Impact of Chronic Kidney Disease on Long-Term Outcomes in Type 2 Diabetic Patients With Coronary Artery Disease on Surgical, Angioplasty, or Medical Treatment

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Background. **Coronary artery disease (CAD) among patients with diabetes and chronic kidney disease (CKD) is not well studied, and the best treatment for this condition is not established. Our aim was to compare three therapeutic strategies for CAD in diabetic patients stratified by renal function.**

Methods. **Patients with multivessel CAD that underwent coronary artery bypass graft (CABG), angioplasty (percutaneous coronary intervention [PCI]), or medical therapy alone (MT) were included. Data were analyzed according to glomerular filtration rate in three strata: normal (>90 mL/min), mild CKD (60 to 89 mL/min), and moderate CKD (30 to 59 mL/min). End points comprised overall rate of mortality, acute myocardial infarction, and need for additional revascularization.**

Results. **Among patients with normal renal function (n = 270), 122 underwent CABG, 72 PCI, and 76 MT; among patients with mild CKD (n = 367), 167 underwent CABG, 92 PCI, and 108 MT; and among patients with moderate CKD (n = 126), 46 underwent CABG, 40 PCI, and 40 MT. Event-free survival was 80.4%, 75.7%, 67.5% for strata 1, 2, and 3, respectively ($p = 0.037$). Survival rates among patients with no, mild, and moderate CKD are 91.1%, 89.6%, and 76.2%, respectively ($p = 0.001$) (hazard ratio 0.69; 95% confidence interval 0.51 to 0.95; $p = 0.024$ for stratum 1 versus 3). We found no differences for overall number of deaths or acute myocardial infarctions irrespective of strata. The need of new revascularization was different in all strata, favoring CABG ($p < 0.001$, $p < 0.001$, and $p = 0.029$ for no, mild, and moderate CKD, respectively).**

Conclusions. **Mortality rates were higher in patients with mild and moderate CKD. Higher event-free survival was observed in the CABG group among patients with no and mild CKD. Besides, CABG was associated with less need for new revascularization compared with PCI and MT in all renal function strata. This trial was registered at http://www.controlled-trials.com as ISRCTN66068876.**

(Ann Thorac Surg 2016;101:1735–44)

Chronic kidney disease (CKD) affects approximately 13% of the population in the United States [1]. The relation between CKD and coronary artery disease (CAD) is well known; approximately one-half of the deaths in patients with terminal CKD is because of cardiovascular disease. Most patient deaths are attributed to CAD, leading to sudden death and acute coronary syndromes [1, 2].

Higher rates of cardiovascular disease mortality can be observed even in the initial stages of CKD [3], and this rate of mortality increases according to the progression of renal disease [4]. Moreover, patients with CAD with CKD have a worse prognosis than patients without CKD, despite the treatment option chosen for CAD [5].

The National Health and Nutrition Examination Surveys found that patients with glomerular filtration rate (GFR) of 60 to 90 mL/min per 1.73 m^2 had higher rates of cardiovascular disease mortality than patients with normal GFR rates [6]. Similarly, the Atherosclerosis Risk in the Communities study found that, when considered as a continuous variable, a drop of 10 mL/min per 1.73 m^2 in GFR was responsible for a 5% to 6% incremental increase in cardiovascular risk of death [7].

Trials to compare different treatment strategies for CAD among patients with CKD are lacking. Most studies are registry-based [8] or subanalyses from randomized clinical trials, such as MASS (Medicine, Angioplasty, or

Accepted for publication Oct 12, 2015.

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Published by Elsevier

0003-4975/$36.00
http://dx.doi.org/10.1016/j.athoracsur.2015.10.036

Abbreviations and Acronyms

AMI	= acute myocardial infarction
APPROACH	= Alberta Provincial Project for Outcome Assessments in Coronary Heart Disease
BARI	= Bypass Angioplasty Revascularization Investigation
BMS	= bare metal stent
CABG	= coronary artery bypass graft
CAD	= coronary artery disease
CKD	= chronic kidney disease
CO	= confidence interval
DES	= drug eluting stent
DM	= diabetes mellitus
GFR	= glomerular filtration rate
HR	= hazard ratio
LVEF	= left ventricular ejection fraction
MASS	= Medicine, Angioplasty, or Surgery Study
MT	= medical treatment
PCI	= percutaneous coronary intervention

Surgery Study) II [5], BARI (Bypass Angioplasty Revascularization Investigation) [9], and ARTS (Arterial Revascularization Therapies Study) [10]. Results are conflicting, and there is no consensus for the best treatment option for CAD among the CKD population.

The prognosis can be worse when diabetes mellitus (DM) is associated with CAD and CKD. A substudy of the BARI trial observed a 7-year survival rate of 33% among patients with CKD and DM with CAD who underwent coronary artery bypass graft (CABG) or balloon angioplasty (percutaneous coronary intervention [PCI]) [9]. Note that this is a subset of patients with CAD with a poor prognosis, and prospective long-term studies that address the best treatment option for CAD in this population are lacking.

The objective of this study was to compare three different therapeutic strategies for multivessel CAD among diabetic patients stratified by renal function.

Material and Methods

Study Design and Definitions

This was a single center, prospective, registry-based study that enrolled patients from the MASS Group Database at the Heart Institute from the University of São Paulo. The MASS Registry comprises patients with CAD who were assessed by our study group after undergoing angiography and included before a decision about treatment and was an important part of the MASS II study design (MASS II registration number SRCTN66068876). For this specific study, patients with type 2 DM with multivessel CAD and normal ventricular function were allocated to one of the treatment options: CABG, PCI, or optimized medical therapy alone (MT) (Fig 1). Data were analyzed according to estimated GFR by the Cockcroft-Gault formula [11], leading to three strata: normal (creatinine clearance: >90 mL/min), mild CKD (60 to 89 mL/min), and moderate CKD (30 to 59 mL/min). Type 2 DM was defined as the presence of serum glucose concentration ≥126 mg/dL on at least two separate occasions. We also considered as diabetic those patients with a previous diagnosis and taking specific medication. Those criteria are the most accepted definition for DM by the most recent specific guidelines [12]. We defined patients with multivessel CAD as those with stenosis >70% on

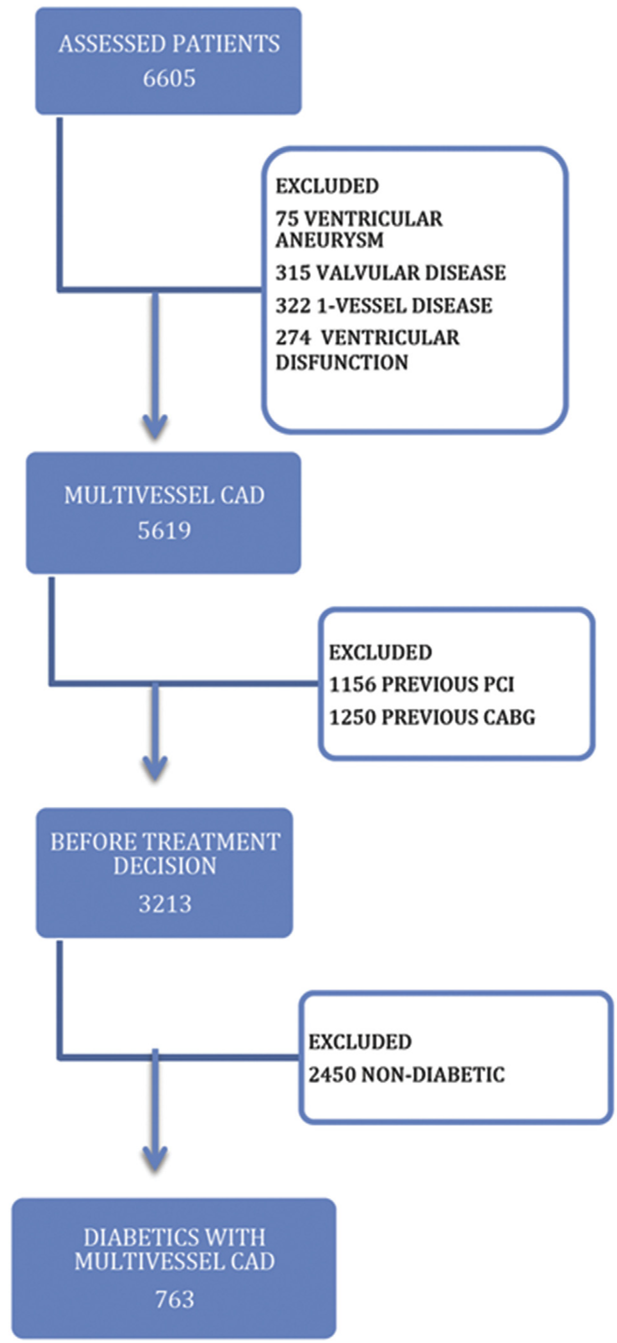


Fig 1. Study design. Flowchart showing selection of patients included in this study. (CABG = coronary artery bypass graft; CAD = coronary artery disease; PCI = percutaneous coronary intervention.)

angiography in at least two major coronary arteries or their major branches. Normal ventricular function was defined by left ventricular ejection fraction (LVEF) ≥0.50.

Treatment Protocol

Device choice included bare metal stents (BMSs) and drug-eluting stents (DESs). The interventional cardiologist was encouraged to treat all arteries that were likely to contribute to ischemia, had lesions with >70% diameter stenosis, or both. Angioplasty was performed according to a standard protocol that included administration of aspirin before the procedure. Patients treated with coronary stents were maintained on thienopiridines according to specific guidelines.

For patients assigned to undergo a surgical procedure, the cardiac surgeon was encouraged to intervene in all feasible stenosed arteries as an attempt to accomplish complete revascularization. Use of internal mammary conduits was strongly advised for all patients. CABG was executed with the use of standard surgical techniques, with the patient under hypothermic arrest, with the use of blood cardioplegia when the on-pump procedure was performed. Off-pump procedures were also used.

Medical treatment was performed to keep the patient free of symptoms. In addition, an attempt was made to reach goals over time for blood pressure and lipid and glucose concentrations, as recommended by specific guidelines.

Patients gave written informed consent and were included in this registry. The Ethics Committee of the Heart Institute of the University of São Paulo Medical School in São Paulo, Brazil, approved the study, and all procedures were performed in accordance with the Declaration of Helsinki.

Study End Points

End points considered were overall number of deaths, acute myocardial infarction (AMI), and need for revascularization as a combined end point, or the total number of each component isolated in the follow-up.

AMI was defined as the presence of pronounced new Q waves in at least two electrocardiographic leads or symptoms compatible with MI associated with creatine kinase-MB fraction concentrations that were more than three times the upper limit of the reference range.

Patients were followed with at least two office visits in a year.

Statistical Analysis

Event rates were estimated by 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 hazard analysis. Then, Cox proportional hazard survival analysis was performed to assess whether the associations of groups with all-cause mortality and other end points considered were independent of potential confounders.

Demographic and clinical variables and treatment applied were included in the analysis. Other variables were also tested for significance, including LVEF, metabolic profile, arterial pattern, smoking status, and renal function. Multivariable model was constructed to examine univariate Cox models, and variables that were at least marginally associated with the end point ($p < 0.20$) were included in a model in which stepwise selection was used for predictor selection at each step. Additional candidate variables were included into the model if there were significant treatment-by -predictor interactions ($p < 0.05$). Results are described as relative risks (hazard ratio [HR]) with 95% confidence intervals (CIs). Mean values of continuous variables were compared by one-way analysis of variance, followed by the Tukey multiple-comparisons test. The χ^2 test was used to compare qualitative variables in groups. The Fisher exact test was used for categorical variables. Wilcoxon scores were used for categorical variables with an ordinal scale. Discrete variables are expressed as counts and percentages. Tests were two-tailed, and values of p less than 0.05 were considered statistically significant. All statistical analyses were performed with the statistical package SPSS 21.0 (SPSS Inc, Chicago, IL).

Results

From May 1995 to October 2010 6,605 patients with CAD were screened, and 763 subjects with multivessel CAD and preserved ventricular function were included in this study (Fig 1).

Diabetic patients with CAD (n = 763) were followed for a mean time of 5.4 years and stratified according to GFR into three strata: 270 with normal function (122 underwent CABG, 76 MT, and 72 PCI), 367 with mild CKD (167 underwent CABG, 108 MT, and 92 PCI), and 126 with moderate CKD (46 underwent CABG, 40 MT, and 40 PCI).

Baseline Characteristics

Baseline characteristics were similar among groups, except for a higher percentage of three-vessel disease among patients in the CABG group in the normal and moderate CKD strata, and among patients in the normal stratum there were fewer smokers in the PCI group. In addition, patients with CKD were older than patients in the normal stratum (Table 1). Off-pump technique was more frequent among patients with no CKD ($p = 0.03$), and involvement of left anterior descending artery was more prevalent in the CABG group than the MT and PCI groups in patients with preserved renal function and mild CKD ($p < 0.001$).

Outcomes

COMBINED EVENTS. There were 53 occurrences of the combined end point in the preserved renal function stratum, 89 in the mild CKD stratum, and 41 in the moderate CKD stratum. Multivariate Cox regression analyses identified smoking status and treatment choice as predictors of combined events ($p < 0.01$ for both). Event-free survival was 80.4%, 75.7%, and 67.5%, respectively ($p = 0.037$) (HR 0.49, 95% CI: 0.27 to 0.88, $p = 0.018$ for preserved renal

Table 1. Baseline Characteristics of Subjects Who Underwent Medical Treatment, Percutaneous Coronary Intervention, or Coronary Bypass Surgery According to Renal Function

	No CKD (N = 270)			Mild CKD (N = 367)			Moderate CKD (N = 126)		
Characteristic	CABG (n = 122)	MT (n = 76)	PCI (n = 72)	CABG (n = 167)	MT (n = 108)	PCI (n = 92)	CABG (n = 46)	MT (n = 40)	PCI (n = 40)
Age,[a] years	56 ± 9	58 ± 9	58 ± 8	62 ± 7	63 ± 8	63 ± 8	67 ± 7	69 ± 6	68 ± 6
Male	69.7	76.3	59.7	67.1	66.7	60.9	65.2	60	52.5
Hypertension[b]	72.1	61.8	77.8	76	67.6	79.3	71.7	67.5	77.5
Smoker[c]	20.5	22.4	8.3	18	9.3	15.2	13	15	2.5
Clearance[a]	106 ± 18	110 ± 21	111 ± 19	77 ± 8	75 ± 8	76 ± 9	51 ± 6	48 ± 7	50 ± 7
TC, mg/dL	193 ± 49	192 ± 45	193 ± 49	198 ± 47	198 ± 43	196 ± 54	196 ± 53	187 ± 50	184 ± 46
HDL, mg/dL	41 ± 11	39 ± 9	39 ± 10	39 ± 10	42 ± 12	40 ± 10	39 ± 11	44 ± 13	37 ± 10
LDL, mg/dL	121 ± 43	118 ± 42	119 ± 40	123 ± 42	124 ± 40	118 ± 44	121 ± 47	115 ± 38	108 ± 40
TG, mg/dL	202 ± 189	184 ± 136	172 ± 93	181 ± 102	181 ± 97	238 ± 415	178 ± 71	162 ± 93	195 ± 86
Fasting glucose, g/dL	160 ± 66	173 ± 68	167 ± 66	162 ± 60	167 ± 63	164 ± 67	169 ± 65	153 ± 63	169 ± 56
A1c	7.7 ± 2.0	7.9 ± 2.0	7.9 ± 2.1	7.9 ± 2.0	8.1 ± 2.0	8.1 ± 1.9	7.7 ± 2.0	7.7 ± 1.6	7.8 ± 1.6
LVEF[d]	58 ± 14	56 ± 17	57 ± 16	63 ± 11	60 ± 13	59 ± 15	61 ± 14	56 ± 20	57 ± 17
Three-vessel disease[e]	78.7	64.5	45.8	71.9	64.8	58.7	87	60	60
LAD[f]	99.8	86.8	84.7	97.6	81.3	89.1	95.7	85	97.5
OPCAB[g]	31.1	NA	NA	28.1	NA	NA	17.4	NA	NA
LIMA	95.1	NA	NA	91.6	NA	NA	95.7	NA	NA
Patients with DES	NA	NA	48.6	NA	NA	43.4	NA	NA	52.5

[a] $p < 0.05$ for comparisons among the renal function strata. [b] $p = 0.04$ among groups in the no CKD stratum. [c] $p = 0.02$ for the normal versus the moderate CKD stratum and $P = 0.01$ among groups in the no CKD stratum. [d] $p < 0.05$ for the no CKD versus the mild CKD stratum. [e] $p < 0.01$ among groups in the no CKD stratum and $p = 0.02$ among groups in the moderate CKD stratum. [f] $p < 0.001$ among groups in the no CKD and mild CKD strata and $p = 0.05$ among groups in the moderate CKD stratum. [g] $p = 0.03$ for comparisons among the renal function strata.

Values are percentages or mean ± standard deviation.

A1c = glycated hemoglobin; CABG = coronary artery bypass graft surgery; CKD = chronic kidney disease; DES = drug-eluting stent; HDL = high-density lipoprotein; LAD = left anterior descending artery; LDL = low-density lipoprotein; LIMA = left internal mammary artery; LVEF = left ventricle ejection fraction; MT = medical treatment; NA = not applicable; OPCAB = off-pump coronary artery bypass; PCI = percutaneous coronary intervention; TC = total cholesterol; TG = triglycerides.

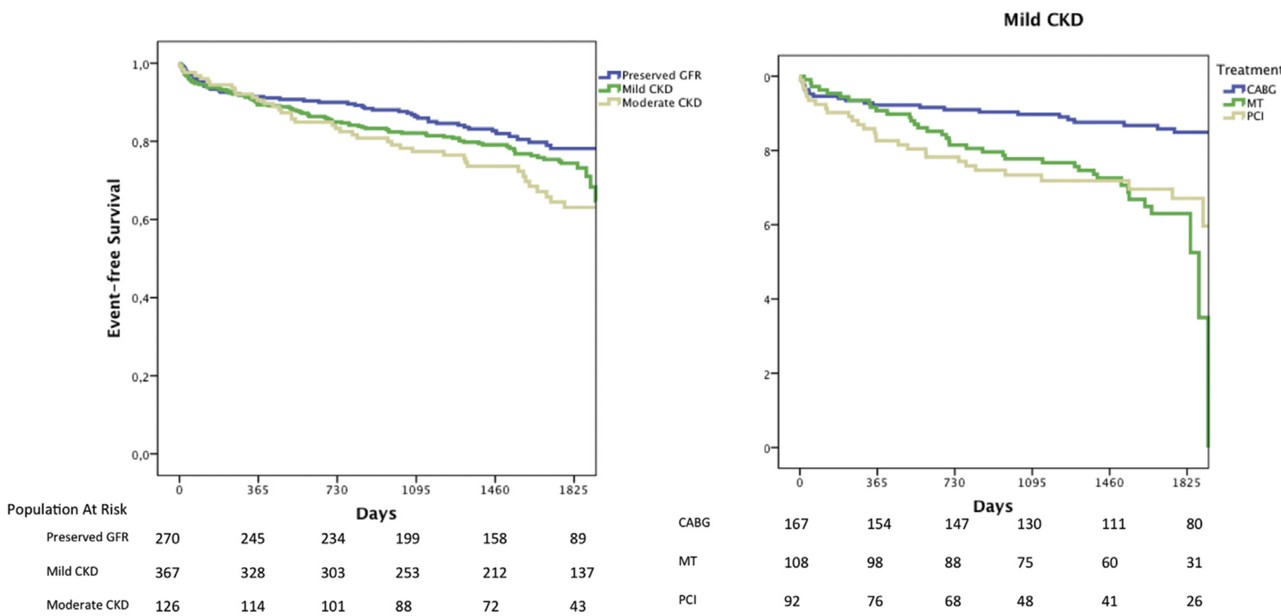


Fig 2. Event-free survival among patients according to CKD status and in the mild CKD stratum according to treatment. Kaplan-Meier curves of each CKD stratum for survival (left) and for each treatment strategy in the mild CKD stratum (right). (CKD = chronic kidney disease; GFR = glomerular filtration rate; MT = medical treatment; PCI = percutaneous coronary intervention.)

function versus moderate CKD; HR 0.63, 95% CI: 0.39 to 1.03, $p = 0.07$ for mild versus moderate CKD) (Fig 2).

Event rates are described in Table 2. By comparing treatment groups in each stratum of renal function, we observed that in the preserved renal function stratum event-free survival was 89.3% for the CABG group, 72.4% for the MT group, and 73.6% for the PCI group ($p = 0.004$) (HR 4.4, 95% CI: 1.51 to 12.8, $p = 0.006$; and HR 5.47, 95% CI: 2.07 to 14.44, $p = 0.01$ for PCI and MT compared with CABG, respectively). In the mild CKD stratum, event-free survival was 86.2% for the CABG group, 65.7% for the MT group, and 68.5% for the PCI group ($p < 0.001$) (HR 1.12, 95% CI: 0.29 to 4.32, $p = 0.86$; HR 2.55, 95% CI: 1.01 to 6.45, $p = 0.04$ for PCI and MT compared with CABG, respectively) (Fig 2; Table 3). No differences in event-free survival were observed among treatment groups in the moderate CKD stratum ($p = 0.117$).

By comparing different renal function strata in each therapeutic group, we observed a trend to higher incidence of combined events in the moderate CKD stratum in the CABG group. Event-free survival was 89.3%, 86.2%, and 76.1% for preserved renal function, mild CKD, and moderate CKD strata, respectively ($p = 0.08$) (HR 0.74, 95% CI: 0.36 to 1.51, $p = 0.41$ for mild versus moderate CKD; HR 0.20, 95% CI: 0.07 to 0.55, $p = 0.02$ for preserved renal function versus moderate CKD) (Table 4). We saw no difference among event-free survival of different renal function strata in the MT or PCI groups ($p = 0.591$ and $p = 0.528$, respectively).

DEATH. Survival rates were, respectively, 91.1%, 89.6%, and 76.2% ($p = 0.001$) for normal GFR, mild CKD, and moderate CKD. The risk of death decreased 0.69-fold (95% CI: 0.51 to 0.95, $p = 0.024$) and 0.8-fold (95% CI: 0.6 to 1.06, $p = 0.131$) in patients with no CKD and mild CKD, respectively, compared with moderate CKD (Fig 3). No difference was found in 30-day or 1-year mortality rates, but 3-year mortality rates were higher among patients with moderate CKD ($p = 0.01$) (Table 2).

Multivariate Cox regression analyses identified smoking and CKD status as predictors of death ($p = 0.01$ and $p = 0.007$ respectively).

We found no difference in rate of mortality when we compared treatment groups in each renal function stratum ($p = 0.152$ for preserved renal function stratum, $p = 0.288$ for mild CKD, and $p = 0.985$ for moderate CKD). Comparison of DESs with BMSs we found no difference for death (HR 0.87, 95% CI: 0.22 to 3.48, $p = 0.761$). However, comparison of renal function strata in the CABG group resulted in survival rates of 93.4%, 91%, and 78.3% for preserved function, mild CKD, and moderate CKD, respectively ($p = 0.005$) (HR 0.38, 95% CI: 0.13 to 1.07, $p = 0.06$ for preserved function versus moderate CKD; HR 0.42, 95% CI: 0.18 to 0.99, $p = 0.04$ for mild versus moderate CKD) (Fig 3). This difference was not significant when 30-day or 1-year mortality was considered but was significant at 3 years ($p = 0.54$, $p = 0.94$, and $p = 0.01$, respectively) (Table 2). No statistical difference was observed in survival rates of renal strata in the MT or PCI treatment groups ($p = 0.42$ and $p = 0.14$, respectively).

MYOCARDIAL INFARCTION. No differences for survival free of AMI were observed when different renal function strata, different treatments in each renal stratum, or different renal strata in each treatment group were compared.

NEW REVASCULARIZATION PROCEDURE. Survival free of additional revascularization was 90%, 88%, and 91.3%, respectively, for normal GRF, mild CKD, and moderate

Table 2. Event Rates Among Treatment Groups According to Renal Function Strata

Event	No CKD (N = 270)				Mild CKD (N = 367)				Moderate CKD (N = 126)			
	CABG (n = 122)	MT (n = 76)	PCI (n = 72)	Total	CABG (n = 167)	MT (n = 108)	PCI (n = 92)	Total	CABG (n = 46)	MT (n = 40)	PCI (n = 40)	Total
Combined events	13 (10.7)	21 (27.6)	19 (26.4)	53 (19.6)	23 (13.8)	37 (34.3)	29 (31.5)	89 (24.3)	11 (23.9)	14 (35)	16 (40)	41 (32.5)
Overall death	8 (6.6)	10 (13.2)	6 (8.3)	24 (8.9)	15 (9.0)	14 (13)	9 (9.8)	38 (10.4)	10 (21.7)	11 (27.5)	9 (22.5)	30 (23.8)
30-Day death	1 (0.8)	0 (0.0)	0 (0.0)	1 (0.4)	3 (1.8)	0 (0.0)	1 (1.1)	4 (1.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
1-Year death	4 (3.3)	0 (0.0)	1 (1.4)	5 (1.9)	6 (3.6)	2 (1.9)	5 (5.4)	13 (3.5)	2 (4.3)	0 (0.0)	3 (7.5)	5 (4.0)
3-Year death	7 (5.7)	2 (2.6)	3 (4.2)	12 (4.4)	9 (5.4)	10 (9.3)	7 (7.6)	26 (7.1)	8 (17.4)	2 (5.0)	6 (15.0)	16 (12.7)
AMI	4 (3.3)	5 (6.6)	6 (8.3)	15 (5.6)	8 (4.8)	7 (6.5)	5 (5.4)	20 (5.4)	3 (6.5)	4 (10)	5 (12.5)	12 (9.5)
Revascularization	2 (1.6)	12 (15.8)	13 (18.1)	27 (10)	4 (2.4)	22 (20.4)	18 (19.6)	44 (12)	0 (0.0)	5 (12.5)	6 (15)	11 (8.7)
Mean follow-up time, year	5.6	4.8	5.3	—	5.5	4.8	5.1	—	4.7	5.3	5.1	–

Values are no. (%).

AMI = acute myocardial infarction; CABG = coronary artery bypass graft surgery; CKD = chronic kidney disease; MT = medical treatment; PCI = percutaneous coronary intervention.

CKD ($p = 0.92$) (HR 1.33, 95% CI: 0.86 to 2.05, $p = 0.19$; HR 1.34, 95%CI: 0.86 to 2.08, $p = 0.19$ for normal and mild CKD versus moderate CKD, respectively). When treatments were compared, CABG had higher survival free of new revascularization procedure rates in all three renal function strata ($p < 0.001$ for preserved renal function, $p < 0.001$ for mild CKD, and $p = 0.029$ for moderate CKD) (Fig 4). By comparing specifically DESs with BMSs, we found no difference for new revascularization (HR 0.63, 95% CI: 0.29 to 1.35, $p = 0.210$). However, when compared specifically with DESs, CABG is superior in all renal function strata ($p = 0.04$, $p < 0.001$, $p = 0.001$ in no CKD, mild CKD, and moderate CKD, respectively). By comparing strata of renal function in each treatment group, we saw no statistical difference for this end point.

Multivariate Cox regression analyses identified treatment strategy, total cholesterol, and LVEF as predictors of revascularization procedure in follow-up ($p < 0.001$, $p = 0.004$, and $p = 0.03$, respectively).

Comment

Compared with normal and mild CKD, patients with moderate CKD had higher rates of mortality. This fact was reported by studies that found that mortality rates increase as the GFR decreases in the general population [6, 7]. Go and colleagues [13] in a large study of 1,120,295 and 6.3% subjects with CAD observed a higher mortality risk directly proportional to GFR decline. Note that these studies did not have a large proportion of patients with DM or CAD, so these results could not be extrapolated for this specific population. The present study confirms the negative impact of CKD even in a population with a known poor prognosis such as diabetic patients with CAD [14].

Other important data from the present study are the higher rates of combined events and mortality in the population with moderate CKD in the CABG group. CABG is the most invasive treatment for CAD, and renal function is one of the prognostic factors associated with adverse events in this population [15, 16]. A meta-analysis, including 44 trials related to cardiac and vascular surgical procedures, observed a higher risk of death in a short- and long-term follow-up in subjects with GFR <60 mL/min [16]. In addition, evidence indicates that GFR estimated by the Cockroft-Gault method is superior to the Modification of Diet in Renal Disease study equation in predicting adverse events in short- and long-term follow-up [17]. Risk scores for CABG already include GFR estimated by Cockroft Gault as a risk variable for adverse events [18].

However, by comparing different therapeutic strategies for CAD in each renal function stratum, we found no differences related to death or AMI, but lower rates of additional revascularization procedures that favored CABG despite CKD status. Previous studies have assessed this question in several ways, leading to different results. Most of these apparent conflicting results are because of differences in the population under study, mainly driven by diverse criteria for CKD (and so,

Table 3. Hazard Ratios Estimated With the Cox Proportional Hazards Regression Model for Different Treatment Modalities[a]

End points	HR	95% CI	*p* Value
Combined events			
Preserved GFR			
MT versus CABG	5.47	2.07–14.44	0.01
PCI versus CABG	4.40	1.51–12.8	0.006
Mild CKD			
MT versus CABG	2.55	1.01–6.45	0.04
PCI versus CABG	1.12	0.29–4.32	0.86
Moderate CKD			
MT versus CABG	1.00	0.46–2.42	0.99
PCI versus CABG	0.75	0.24–2.30	0.62
Death			
Preserved GFR			
MT versus CABG	2.43	0.92–6.30	0.71
PCI versus CABG	1.20	0.41–3.47	0.73
Mild CKD			
MT versus CABG	1.94	0.12–19.04	0.56
PCI versus CABG	1.34	0.14–12.82	0.79
Moderate CKD			
MT versus CABG	1.56	0.53–4.55	0.41
PCI versus CABG	0.51	0.12–2.11	0.35
AMI			
Preserved GFR			
MT versus CABG	2.09	0.55–7.9	0.27
PCI versus CABG	2.59	0.73–9.2	0.13
Mild CKD			
MT versus CABG	1.54	0.52–4.52	0.43
PCI versus CABG	1.26	0.40–3.92	0.68
Moderate CKD			
MT versus CABG	1.39	0.31–6.23	0.66
PCI versus CABG	2.15	0.51–9.09	0.29
New revascularization			
Preserved GFR			
MT versus CABG	9.76	2.10–45.36	0.004
PCI versus CABG	18.1	3.62–91.10	<0.001
Mild CKD			
MT versus CABG	5.04	1.58–16.08	0.006
PCI versus CABG	4.68	1.29–16.91	0.018
Moderate CKD			
MT versus CABG	7.20	0.71–72.2	0.09
PCI versus CABG	9.39	1.01–87.4	0.04

[a] Adjusted for age, left ventricle ejection fraction, three-vessel disease, high-density lipoprotein, smoker status, male sex, and hypertension.

AMI = acute myocardial infarction; CABG = coronary artery grafting; CKD = chronic kidney disease; CI = confidence interval; GFR = glomerular filtration rate; HR = hazard ratio; MT = medical treatment; PCI = percutaneous coronary intervention.

Table 4. Hazard Ratios Estimated From Cox Proportional Hazards Regression Model for Different Renal Function Strata in Each Treatment Group[a]

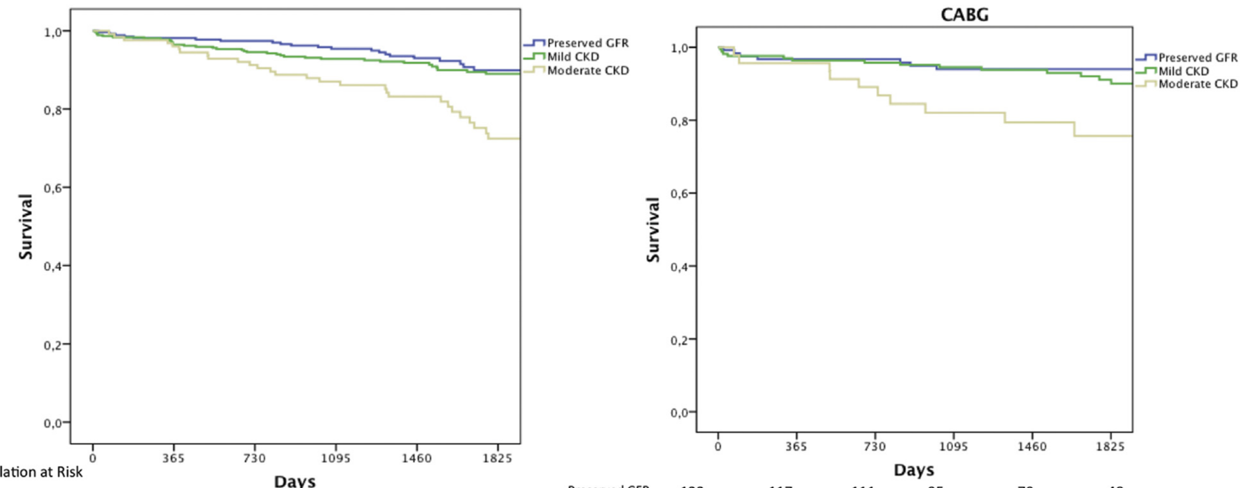
End points	HR	95% CI	*p* Value
Combined events			
CABG treatment			
Preserved GFR moderate CKD	0.20	0.07–0.55	0.02
Mild CKD versus moderate CKD	0.74	0.36–1.51	0.41
MT treatment			
Preserved GFR moderate CKD	1.25	0.49–3.20	0.63
Mild CKD versus moderate CKD	0.70	0.29–1.69	0.43
PCI treatment			
Preserved GFR moderate CKD	0.41	0.11–1.47	0.17
Mild CKD versus moderate CKD	0.44	0.14–1.38	1.16
Death			
CABG treatment			
Preserved GFR moderate CKD	0.38	0.13–1.07	0.06
Mild CKD versus moderate CKD	0.42	0.18–0.99	0.04
MT treatment			
Preserved GFR moderate CKD	1.12	0.41–3.05	0.81
Mild CKD versus moderate CKD	0.81	0.35–1.90	0.64
PCI treatment			
Preserved GFR moderate CKD	0.38	0.11–1.29	0.12
Mild CKD versus moderate CKD	0.15	0.17–1.33	0.73
AMI			
CABG treatment			
Preserved GFR moderate CKD	0.68	0.12–3.84	0.67
Mild CKD versus moderate CKD	0.96	0.19–4.76	0.96
MT treatment			
Preserved GFR moderate CKD	2.10	0.38–11.58	0.39
Mild CKD versus moderate CKD	0.95	0.16–5.56	0.95
PCI treatment			
Preserved GFR moderate CKD	0.51	0.10–2.61	0.42
Mild CKD versus moderate CKD	0.16	0.01–1.61	0.12
New revascularization			
CABG treatment			
Preserved GFR moderate CKD	1.95	0.03–111.95	0.74
Mild CKD versus moderate CKD	5.74	0.08–374.00	0.41
MT treatment			
Preserved GFR moderate CKD	4.20	0.78–23.45	0.09
Mild CKD versus moderate CKD	2.55	0.49–13.12	0.26
PCI treatment			
Preserved GFR moderate CKD	1.08	0.23–4.99	0.91
Mild CKD versus moderate CKD	1.03	0.20–4.01	0.96

[a] Adjusted for age, left ventricle ejection fraction, three-vessel disease, high-density lipoprotein, smoker status, male sex, and hypertension.

AMI = acute myocardial infarction; CABG = coronary artery bypass grafting; CI = confidence interval; CKD = chronic kidney disease; GFR = glomerular filtration rate; HR = hazard ratio; MT = medical treatment; PCI = percutaneous coronary intervention.

in CKD severity) and in treatment for CAD (most comparing two interventional procedures).

The APPROACH (Alberta Provincial Project for Outcome Assessments in Coronary Heart Disease) registry [19], comparing treatment strategies for CAD in different renal function status, found that CABG was associated with better survival than no revascularization in all categories of kidney function. Results are different from results in our study, because we observed no advantage in terms of reduction in mortality by comparing treatments across CKD strata. However, APPROACH registry included subjects with CAD irrespective of DM



Population at Risk

	0	365	730	1095	1460	1825
Preserved GFR	270	263	253	220	178	100
Mild CKD	367	355	338	287	246	166
Moderate CKD	126	122	111	98	87	49

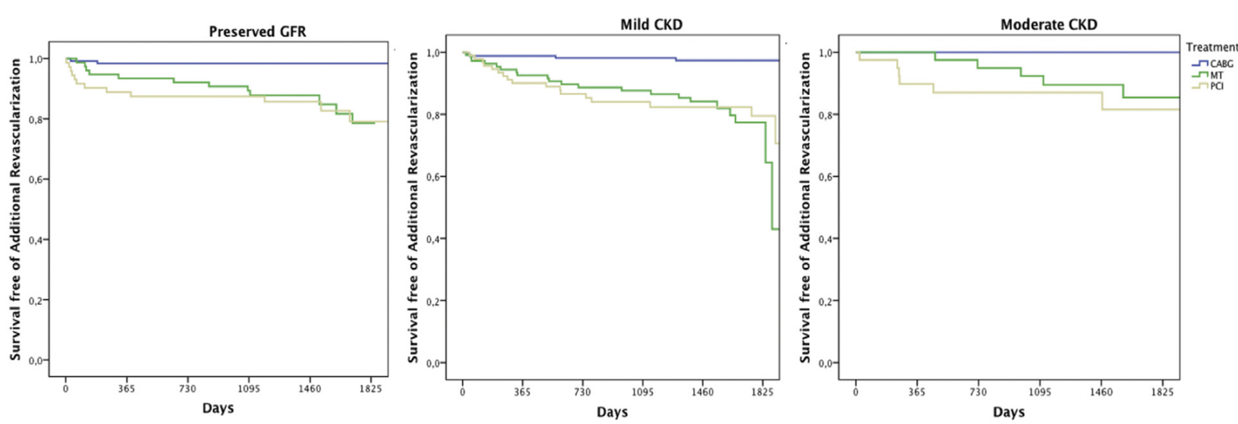
	0	365	730	1095	1460	1825
Preserved GFR	122	117	111	95	79	48
Mild CKD	167	161	155	137	118	86
Moderate CKD	46	44	39	34	27	18

Fig 3. Survival among patients according to CKD status. Kaplan-Meier curves of each CKD stratum for survival (left) and among patients in the CABG group according to renal function stratum (right). (CABG = coronary artery bypass graft; CKD = chronic kidney disease; GFR = glomerular filtration rate.)

status and a criterion for CKD that takes into account a single creatinine concentration and dialysis. Moreover, it included patients with left ventricle systolic dysfunction, and left main disease, which could explain the benefits of CABG.

Reddan and colleagues [8] performed a comparison of three therapeutic strategies for CAD in subjects with CKD staged by using the Cockcroft-Gault formula, ranging from normal to end-stage renal disease. Patients with cardiac-related heart failure, left main artery disease, and even single-vessel disease were included. CABG and PCI were associated with a survival benefit among patients with normal and mildly and moderately impaired renal function compared with MT alone. However, among patients with severe CKD, CABG was associated with a greater reduction in mortality than PCI and MT alone.

A previous publication that included patients randomly assigned from the MASS II trial observed that, in patients with mild CKD, CABG had a statistically higher percentage of event-free survival and lower percentage of mortality than did PCI or MT [5]. No differences among



Population at Risk

	Preserved GFR 0	365	730	1095	1460	1825	Mild CKD 0	365	730	1095	1460	1825	Moderate CKD 0	365	730	1095	1460	1825
CABG	122	117	111	95	79	48	167	157	150	133	114	83	46	44	39	34	27	18
MT	167	161	155	137	118	86	108	98	90	76	62	32	40	40	37	34	28	16
PCI	46	44	39	34	27	18	92	78	70	51	45	27	40	33	29	26	21	10

Fig 4. Survival free of additional revascularization in three different renal function strata according to treatment. Kaplan-Meier curves of each treatment strategy among patients with preserved renal function (left), mild CKD (center), and moderate CKD (right). (CABG = coronary artery bypass graft; CKD = chronic kidney disease; GFR = glomerular filtration rate; MT = medical treatment; PCI = percutaneous coronary intervention.)

treatments were seen in the normal renal function or moderate CKD strata. It is important to remember that diabetic and nondiabetic patients were evaluated in this subanalysis.

Wang and colleagues [20] found in patients with CKD with multivessel CAD that, compared with PCI with a DES, CABG had a similar incidence of death, AMI, or stroke, but it was associated with decreased repeat revascularization in the three-vessel population in a 2-year follow-up. In the same way, Ashrith and colleagues [21] did not find differences in mortality by comparing CABG and PCI with DESs in a population with CKD in a long-term follow-up. Results are closer to ours and reflect more contemporary practice, considering the choice of DESs in the PCI arm. However, it did not specifically address diabetic patients and had a shorter follow-up than the present study.

More recent published trials designed to compare treatment strategies for CAD in diabetic subjects, such as BARI-2D [22] and FREEDOM (Future Revascularization Evaluation in Patients With Diabetes Mellitus: Optimal Management of Multivessel Disease) trial [23], did not assess the effects of renal function on the performance of therapeutic strategies.

Our study is unique. First, only diabetic subjects were studied in a single-center study. Second, the design is a three-therapeutic arm design with an exclusive medical treatment arm. Finally, a study of a high range of GRF comprising at least two categories of CKD. To the best of our knowledge, no specific trial is designed to study different therapies for CAD in a diabetic population with CKD.

Clinical implications of this study include a recommendation to estimate creatinine clearance to establish prognosis among diabetic patients with CAD and to choose the therapeutic strategy, favoring CABG, to reduce adverse events.

Although this study describes the epidemiology and outcomes for patients with CAD, DM, and CKD, its conclusions should be interpreted in the setting of certain limitations. Indication bias may affect the results of any observational study because the indication for treatment may affect the outcomes. Scores of angiographic complexity, such as SYNTAX (Synergy Between PCI With Taxus and Cardiac Surgery) score, were not used in our population to guide interventional therapy. These results are not applicable to the entire population of patients with CAD, DM, and CKD considering different clinical settings related to these conditions, and therapeutic decisions must be individualized. Patients with terminal CKD or undergoing hemodialysis were not included in this study. Large prospective randomized trials designed to study the effect of renal function in the treatment of CAD among diabetic patients may be necessary.

In conclusion, among type 2 diabetic patients with CAD, mortality rates were progressively higher in patients with mild and moderate CKD. However, we observed higher event-free survival among patients in the CABG group in the preserved renal function and mild CKD strata. Besides, CABG was associated with less need for additional revascularization compared with PCI and MT in all renal function strata considered.

Funding was provided by a research grant from the Zerbini Foundation, São Paulo, Brazil. Medical writing support was provided by Ann Conti Morcos of MorcosMedia.

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Mark your calendar for the 53rd Annual Meeting of The Society of Thoracic Surgeons (STS) to be held at the George R. Brown Convention Center in Houston, Texas, January 21-25, 2017. The STS Annual Meeting offers you a chance to meet the experts, network with colleagues from around the world, and participate in a dynamic learning experience.

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An advance program with information about housing and registration will be mailed this fall to STS members and recent meeting attendees. Nonmembers may contact the Society to receive a copy of the printed advance program; however, detailed up-to-date meeting information will be available on the STS website at www.sts.org/annualmeeting.

We hope to see you in Houston.

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Secretary

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