additionally, levels of both atrial natriuretic peptide and brain natriuretic peptide correlate with left ventricular function and predict mortality in CKD patients as they do in the non-CKD CHF population.[14] In the non-CKD population, indices of myocyte apoptosis are increased in patients with CHF. Anemia and left ventricular (LV) systolic dysfunction are strongly related to CHF.[15] On the other hand, diabetes, often associated with heart disease and nephropathy, complicates the understanding of this intricate pathophysiological mechanism.

A recent study pointed out that these mechanisms are attributed to metabolic disturbances; myocardial fibrosis, such as increases in angiotensin II, IGF-inflammatory cytokines, and small vessel disease, for example microangiopathy, and endothelial dysfunction. Additionally, such mechanisms may play an important role in cardiac autonomic neuropathy and insulin resistance. These mechanisms can operate in association with or in isolation from to a greater or lesser extent, or even not interfere in the evolution of the disease.[16]

Thus, associated with diabetes, renal failure was a determining factor of worse prognosis in patients with ventricular dysfunction. In this scenario, the SOLVD–Study, which included only patients with ventricular dysfunction but without identifying diabetic patients, reported that there was a statistically significant interaction ($P = .022$) between predicted glomerular filtration rate and all-cause mortality. Thus, the lower level of the glomerular filtration rate was associated with higher all-cause mortality than expected from the sum of the individual effects.[17,18] Our study confirms the influence of renal function on the worse prognosis of patients with ventricular dysfunction. In addition, study results suggest that the association of lower glomerular filtration rate strongly interferes with the mortality of these patients. Thus, it remains to be seen whether CKD was the cause or effect of this worse prognosis.

4.1. Considerations about the study

The observational nature of this analysis was based on patients routinely followed at a cardiology outpatient clinic of a tertiary hospital. Thus, this sample included stable coronary patients who received different treatment modalities for CAD and were followed in long-term follow-up. This sample, therefore, represents the "real world" of patients under these conditions. Randomized studies, aimed at assessing the progression of ventricular dysfunction, and their respective aggravating factors, are necessary for a better understanding of the condition. However, randomization may face ethical obstacles. Observational studies can fill these methodological gaps and answer questions raised in specialized medical care.

5. Conclusion

This study found a higher risk of MACE and overall death related to CKD in the entire cohort. However, this deleterious effect was seen only among those with reduced LVEF and no deleterious effects of CKD in patients with CAD when ventricular function was preserved.

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