Renal function and coronary bypass surgery in patients with ischemic heart failure

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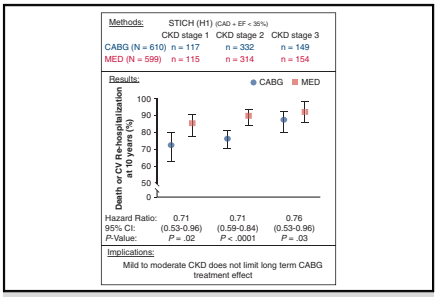
ABSTRACT

Objective: Chronic kidney disease is a known risk factor in cardiovascular disease, but its influence on treatment effect of bypass surgery remains unclear. We assessed the influence of chronic kidney disease on 10-year mortality and cardiovascular outcomes in patients with ischemic heart failure treated with medical therapy (medical treatment) with or without coronary artery bypass grafting.

Methods: We calculated the baseline estimated glomerular filtration rate (Chronic Kidney Disease Epidemiology Collaboration formula, chronic kidney disease stages 1-5) from 1209 patients randomized to medical treatment or coronary artery bypass grafting in the Surgical Treatment for IsChemic Heart failure trial and assessed its effect on outcome.

Results: In the overall Surgical Treatment for IsChemic Heart failure cohort, patients with chronic kidney disease stages 3 to 5 were older than those with stages 1 and 2 (66-71 years vs 54-59 years) and had more comorbidities. Multivariable modeling revealed an inverse association between estimated glomerular filtration rate and risk of death, cardiovascular death, or cardiovascular rehospitalization (all $P < .001$, but not for stroke, $P = .697$). Baseline characteristics of the 2 treatment arms were equal for each chronic kidney disease stage. There were significant improvements in death or cardiovascular rehospitalization with coronary artery bypass grafting (stage 1: hazard ratio, 0.71; confidence interval, 0.53-0.96, $P = .02$; stage 2: hazard ratio, 0.71; confidence interval, 0.59-0.84, $P < .0001$; stage 3: hazard ratio, 0.76; confidence interval, 0.53-0.96, $P = .03$). These data were inconclusive in stages 4 and 5 for insufficient patient numbers (N = 28). There was no significant interaction of estimated glomerular filtration rate with the treatment effect of coronary artery bypass grafting ($P = .25$ for death and $P = .54$ for death or cardiovascular rehospitalization).

Conclusions: Chronic kidney disease is an independent risk factor for mortality in patients with ischemic heart failure with or without coronary artery bypass grafting. However, mild to moderate chronic kidney disease does not appear to influence long-term treatment effects of coronary artery bypass grafting. (J Thorac Cardiovasc Surg 2020;■:1-9)



Death or CV rehospitalization at 10 years after randomization of STICH patients to CABG or medical treatment separated into the 3 CKD groups based on their eGFR. Note that CABG was superior to medical treatment in patients with mild to moderate CKD.

ADULT

CENTRAL MESSAGE

Mild to moderate CKD does not limit the survival advantage afforded by CABG in HF patients with reduced ejection fraction.

PERSPECTIVE

CKD is a risk factor in surgery, and patients with CKD may not be offered surgery. However, the CKD impact on CABG treatment effect has not been assessed. We demonstrate that in patients with HF amenable for bypass surgery, the life-prolonging effect of CABG is not affected by mild to moderate CKD.

See Commentary on page XXX.

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Abbreviations and Acronyms

CABG = coronary artery bypass grafting
CAD = coronary artery disease
CKD = chronic kidney disease
CV = cardiovascular
eGFR = estimated glomerular filtration rate
HF = heart failure
HR = hazard ratio
LVEF = left ventricular ejection fraction
NHLBI = National Heart, Lung, and Blood Institute
PCI = percutaneous coronary intervention
STICH = Surgical Treatment for Ischemic Heart failure

Scanning this QR code will take you to the article title page to access supplementary information.

Chronic kidney disease (CKD) is a known risk factor in cardiovascular (CV) disease.[1,2] Several investigations demonstrate an independent effect of chronically impaired renal function on mortality in patients with CAD and heart failure (HF). In almost all large investigations assessing risk factors for cardiac surgery, CKD is one of the key factors.[3-8] Thus, the question may arise whether the increased operative risk limits the potential benefits obtained from surgery.

In patients with coronary artery disease (CAD), coronary bypass grafting may be associated with an improvement in survival.[9,10] This survival effect is most visible in patients with severe CAD[9] and in patients with systolic HF. The latter was demonstrated by us with the primary outcome of the Surgical Treatment for Ischemic Heart Failure (STICH) trial.[11] In all of these investigations, CKD was associated with increased mortality. However, the direct impact of CKD on CABG's treatment effect was not assessed in these trials. Thus far, only limited information is available mainly based on retrospective database analyses applying propensity risk adjustments.[12-14] However, in real life, the presence of CKD already appears to be a predictor for not referring patients to CABG.[15]

We aimed to assess the influence of CKD on outcome in patients with ischemic HF included in the STICH trial treated with medical therapy (medical treatment) with or without CABG (Video 1).

VIDEO 1. Findings and implications of this article. Video available at: https://www.jtcvs.org/article/S0022-5223(20)30742-X/fulltext.

MATERIALS AND METHODS

Study Characteristics

STICH was a prospective, multicenter, randomized trial sponsored by the National Heart, Lung, and Blood Institute that enrolled 1212 individuals from 22 countries and 99 sites. STICH trial hypothesis 1 enrollment criteria, as well as the main results, have been published.[11,16] Briefly, patients with CAD and left ventricular ejection fraction (LVEF) 35% or less who were deemed suitable for surgical revascularization were randomized to CABG versus medical treatment alone and followed up for a median of 9.8 years after a protocol amendment to the initial planned 5 years follow-up. National Heart, Lung, and Blood Institute and Institutional Review Boards from each participant site approved the protocol before trial start. All patients provided written informed consent.

Patient Grouping by Chronic Kidney Disease Stage

We included 1209 STICH patients with preoperative creatinine information. We calculated baseline estimated glomerular filtration rate (eGFR, Chronic Kidney Disease Epidemiology Collaboration formula)

and classified patients by established CKD stages. Stage 1 with eGFR 90 mL/min or greater (n = 232), stage 2 with eGFR 60 to 89 mL/min (n = 646), stage 3 with eGFR 30 to 59 mL/min (n = 303), and stages 4 and 5 with eGFR less than 30 mL/min (n = 28) (Figure E1). Because the number of patients in the 2 treatment arms of CKD stages 4 and 5 were 12 and 16 and quickly fell below 10, we did not illustrate this group in Figures 1 to 5. The study was based on an intention-to-treat analysis. The crossover rate from medical treatment to CABG was low, with 10% in the first 12 months and was the same in both directions.[17]

Statistical Analysis

Baseline characteristics were summarized by eGFR stage. Categoric variables were reported as counts (percentages). Continuous variables were reported as median (25th and 75th percentiles). Baseline comparisons across eGFR stage were conducted using general linear model for continuous variables and Cochran–Mantel–Haenzsel for categoric variables. A Fine-Gray methodology[18] for end points with the competing risk of death, such as CV death or CV hospitalization, was used as non-CV death is considered as a competing risk for CV death (ie, non-CV death would prohibit the occurrence of CV death, event of interest). While assessing stroke, the competing risk of all-cause death was taken into account. Adjusted Cox proportional model was generated. For continuous variables, we examined the relationships between individual variable and major clinical outcomes using a flexible model-fitting approach involving restricted cubic spline functions. These functions were graphically and statistically examined to assess the linearity of the relationship with the log hazard ratio (HR). If this relationship is nonlinear, then shape will be characterized using a cubic-spline function.[19] eGFR was modeled with a cubic-spline function for CV hospitalization end point. For all other outcomes, eGFR was modeled in a linear fashion. The proportionality of the hazards in the Cox was checked and tested. The Kaplan–Meier time-to-event curves were used and presented. An interaction term of treatment and CKD stage was added to Cox model and tested using Wald statistic. In addition, we used the Andersen-Gill model with robust standard errors to account for correlated events within a patient[20] to analyze the association between eGFR and repeated CV rehospitalizations. All statistical analyses were performed using SAS version 9.4 (SAS Institute Inc, Cary, NC).

RESULTS

Table 1 shows the demographic data of the overall STICH cohort as well as separated by CKD stages. Of the 1209 patients, 610 were randomized to CABG and 599 to medical treatment. Patients in CKD stages 3 to 5 were older and had more comorbidities. Comparing CABG with medical treatment, there were no differences in the baseline characteristics between the 2 treatment arms for each CKD stage (Table E1). Table 2 shows the operative data of the patients who underwent bypass surgery. The majority of patients were operated using cardiopulmonary bypass (on-pump), and the number of grafts did not differ among CKD groups.

Figure 1 shows Kaplan–Meier estimates of all-cause mortality by CKD stage. Long-term mortality in CKD stage 3 was significantly higher compared with those in stages 1 and 2. It was worst in CKD stages 4 and 5 (data not shown for low patient numbers). Adjusted Cox regression model revealed an association between the risk of death and eGFR (HR, 0.94; 95% confidence interval [CI], 0.92-0.97, for each 5 mL/min increase in GFR; $P < .001$). The same was true for CV death and CV rehospitalization (both $P < .001$) and for repeated CV rehospitalizations

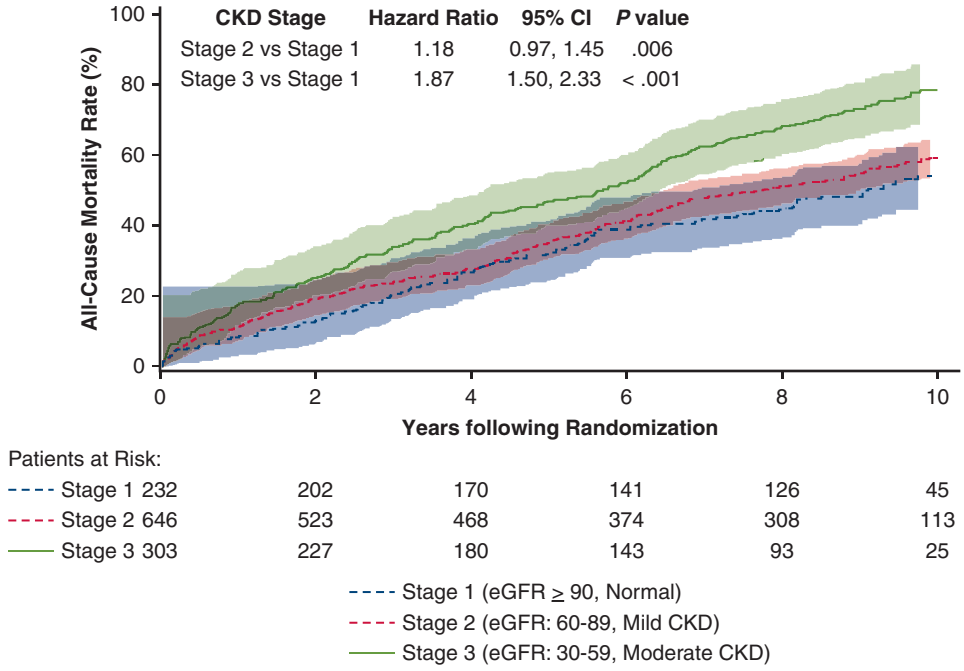
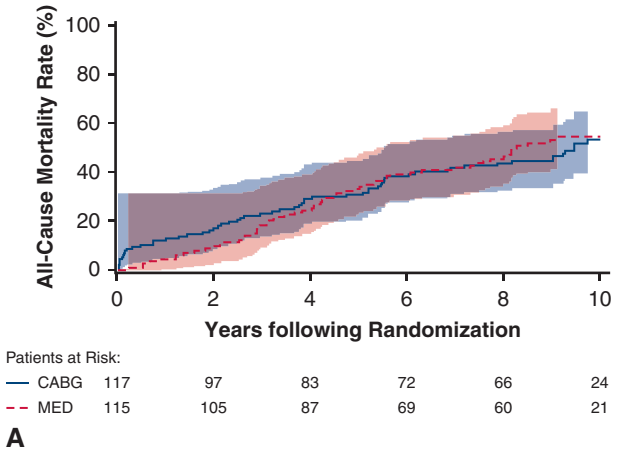


FIGURE 1. Kaplan–Meier all-cause mortality estimates of the entire STICH population (medical treatment and medical treatment + CABG) separated into CKD stages 1, 2, and 3. Statistical comparisons of the different CKD stages are shown with the number of patients at risk by CKD stage below. Note that the worse the renal function is, the higher is all-cause mortality. Patients in CKD stages 4 and 5 were omitted for low patient numbers (N = 28). *CKD*, Chronic kidney disease; *CI*, confidence interval; *eGFR*, estimated glomerular filtration rate.



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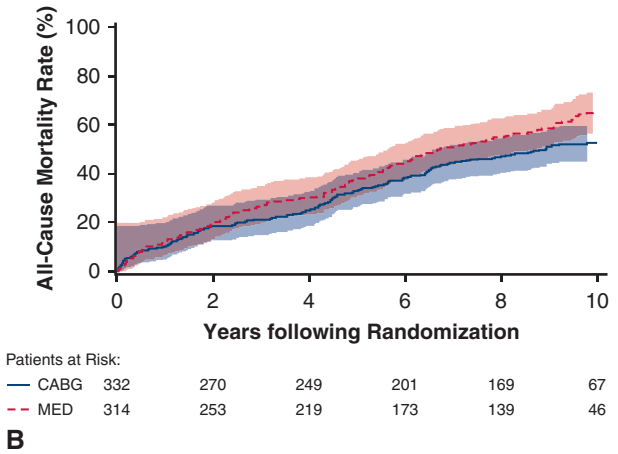

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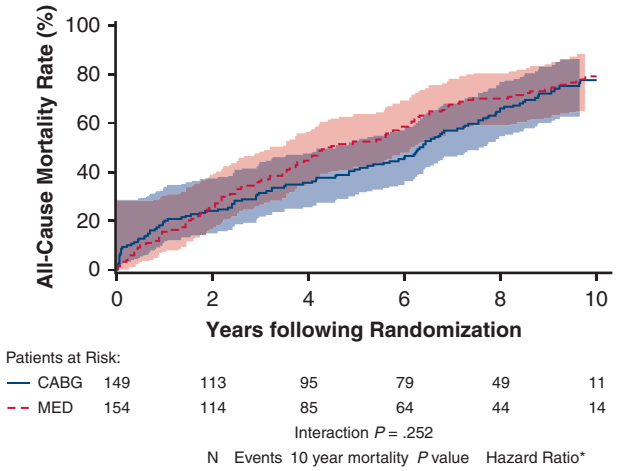
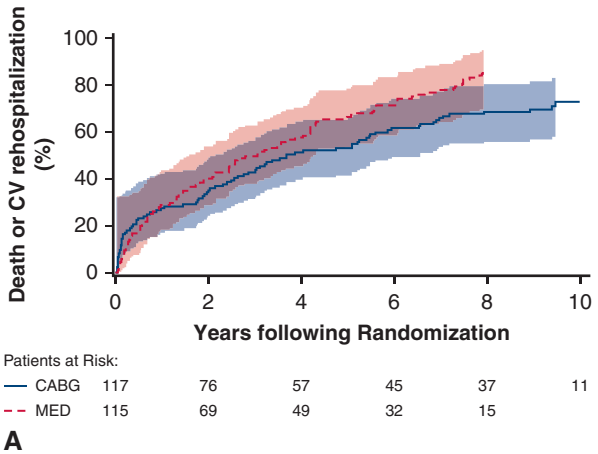


Interaction $P = .252$

	N	Events	10 year mortality rate	P value	Hazard Ratio*
eGFR ≥ 90	232	121	48.6	.72	0.94 (0.66, 1.34)
eGFR ≥ 60- < 90	646	378	50.8	.01	0.77 (0.63, 0.94)
eGFR ≥ 30- < 60	303	230	70.9	.37	0.89 (0.69, 1.15)

C

FIGURE 2. Kaplan–Meier all-cause estimates for all-cause mortality by treatment group separated into 3 panels with CKD stage 1 (A), CKD stage 2 (B), and CKD stage 3 (C). N values per group, number of events, and 10-year mortality rate. The statistics (*P* value and HRs) are univariate comparisons of CABG versus medical treatment for each group. *CABG*, Coronary artery bypass grafting; *MED*, medical treatment; *eGFR*, estimated glomerular filtration rate.



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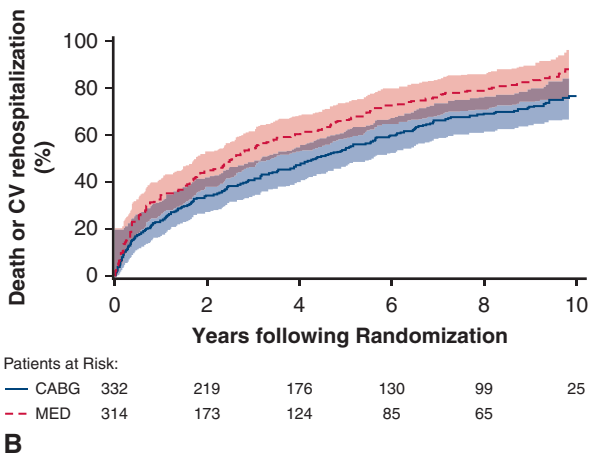

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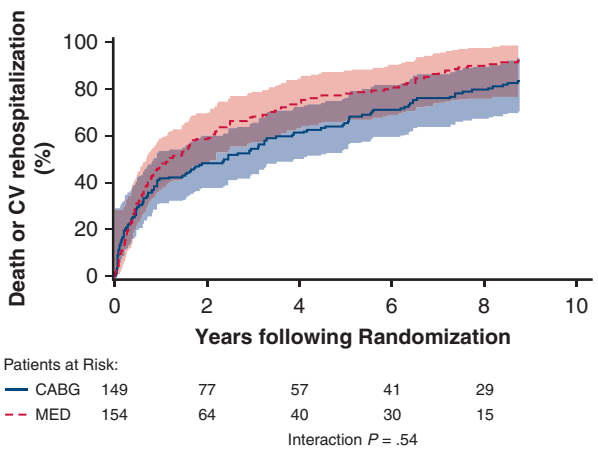

Interaction $P = .54$

	N	Events	10 year death/ CV hosp rate	P value	Hazard Ratio*
eGFR ≥ 90	232	183	77.4	.02	0.71 (0.53, 0.96)
eGFR ≥ 60- < 90	646	513	77.0	< .0001	0.71 (0.59, 0.84)
eGFR ≥ 30- < 60	303	268	88.3	.03	0.76 (0.53, 0.96)

C

FIGURE 3. Kaplan–Meier estimates for death or CV hospitalization by treatment group separated into 3 panels with CKD stage 1 (A), CKD stage 2 (B), and CKD stage 3 (C). N values per group, number of events, and 10-year mortality rate. The statistics (*P* value and HRs) are univariate comparisons of CABG versus medical treatment for each group. The graphs have been truncated once the number of patients at risk were below 10. *CV*, Cardiovascular; *CABG*, coronary artery bypass grafting; *MED*, medical treatment; *eGFR*, estimated glomerular filtration rate.

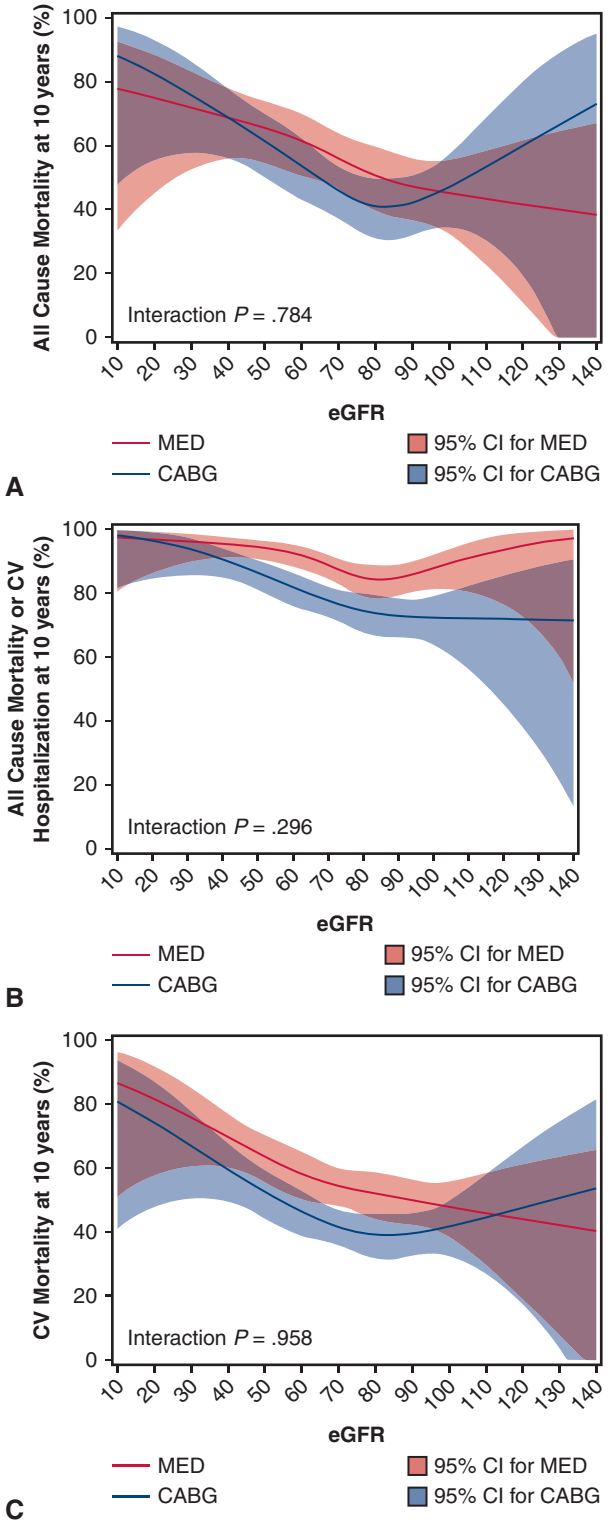

FIGURE 4. Spline curves illustrating the risk all cause death (A), death or CV hospitalization (B), and CV mortality (C) at 10 years for medical treatment and CABG + medical treatment as a function of patients' eGFR. Shaded areas illustrate the CIs. The interaction *P* value reports the association of eGFR and treatment interaction with respect to each end point of interest. Note that CABG was superior to medical treatment in all patients with an eGFR between 30 and 90 mL/min. The difference becomes larger if the combined end point of mortality plus CV rehospitalization or CV mortality was used. The lower and upper ends of the curves represent a few patients, which is reflected by the broader CI areas. *MED*, Medical treatment; *CABG*, coronary artery bypass grafting; *CI*, confidence interval; *eGFR*, estimated glomerular filtration rate; *CV*, cardiovascular.

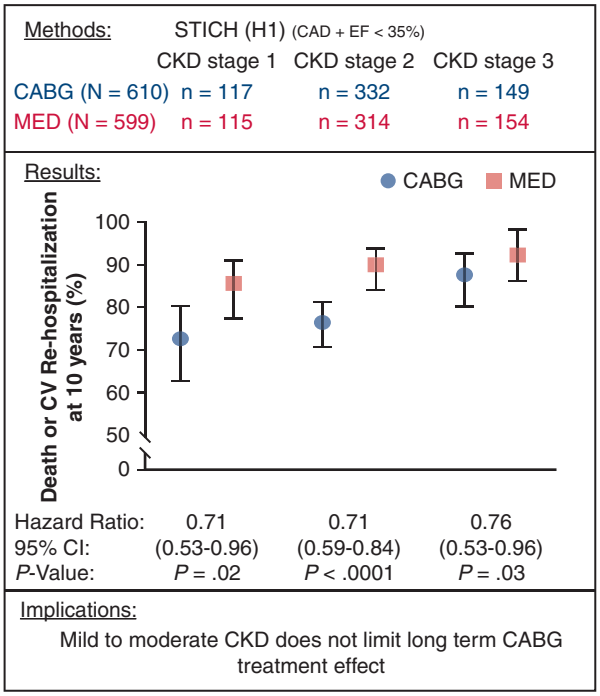

FIGURE 5. Death or cardiovascular rehospitalization at 10 years after randomization of STICH patients to CABG or medical treatment separated into the 3 CKD groups based on their eGFR. Note that CABG was superior to medical treatment in patients with mild to moderate CKD. *STICH*, Surgical Treatment of IsChemic Heart failure; *CAD*, coronary artery disease; *EF*, ejection fraction; *CABG*, coronary artery bypass grafting; *MED*, medical treatment; *CV*, cardiovascular; *CI*, confidence interval; *CKD*, chronic kidney disease.

($P < .001$) but not for stroke ($P = .169$). Creatinine alone also qualified as independent risk factor for mortality and for mortality and CV rehospitalization. Additional independent preoperative risk factors were age, gender, prior myocardial infarction, atrial fibrillation, moderate/severe mitral regurgitation, ejection fraction, body mass index, Canadian Cardiovascular Society angina class, and the number of diseased vessels.

The previously published primary outcome of the STICH trial demonstrated significant mortality reduction with CABG in the overall cohort (HR, 0.84; CI, 0.73-0.94, $P = .02$).[11] Figure 2 shows Kaplan–Meier estimates for all-cause mortality in this population in CKD groups 1, 2, and 3 comparing patients with only medical treatment (medical treatment) with those with additional bypass surgery (CABG). In CKD stages 2 and 3, there was a lower

TABLE 1. Baseline characteristics by estimated glomerular filtration rate groups for STICH Hypothesis I patients

Baseline characteristics	All patients (N = 1209)	Stage 1 (N = 232)	Stage 2 (N = 646)	Stage 3 (N = 303)	Stages 4 and 5 (N = 28)	*P* value
Randomized treatment						.5212
Medical treatment	599 (49.5%)	115 (49.6%)	314 (48.6%)	154 (50.8%)	16 (57.1%)	
CABG	610 (50.5%)	117 (50.4%)	332 (51.4%)	149 (49.2%)	12 (42.9%)	
Age (y)						<.0001
N	1209	232	646	303	28	
Median (25th, 75th)	59.7 (53.6, 67.2)	54.5 (50.0, 60.1)	58.9 (53.3, 66.2)	66.1 (58.7, 71.8)	70.7 (63.6, 75.2)	
Male	1061 (87.8%)	208 (89.7%)	575 (89.0%)	256 (84.5%)	22 (78.6%)	.0184
BMI						.0069
N	1209	232	646	303	28	
Median (25th, 75th)	26.8 (24.0, 29.8)	25.9 (23.1, 28.7)	26.9 (24.2, 30.1)	27.4 (24.3, 30.0)	25.3 (23.7, 28.9)	
Hypertension	727 (60.1%)	109 (47.0%)	401 (62.1%)	198 (65.3%)	19 (67.9%)	<.0001
Hyperlipidemia	729 (60.4%)	123 (53.0%)	394 (61.2%)	193 (63.7%)	19 (67.9%)	.0111
Diabetes	478 (39.5%)	97 (41.8%)	223 (34.5%)	138 (45.5%)	20 (71.4%)	.0124
Stroke	92 (7.6%)	14 (6.0%)	47 (7.3%)	26 (8.6%)	5 (17.9%)	.0647
Peripheral vascular disease	184 (15.2%)	31 (13.4%)	77 (11.9%)	70 (23.1%)	6 (21.4%)	.0005
Atrial fibrillation flutter	153 (12.7%)	19 (8.2%)	80 (12.4%)	50 (16.5%)	4 (14.3%)	.0062
Current angina class						.0078
0	442 (36.6%)	71 (30.6%)	233 (36.1%)	123 (40.6%)	15 (53.6%)	
I	185 (15.3%)	28 (12.1%)	102 (15.8%)	53 (17.5%)	2 (7.1%)	
II	524 (43.3%)	124 (53.4%)	271 (42.0%)	119 (39.3%)	10 (35.7%)	
III	48 (4.0%)	9 (3.9%)	31 (4.8%)	8 (2.6%)	0 (0.0%)	
IV	10 (0.8%)	0 (0.0%)	9 (1.4%)	0 (0.0%)	1 (3.6%)	
Current angina class ≥II	582 (75.9%)	133 (82.6%)	311 (75.3%)	127 (70.6%)	11 (84.6%)	.0319
Current NYHA						.0050
I	138 (11.4%)	27 (11.6%)	89 (13.8%)	20 (6.6%)	2 (7.1%)	
II	625 (51.7%)	130 (56.0%)	334 (51.7%)	148 (48.8%)	13 (46.4%)	
III	411 (34.0%)	71 (30.6%)	205 (31.7%)	123 (40.6%)	12 (42.9%)	
IV	35 (2.9%)	4 (1.7%)	18 (2.8%)	12 (4.0%)	1 (3.6%)	
LVEF (%)						.0325
N	1209	232	646	303	28	
Median (25th, 75th)	27.0 (21.8, 33.0)	28.0 (22.9, 35.0)	27.0 (21.1, 33.0)	26.1 (21.2, 33.8)	25.5 (21.3, 31.6)	
Moderate severe MR	219 (18.2%)	40 (17.2%)	113 (17.5%)	60 (19.9%)	6 (21.4%)	.3374
3 vessel/stenosis ≥75%	441 (36.5%)	79 (34.1%)	211 (32.7%)	138 (45.5%)	13 (46.4%)	.0014
Creatinine (mg/dL)						<.0001
N	1209	232	646	303	28	
Median (25th, 75th)	1.1 (0.9, 1.3)	0.8 (0.7, 0.9)	1.1 (1.0, 1.2)	1.4 (1.3, 1.6)	2.5 (2.2, 3.1)	
Hemoglobin (g/dL)						<.0001
N	1209	232	646	303	28	
Median (25th, 75th)	13.9 (12.7, 14.9)	13.9 (13.0, 15.1)	14.0 (12.8, 15.0)	13.6 (12.3, 14.5)	12.5 (11.8, 13.6)	
Mitral valve procedure	63 (12.4%)	13 (12.7%)	35 (12.8%)	13 (10.6%)	2 (22.2%)	.8732
Previous PCI	156 (12.9%)	33 (14.2%)	78 (12.1%)	41 (13.5%)	4 (14.3%)	.9634
Previous CABG	36 (3.0%)	6 (2.6%)	20 (3.1%)	9 (3.0%)	1 (3.6%)	.7759
No. of diseased vessels (75%)						.0047
0	25 (2.1%)	1 (0.4%)	17 (2.6%)	6 (2.0%)	1 (3.6%)	
1	282 (23.3%)	64 (27.6%)	154 (23.9%)	56 (18.5%)	8 (28.6%)	
2	460 (38.1%)	88 (37.9%)	263 (40.8%)	103 (34.0%)	6 (21.4%)	
3	441 (36.5%)	79 (34.1%)	211 (32.7%)	138 (45.5%)	13 (46.4%)	

(Continued)

TABLE 1. Continued

Baseline characteristics	All patients (N = 1209)	Stage 1 (N = 232)	Stage 2 (N = 646)	Stage 3 (N = 303)	Stages 4 and 5 (N = 28)	*P* value
Left main stenosis ≥50%	32 (2.6%)	2 (0.9%)	13 (2.0%)	15 (5.0%)	2 (7.1%)	.0007
Proximal LAD stenosis ≥75%	823 (68.1%)	168 (72.4%)	435 (67.4%)	207 (68.3%)	13 (46.4%)	.0666
Baseline ESVI (mL/m^2)						.4944
N	1112	219	596	277	20	
Median (25th, 75th)	77.7 (59.7, 99.9)	77.9 (57.4, 99.9)	79.0 (61.9, 100.8)	75.9 (58.2, 99.0)	73.5 (66.4, 89.0)	
Baseline EDVI (mL/m^2)						.2688
N	951	185	511	235	20	
Median (25th, 75th)	111.0 (89.5, 135.4)	113.2 (89.6, 138.3)	112.1 (89.2, 137.2)	108.3 (88.2, 134.1)	103.4 (93.3, 116.8)	
Baseline eGFR (mL/m^2)						<.0001
N	1209	232	646	303	28	
Median (25th, 75th)	71.6 (58.6, 85.8)	97.9 (94.0, 102.9)	73.7 (67.3, 81.1)	51.3 (44.1, 56.1)	24.8 (17.4, 28.4)	
On pump (CABG patients only)						.1126
No	116 (20.9%)	30 (27.5%)	60 (20.0%)	23 (16.9%)	3 (30.0%)	
Yes	439 (79.1%)	79 (72.5%)	240 (80.0%)	113 (83.1%)	7 (70.0%)	

Stage 1: eGFR ≥90 mL/min. Stage 2: eGFR 60 ≤90 mL/min. Stage 3: eGFR 30-<60 mL/min. Stage 4: eGFR <30 mL/min. *CABG*, Coronary artery bypass grafting; *BMI*, body mass index; *NYHA*, New York Association; *LVEF*, left ventricular ejection fraction; *MR*, mitral regurgitation; *PCI*, percutaneous coronary intervention; *LAD*, left anterior descending; *ESVI*, end-systolic volume index; *EDVI*, end-diastolic volume index; *eGFR*, estimated glomerular filtration rate.

TABLE 2. Operative data

Baseline characteristics	All patients (N = 610)	Stage 1 (N = 117)	Stage 2 (N = 332)	Stage 3 (N = 149)	Stages 4 and 5 (N = 12)	*P* value
No. of conduits						.2676
0	2 (0.4%)	0 (0.0%)	2 (0.7%)	0 (0.0%)	0 (0.0%)	
1	69 (12.4%)	13 (11.9%)	35 (11.6%)	17 (12.5%)	4 (40.0%)	
2	175 (31.4%)	29 (26.6%)	98 (32.5%)	45 (33.1%)	3 (30.0%)	
3	236 (42.4%)	47 (43.1%)	130 (43.0%)	57 (41.9%)	2 (20.0%)	
4	68 (12.2%)	19 (17.4%)	34 (11.3%)	14 (10.3%)	1 (10.0%)	
5	5 (0.9%)	1 (0.9%)	3 (1.0%)	1 (0.7%)	0 (0.0%)	
≥6	2 (0.4%)	0 (0.0%)	0 (0.0%)	2 (1.5%)	0 (0.0%)	
Total No. of distal anastomoses						.3898
0	9 (1.6%)	0 (0.0%)	6 (2.0%)	3 (2.2%)	0 (0.0%)	
1	63 (11.3%)	12 (11.0%)	31 (10.3%)	16 (11.8%)	4 (40.0%)	
2	128 (23.0%)	22 (20.2%)	75 (24.9%)	28 (20.6%)	3 (30.0%)	
3	221 (39.7%)	44 (40.4%)	116 (38.5%)	59 (43.4%)	2 (20.0%)	
4	98 (17.6%)	22 (20.2%)	53 (17.6%)	22 (16.2%)	1 (10.0%)	
5	32 (5.8%)	8 (7.3%)	19 (6.3%)	5 (3.7%)	0 (0.0%)	
≥6	5 (0.9%)	1 (0.9%)	1 (0.3%)	3 (2.2%)	0 (0.0%)	
Procedure on mitral valve performed	63 (12.4%)	13 (12.7%)	35 (12.8%)	13 (10.6%)	2 (22.2%)	.8732
Cardioplegia						.0780
None	151 (27.3%)	36 (33.3%)	79 (26.3%)	33 (24.4%)	3 (30.0%)	
Crystalloid	122 (22.1%)	27 (25.0%)	70 (23.3%)	24 (17.8%)	1 (10.0%)	
Blood	265 (47.9%)	42 (38.9%)	143 (47.7%)	74 (54.8%)	6 (60.0%)	
Both	15 (2.7%)	3 (2.8%)	8 (2.7%)	4 (3.0%)	0 (0.0%)	
Acuteness of operation						.0366
Elective	530 (95.3%)	105 (96.3%)	288 (95.7%)	129 (94.9%)	8 (80.0%)	
Urgent	21 (3.8%)	3 (2.8%)	12 (4.0%)	5 (3.7%)	1 (10.0%)	
Ongoing ischemia	3 (0.5%)	1 (0.9%)	1 (0.3%)	1 (0.7%)	0 (0.0%)	
Hemodynamic instability	2 (0.4%)	0 (0.0%)	0 (0.0%)	1 (0.7%)	1 (10.0%)	
On pump	439 (79.1%)	79 (72.5%)	240 (80.0%)	113 (83.1%)	7 (70.0%)	.1126

Stage 1: eGFR ≥90 mL/min. Stage 2: eGFR 60 ≤90 mL/min. Stage 3: eGFR 30-<60 mL/min. Stage 4: eGFR <30 mL/min.

mortality associated with CABG over time, with significant risk reduction in CKD stage 2 (ie, eGFR 60-89 mL/min, $P = .01$). In patients with eGFR above 90 or below 30 mL/min, this difference was not apparent, but patient numbers and event rates were lower. Interaction between treatment and CKD stages was tested using Wald statistic ($P = .252$), indicating that renal function does not appear to interfere with CABG's treatment effect on all-cause mortality.

Figure 3 shows Kaplan–Meier estimates for death or CV rehospitalization in the same way as Figure 2. In this combined end point, CABG outperforms medical treatment in all patients with an eGFR above 30 mL/min (ie, CKD stages 1, 2, and 3). Interaction testing ($P = .54$) again indicates that kidney function does not influence CABG's treatment effect on death or CV hospitalization. Further analyses assessing the influence of CKD stage on stroke and CV mortality also did not result in a significant interaction with P values of .872 (stroke) and .967 (CV mortality).

Figure 4 shows spline curves of the medical treatment and CABG groups for all-cause death at 10 years (Figure 4, *A*), all-cause death or CV hospitalization at 10 years (Figure 4, *B*), and CV mortality (Figure 4, *C*) as a function of eGFR. The curves graphically illustrate that patients with an eGFR above 30 mL/min derive an outcome advantage from CABG. The CABG curve exceeds the medical treatment curve for all-cause mortality at low and high eGFR values. This crossing is not apparent if the end point CV hospitalization is included and only happens at high eGFR rates for the CV mortality end point.

DISCUSSION

We demonstrate in this secondary analysis of the STICH Trial that CKD is an independent risk factor for mortality in patients with ischemic HF with or without CABG. However, mild to moderate CKD does not appear to influence the long-term treatment effect of CABG.

It is generally accepted that CKD is a risk for patients undergoing surgery.[3-8] However, it is not clear whether this increased risk potentially limits the treatment effect of CABG. The evidence for a survival advantage of patients with complex CAD is accumulating.[9,10,21] Thus, the role of CKD as risk factor is becoming more relevant. Thus far, all studies are based on databank analyses and propensity matching. For instance, Roberts and colleagues[13] report superior outcomes for CABG versus percutaneous coronary intervention (PCI) or medical therapy independently of eGFR. A large survival advantage for CABG was documented in diabetic patients with stable CAD.[22] Many of these patients had CKD and normal ejection fraction. The benefit of CABG does not seem to be limited to the presence of low ejection fraction or CKD. Yet, in real life, the presence of CKD appears to be an independent predictor of referral to PCI.[15] We report that mild to moderate CKD does not impair the treatment effect of CABG, an outcome that may be superior to PCI in many patients.[23]

The independence of the CABG treatment effect from CKD can especially be seen when examining the secondary end points death or CV hospitalization and CV mortality. Even for mortality, the Kaplan–Meier curves show a clear divergence in the groups with decent patient numbers (CKD stages 2 and 3). Thus, the results suggest that patients fulfilling the STICH inclusion criteria (primarily CAD amenable to CABG plus EF <35%) are well advised with a recommendation for CABG if the eGFR is above 30 mL/min. Adapting off-pump techniques for bypass surgery may further improve surgical outcomes in the presence of CKD.[24]

For patients with eGFR above 90 (CKD stage 1), the numbers are inconclusive. It is possible that kidney dysfunction is not measured appropriately by eGFR. CKD (specifically in diabetic patients) may be present despite high eGFR and is characterized by albuminuria,[5] which was not assessed in the STICH population. For patients with eGFR below 30 mL/min (CKD stages 4 and 5), the numbers are too low to draw any meaningful conclusions. Other studies provide information possibly filling the gap. In a large registry analysis comparing CABG with percutaneous intervention with modern drug-eluting stents, Bangalore and colleagues[12] demonstrate that CABG is superior to drug-eluting stents in preventing death even in patients on dialysis.[12] Roberts and colleagues[13] show (in the quoted PCI vs CABG comparison in more than 5000 patients from a database) that even in patients of CKD stages 4 and 5, CAGB appears superior to medical treatment and PCI. In general, it appears that one should not shy away from CABG if CKD is present.

Study Limitations

The study had limited patient numbers in the highest and lowest CKD stages. Although renal function was not part of the inclusion or exclusion criteria for the study, enrollment bias may have been responsible for the lower numbers of patients with advanced CKD. However, we still found significant variations of renal function in the enrolled patients. We provide strong evidence that mild to moderate CKD does not limit CABG's treatment effect. However, because the STICH trial was not powered for interaction testing and residual confounding cannot truly be excluded, the conclusions have to be taken with caution.

CONCLUSIONS

We demonstrate in this analysis of the STICH Trial that CKD is an independent risk factor for mortality in patients with ischemic HF with or without CABG. However, mild to moderate CKD does not appear to influence the long-term treatment effect of CABG in patients with systolic HF amenable for CABG (Figure 5).

Conflict of Interest Statement

Dr Velazquez received research grants (significant) from Novartis, Amgen, the National Heart, Lung, and Blood Institute, Pfizer, and Alnylam, and is a consultant/advisory board member (modest) for Novartis, Amgen, and Philips. Dr Rouleau reports personal fees from Duke Clinical Research Institute and consultation fees from Novartis and AstraZeneca. All other authors have nothing to disclose with regard to commercial support.

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This study complies with the Declaration of Helsinki, and locally appointed ethics committees have approved the research protocol. Informed consent has been obtained from patients. Study Protocol and CONSORT Diagram. The study protocol of the STICH trial including a CONSORT diagram has been published.[16]

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Key Words: coronary artery bypass grafting, CABG treatment effect, chronic kidney disease, medical therapy, survival

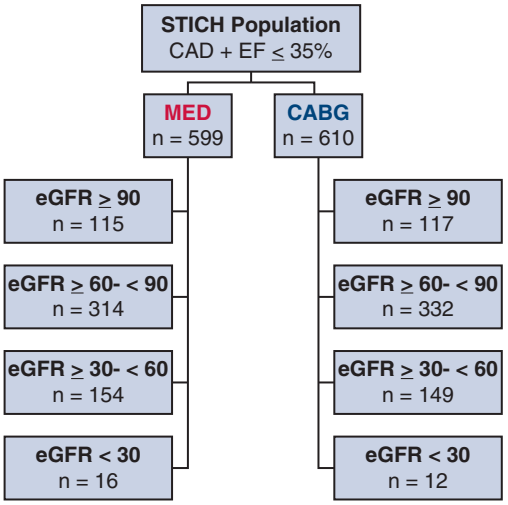

FIGURE E1. Flow chart of the Surgical Treatment for Ischemic Heart Failure (*STICH*) study population divided into estimated glomerular filtration rate (*eGFR*) groups.

TABLE E1. Baseline characteristics for coronary artery bypass grafting and medical treatment patients by chronic kidney disease stage

Baseline characteristics	Stage 1		Stage 2		Stage 3		Stage 4	
	Medical treatment (N = 115)	CABG (N = 117)	Medical treatment (N = 314)	CABG (N = 332)	Medical treatment (N = 154)	CABG (N = 149)	Medical treatment (N = 16)	CABG (N = 12)
Age (y)								
N	115	117	314	332	154	149	16	12
Median (25th, 75th)	53.9 (49.9, 60.1)	55.2 (50.1, 60.3)	57.6 (53.3, 65.6)	59.6 (53.2, 66.7)	65.8 (57.7, 71.0)	66.1 (60.0, 72.2)	67.3 (63.4, 73.5)	72.1 (68.6, 76.3)
Male	101 (87.8%)	107 (91.5%)	279 (88.9%)	296 (89.2%)	130 (84.4%)	126 (84.6%)	14 (87.5%)	8 (66.7%)
BMI								
N	115	117	314	332	154	149	16	12
Median (25th, 75th)	26.1 (23.5, 29.4)	25.6 (23.0, 28.3)	26.8 (23.9, 30.1)	27.3 (24.4, 30.2)	27.4 (24.7, 29.8)	27.3 (23.9, 30.5)	27.1 (23.8, 31.0)	24.5 (23.7, 26.3)
Hypertension	57 (49.6%)	52 (44.4%)	199 (63.4%)	202 (60.8%)	102 (66.2%)	96 (64.4%)	11 (68.8%)	8 (66.7%)
Hyperlipidemia	62 (53.9%)	61 (52.1%)	204 (65.2%)	190 (57.4%)	92 (59.7%)	101 (67.8%)	11 (68.8%)	8 (66.7%)
Diabetes	45 (39.1%)	52 (44.4%)	113 (36.0%)	110 (33.1%)	69 (44.8%)	69 (46.3%)	11 (68.8%)	9 (75.0%)
Stroke	6 (5.2%)	8 (6.8%)	23 (7.3%)	24 (7.2%)	10 (6.5%)	16 (10.7%)	2 (12.5%)	3 (25.0%)
Peripheral vascular disease	16 (13.9%)	15 (12.8%)	44 (14.0%)	33 (9.9%)	34 (22.1%)	36 (24.2%)	1 (6.3%)	5 (41.7%)
Atrial fibrillation flutter	9 (7.8%)	10 (8.5%)	40 (12.7%)	40 (12.0%)	26 (16.9%)	24 (16.1%)	2 (12.5%)	2 (16.7%)
Current angina class								
0	36 (31.3%)	35 (29.9%)	119 (37.9%)	114 (34.3%)	62 (40.3%)	61 (40.9%)	8 (50.0%)	7 (58.3%)
I	15 (13.0%)	13 (11.1%)	52 (16.6%)	50 (15.1%)	21 (13.6%)	32 (21.5%)	1 (6.3%)	1 (8.3%)
II	59 (51.3%)	65 (55.6%)	125 (39.8%)	146 (44.0%)	68 (44.2%)	51 (34.2%)	7 (43.8%)	3 (25.0%)
III	5 (4.3%)	4 (3.4%)	15 (4.8%)	16 (4.8%)	3 (1.9%)	5 (3.4%)		
IV			3 (1.0%)	6 (1.8%)			0 (0.0%)	1 (8.3%)
Current angina class ≥II	64 (81.0%)	69 (84.1%)	143 (73.3%)	168 (77.1%)	71 (77.2%)	56 (63.6%)	7 (87.5%)	4 (80.0%)
Current NYHA								
I	15 (13.0%)	12 (10.3%)	47 (15.0%)	42 (12.7%)	10 (6.5%)	10 (6.7%)	1 (6.3%)	1 (8.3%)
II	63 (54.8%)	67 (57.3%)	163 (51.9%)	171 (51.5%)	71 (46.1%)	77 (51.7%)	9 (56.3%)	4 (33.3%)
III	35 (30.4%)	36 (30.8%)	98 (31.2%)	107 (32.2%)	66 (42.9%)	57 (38.3%)	5 (31.3%)	7 (58.3%)
IV	2 (1.7%)	2 (1.7%)	6 (1.9%)	12 (3.6%)	7 (4.5%)	5 (3.4%)	1 (6.3%)	0 (0.0%)
LVEF (%)								
N	115	117	314	332	154	149	16	12
Median (25th, 75th)	28.0 (22.9, 35.0)	28.0 (22.8, 35.0)	28.0 (21.1, 33.0)	26.6 (21.2, 32.0)	26.9 (21.3, 34.0)	26.0 (21.2, 32.9)	27.0 (21.3, 33.2)	25.0 (20.3, 29.8)
Moderate Severe MR	20 (17.4%)	20 (17.1%)	54 (17.3%)	59 (17.8%)	37 (24.3%)	23 (15.4%)	4 (25.0%)	2 (16.7%)
3 vessel/stenosis ≥75%	38 (33.0%)	41 (35.0%)	100 (31.8%)	111 (33.5%)	69 (44.8%)	69 (46.3%)	6 (37.5%)	7 (58.3%)
Creatinine (mg/dL)								
N	115	117	314	332	154	149	16	12
Median (25th, 75th)	0.8 (0.7, 0.9)	0.8 (0.8, 0.9)	1.1 (1.0, 1.2)	1.1 (1.0, 1.2)	1.4 (1.3, 1.6)	1.4 (1.3, 1.6)	2.5 (2.3, 2.9)	2.4 (2.2, 5.5)

(Continued)

TABLE E1. Continued

Baseline characteristics	Stage 1		Stage 2		Stage 3		Stage 4	
	Medical treatment (N = 115)	CABG (N = 117)	Medical treatment (N = 314)	CABG (N = 332)	Medical treatment (N = 154)	CABG (N = 149)	Medical treatment (N = 16)	CABG (N = 12)
Hemoglobin (g/dL)								
N	115	117	314	332	154	149	16	12
Median (25th, 75th)	13.9 (13.0, 15.2)	13.9 (13.1, 15.0)	14.0 (12.9, 15.1)	14.0 (12.7, 15.0)	13.8 (12.4, 14.6)	13.5 (12.1, 14.5)	12.4 (11.7, 13.6)	12.5 (11.8, 13.8)
Mitral valve procedure	-	13 (12.7%)	-	35 (12.8%)	-	13 (10.6%)	-	2 (22.2%)
Previous PCI	16 (13.9%)	17 (14.5%)	35 (11.1%)	43 (13.0%)	21 (13.6%)	20 (13.4%)	2 (12.5%)	2 (16.7%)
Previous CABG	2 (1.7%)	4 (3.4%)	9 (2.9%)	11 (3.3%)	3 (1.9%)	6 (4.0%)	0 (0.0%)	1 (8.3%)
No. of diseased vessels (75%)								
0	0 (0.0%)	1 (0.9%)	6 (1.9%)	11 (3.3%)	6 (3.9%)	0 (0.0%)	1 (6.3%)	0 (0.0%)
1	35 (30.4%)	29 (24.8%)	79 (25.2%)	75 (22.7%)	27 (17.5%)	29 (19.5%)	5 (31.3%)	3 (25.0%)
2	42 (36.5%)	46 (39.3%)	129 (41.1%)	134 (40.5%)	52 (33.8%)	51 (34.2%)	4 (25.0%)	2 (16.7%)
3	38 (33.0%)	41 (35.0%)	100 (31.8%)	111 (33.5%)	69 (44.8%)	69 (46.3%)	6 (37.5%)	7 (58.3%)
Left main stenosis ≥50%	1 (0.9%)	1 (0.9%)	5 (1.6%)	8 (2.4%)	7 (4.5%)	8 (5.4%)	1 (6.3%)	1 (8.3%)
Proximal LAD stenosis ≥75%	82 (71.3%)	86 (73.5%)	224 (71.3%)	211 (63.7%)	100 (64.9%)	107 (71.8%)	6 (37.5%)	7 (58.3%)
Baseline ESVI (mL/m^2)								
N	108	111	284	312	144	133	14	6
Median (25th, 75th)	75.2 (56.8, 99.6)	78.0 (57.6, 100.0)	78.4 (61.7, 105.0)	80.1 (62.2, 98.1)	77.7 (54.4, 98.3)	72.9 (60.7, 100.9)	74.8 (65.5, 82.9)	70.9 (67.4, 110.0)
Baseline EDVI (mL/m^2)								
N	90	95	242	269	124	111	14	6
Median (25th, 75th)	113.3 (92.7, 135.3)	111.9 (87.6, 139.0)	113.3 (90.6, 141.8)	110.6 (87.4, 131.6)	109.1 (85.3, 132.4)	106.6 (90.2, 139.1)	105.3 (93.9, 114.3)	98.4 (92.8, 127.3)
Baseline eGFR (mL/m^2)								
N	115	117	314	332	154	149	16	12
Median (25th, 75th)	98.5 (93.9, 102.9)	97.8 (94.0, 102.9)	74.0 (67.5, 81.6)	73.0 (67.0, 80.5)	52.1 (44.3, 56.4)	50.5 (43.7, 55.1)	25.5 (19.1, 28.5)	24.8 (8.6, 28.3)
On-pump (CABG patients only)								
No	-	30 (27.5%)	-	60 (20.0%)	-	23 (16.9%)	-	3 (30.0%)
Yes	-	79 (72.5%)	-	240 (80.0%)	-	113 (83.1%)	-	7 (70.0%)

Stage 1: eGFR ≥90 mL/min. Stage 2: eGFR 60 ≤90 mL/min. Stage 3: eGFR 30-<60 mL/min. Stage 4: eGFR <30 mL/min. *CABG*, Coronary artery bypass grafting; *BMI*, body mass index; *NYHA*, New York Association; *LVEF*, left ventricular ejection fraction; *MR*, mitral regurgitation; *PCI*, percutaneous coronary intervention; *LAD*, left anterior descending; *ESVI*, end-systolic volume index; *EDVI*, end-diastolic volume index; *eGFR*, estimated glomerular filtration rate.

000 Renal function and coronary bypass surgery in patients with ischemic heart failure

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Mild to moderate CKD does not limit the survival advantage afforded by CABG in HF patients with reduced ejection fraction.