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Left Main Revascularization With PCI or CABG in Patients With Chronic Kidney Disease

EXCEL Trial

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ABSTRACT

BACKGROUND The optimal revascularization strategy for patients with left main coronary artery disease (LMCAD) and chronic kidney disease (CKD) remains unclear.

OBJECTIVES This study investigated the comparative effectiveness of percutaneous coronary intervention (PCI) versus coronary artery bypass graft (CABG) surgery in patients with LMCAD and low or intermediate anatomical complexity according to baseline renal function from the multicenter randomized EXCEL (Evaluation of XIENCE Versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization) trial.

METHODS CKD was defined as an estimated glomerular filtration rate <60 ml/min/1.73 m^2 using the CKD Epidemiology Collaboration equation. Acute renal failure (ARF) was defined as a serum creatinine increase ≥ 5.0 mg/dl from baseline or a new requirement for dialysis. The primary composite endpoint was the composite of death, myocardial infarction (MI), or stroke at 3-year follow-up.

RESULTS CKD was present in 361 of 1,869 randomized patients (19.3%) in whom baseline estimated glomerular filtration rate was available. Patients with CKD had higher 3-year rates of the primary endpoint compared with those without CKD (20.8% vs. 13.5%; hazard ratio [HR]: 1.60; 95% confidence interval [CI]: 1.22 to 2.09; $p = 0.0005$). ARF within 30 days occurred more commonly in patients with compared with those without CKD (5.0% vs. 0.8%; $p < 0.0001$), and was strongly associated with the 3-year risk of death, stroke, or MI (50.7% vs. 14.4%; HR: 4.59; 95% CI: 2.73 to 7.73; $p < 0.0001$). ARF occurred less commonly after revascularization with PCI compared with CABG both in patients with CKD (2.3% vs. 7.7%; HR: 0.28; 95% CI: 0.09 to 0.87) and in those without CKD (0.3% vs. 1.3%; HR: 0.20; 95% CI: 0.04 to 0.90; $p_{interaction} = 0.71$). There were no significant differences in the rates of the primary composite endpoint after PCI and CABG in patients with CKD (23.4% vs. 18.1%; HR: 1.25; 95% CI: 0.79 to 1.98) and without CKD (13.4% vs. 13.5%; HR: 0.97; 95% CI: 0.73 to 1.27; $p_{interaction} = 0.38$).

CONCLUSIONS Patients with CKD undergoing revascularization for LMCAD in the EXCEL trial had increased rates of ARF and reduced event-free survival. ARF occurred less frequently after PCI compared with CABG. There were no significant differences between PCI and CABG in terms of death, stroke, or MI at 3 years in patients with and without CKD. (EXCEL Clinical Trial [EXCEL]; NCT01205776) (J Am Coll Cardiol 2018;72:754–65)

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Chronic kidney disease (CKD) is an increasingly prevalent condition and is strongly associated with increased cardiovascular morbidity and mortality (1). Renal dysfunction is associated with systemic inflammation, endothelial dysfunction, accelerated atherosclerosis, and enhanced thrombogenicity, which together heighten the risk for cardiovascular and cerebrovascular ischemic events (1–4). CKD is associated with a poor prognosis after coronary artery bypass graft surgery (CABG), due in part to the risk of acute renal failure (ARF) as well as associated comorbidities (2–4). However, the risk of ARF from contrast media, atheroemboli, and other mechanisms is also increased in

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patients with CKD undergoing percutaneous coronary intervention (PCI) (5,6). These risks likely explain why patients with coronary artery disease (CAD) and CKD are less likely to undergo revascularization than those with normal renal function (2–4), despite observational studies suggesting a survival benefit after PCI and CABG in patients with multivessel disease and CKD (4). Few data comparing PCI and CABG in patients with CKD from prospective randomized trials are available to guide clinical decision making in this high-risk group (7–11). We therefore examined the outcomes of patients with left main coronary artery disease (LMCAD) with and without CKD randomized to PCI with everolimus eluting-stents (EES) versus CABG in the EXCEL (Evaluation of XIENCE Versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization) trial (12).

METHODS

STUDY DESIGN. The EXCEL trial design and principal results have been previously reported (12,13). In brief, EXCEL was an international, open-label, multicenter randomized trial that compared PCI using cobalt-chromium fluoropolymer-based EES (Xience, Abbott Vascular, Santa Clara, California) versus CABG in patients with LMCAD. Inclusion criteria were left main (LM) diameter stenosis ≥70%, as estimated visually, or stenosis of 50% to <70% if hemodynamically significant by noninvasive or invasive testing, plus low or intermediate anatomical complexity of CAD as defined by a site-determined SYNTAX (Synergy between PCI with Taxus and Cardiac Surgery) score ≤32. Consensus among the members of the heart team for revascularization with either PCI or CABG was required. Clinical follow-up was performed at 1 month, 6 months, and 1 year, and then annually through 5 years. At the time of the current analysis, all patients have completed 3 years of follow-up. The investigation was approved by the ethics committee or institutional review board at each center, and all patients signed informed consent.

The primary endpoint was the composite of death from any cause, stroke, or myocardial infarction

ABBREVIATIONS AND ACRONYMS

ARF = acute renal failure

CABG = coronary artery bypass graft

CKD = chronic kidney disease

EES = everolimus-eluting stent(s)

eGFR = estimated glomerular filtration rate

LMCAD = left main coronary artery disease

MDRD = Modification of Diet in Renal Disease

PCI = percutaneous coronary intervention

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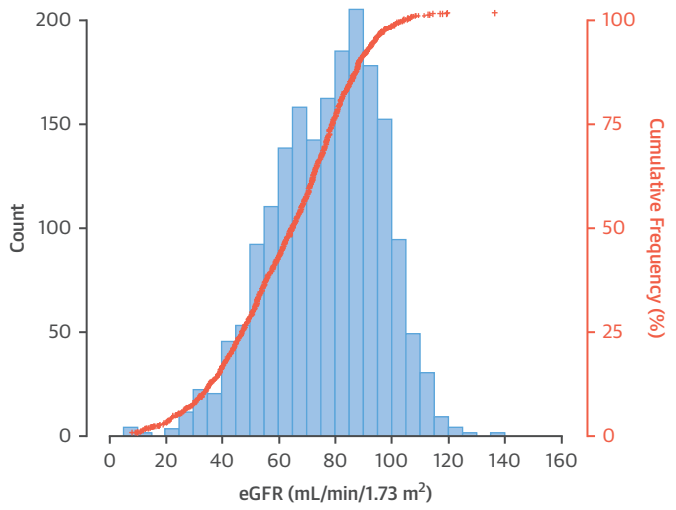
FIGURE 1 Distribution of the Estimated Glomerular Filtration Rate in the EXCEL Trial Population Using The CKD-EPI Equation



The **left y-axis** refers to the histogram of the number of patients with estimated glomerular filtration rate (eGFR) per 5 ml/min/1.73 m^2 increments. The **right y-axis** refers to the cumulative frequency distribution curve of eGFR values. The median (25%, 75%) eGFR was 79.2 (64.0, 91.3) ml/min/1.73 m^2, and the mean ± SD eGFR was 77.2 ± 19.1 ml/min/1.73 m^2 (range 6.5 to 139.2 ml/min/1.73 m^2). CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration.

(MI) at 3 years. Major powered secondary endpoints included this composite rate at 30 days, and death, stroke, MI, or ischemia-driven revascularization at 3 years. Additional secondary endpoints included the components of the primary endpoint, as well as revascularization, stent thrombosis, symptomatic graft occlusion, bleeding complications, and a pre-specified composite of major adverse events occurring within 30 days. These endpoint definitions are reported elsewhere (12). Study monitors collected source documents of all primary and secondary endpoint events for adjudication by an independent clinical events committee. The extent and complexity of CAD and the SYNTAX score were also assessed by an independent angiographic core laboratory.

The present study is a pre-specified subgroup analysis from the EXCEL trial comparing PCI and CABG in patients with and without CKD. CKD was defined as an estimated glomerular filtration rate (eGFR) <60 ml/min/1.73 m^2 (corresponding to CKD stage 3A, 3B, 4, or 5), using the CKD Epidemiology Collaboration (CKD-EPI) equation as per the National Kidney Foundation-Kidney Disease Outcomes Quality Initiative guidelines (Online Table 1) (14,15). This equation is preferentially endorsed by consensus guidelines as superior to other equations to discriminate between patients with versus without renal dysfunction and to predict adverse events in patients with CKD (16,17). ARF was defined in the protocol as a serum creatinine increase ≥5.0 mg/dl from baseline or new requirement for dialysis (including hemodialysis, continuous venovenous hemofiltration, or peritoneal dialysis).

STATISTICAL ANALYSIS. All analyses were performed in the intention-to-treat population, which included all patients according to the group to which they were randomly assigned, regardless of the treatment received. The median duration of follow-up in the current analysis was 3 years (interquartile range: 3 to 3 years). Categorical variables were compared with the use of the chi-square test or Fisher exact test. Continuous variables were compared with the use of the Student's *t*-test or the Wilcoxon rank-sum test for non-normally distributed data. Event rates were based on Kaplan-Meier estimates in time-to-first-event analyses and were compared with the log-rank test. The association between baseline renal function (as a continuous variable) and the 3-year hazard of adverse events was also evaluated using a smoothing spline function. Hazard ratios (HRs) with 95% confidence intervals (CIs) were generated with Cox regression models with treatment as the main effect. The statistical significance of differences in the treatment effect of PCI versus CABG in patients with and without CKD was assessed in Cox regression models for the full trial population, including main effect terms (e.g., CKD and assigned treatment) and interaction terms (e.g., CKD × assigned treatment) for each outcome of interest. Primary analyses were performed using the CKD-EPI formula to define baseline CKD (14). For sensitivity analysis, we assessed the comparative effectiveness of PCI versus CABG implementing alternative equations to estimate baseline renal function, specifically the Modification of Diet in Renal Disease (MDRD) equation (14) and the Cockcroft-Gault equation (18). The renal function equation definitions are shown in Online Table 1. A 2-sided p value ≤0.05 was considered to indicate statistical significance. All statistical analyses were performed with the use of SAS software, version 9.4 (SAS Institute, Cary, North Carolina).

RESULTS

Baseline renal function was evaluable in 1,869 of 1,905 randomized patients (98.1%), among whom CKD was present in 361 (19.3%), 300 (16.1%), and 308 (16.5%) using the CKD-EPI, MDRD, and Cockcroft-Gault equations, respectively. The mean

eGFR using the CKD-EPI and MDRD was 77.2 ± 19.1 ml/min/1.73 m^2 and 81.5 ± 22.8 ml/min/1.73 m^2 in all patients, and 48.6 ± 9.9 ml/min/1.73 m^2 and 49.2 ± 9.7 ml/min/1.73 m^2 in patients with CKD, respectively. The mean creatinine clearance using the Cockcroft-Gault equation was 89.5 ± 32.4 ml/min in all patients and 47.8 ± 9.6 ml/min in those with CKD. The distribution of baseline eGFR using the CKD-EPI equation is illustrated in **Figure 1**. Only 3 of 361 enrolled patients with CKD at baseline were on dialysis (0.8%).

Baseline characteristics in patients with and without CKD estimated with the CKD-EPI equation are reported in **Table 1**. Patients with CKD were older, were more commonly female, and had more comorbidities. Patients with CKD were also more likely to have a history of prior MI, atrial fibrillation, valvular heart disease, and lower left ventricular ejection fraction. Baseline angiographic characteristics and procedural characteristics with PCI or CABG are reported in **Table 2**. There were no significant differences in site-reported or core laboratory-assessed SYNTAX scores between patients with and without CKD; however, patients with CKD were more likely to have diffuse or small-vessel disease. There were no significant differences in the number of non-LM stented or bypassed vessels in patients with and without CKD (**Table 2**). Medication use at discharge and through 3 years in patients with and without CKD were similar, except for greater use of chronic oral anticoagulants in those with CKD (Online Table 2).

TABLE 1 Baseline Characteristics

	Chronic Kidney Disease (n = 361)	No Chronic Kidney Disease (n = 1,508)	p Value
Age, yrs	72.7 ± 7.8	64.3 ± 9.2	<0.0001
Male sex	239/361 (66.2)	1,200/1,508 (79.6)	<0.0001
Medical history			
Hypertension	306/361 (84.8)	1,073/1,508 (71.2)	<0.0001
Hyperlipidemia	266/360 (73.9)	1,038/1,506 (68.9)	<0.0001
Current smoker	44/359 (12.3)	365/1,497 (24.4)	<0.0001
Prior stroke or transient ischemic attack	37/361 (10.2)	80/1,507 (5.3)	0.0005
Congestive heart failure	43/361 (11.9)	79/1,503 (5.3)	<0.0001
Diabetes mellitus	146/361 (40.4)	403/1,508 (26.7)	<0.0001
Insulin-treated	46/361 (12.7)	101/1,508 (6.7)	
Peripheral artery disease	48/359 (13.4)	131/1,503 (8.7)	0.007
Chronic obstructive pulmonary disease	29/361 (8.0)	115/1,505 (7.6)	0.80
Anemia	61/358 (17.0)	121/1,505 (8.0)	<0.0001
Carotid artery disease	45/359 (12.5)	109/1,502 (7.3)	0.001
Cardiac history			
Prior percutaneous coronary intervention	70/360 (19.4)	249/1,507 (16.5)	0.19
Prior myocardial infarction	77/357 (21.6)	246/1,497 (16.4)	0.02
Atrial fibrillation	29/361 (8.0)	42/1,508 (2.8)	<0.0001
Any baseline mitral regurgitation*	115/327 (35.2)	400/1,405 (28.5)	0.02
Any baseline aortic regurgitation*	47/325 (14.5)	143/1,401 (10.2)	0.03
Any baseline tricuspid regurgitation*	94/323 (29.1)	355/1,392 (25.5)	0.18
Left ventricular ejection fraction, %	55.5 ± 10.6	57.5 ± 8.9	0.002
Clinical presentation			
Stable angina	189/360 (52.5)	799/1,502 (53.2)	0.81
Unstable angina	87/360 (24.2)	370/1,502 (24.6)	0.85
Non-STEMI†	43/357 (12.0)	199/1,498 (13.3)	0.52
STEMI†	5/357 (1.4)	22/1,498 (1.5)	0.92
Laboratory measures			
HbA1c, %	6.4 ± 1.3	6.2 ± 1.2	<0.0001
White blood cell count, $\times 10^9$/l	7.8 ± 2.1	7.8 ± 2.1	0.81
Hemoglobin, g/dl	12.7 ± 1.7	13.8 ± 1.5	<0.0001
Platelet count, $\times 10^9$/l	231.6 ± 71.5	226.8 ± 62.4	0.47
Brain natriuretic peptide, mg/l	450.8 ± 981.9	202.2 ± 453.5	<0.0001
High-sensitivity C-reactive protein, mg/l	9.1 ± 15.2	6.3 ± 12.6	0.001
Serum creatinine, mg/dl	1.4 ± 0.7	0.9 ± 0.2	<0.0001

Values are mean ± SD or n/N (%). *All were moderate or less; severe valve disease was an exclusion criterion. †Within 7 days before randomization.
HbA1c = hemoglobin A1c; STEMI = ST-segment elevation myocardial infarction.

EFFECT OF CKD ON OUTCOMES. Patients with compared to those without CKD had higher rates of 30-day composite major adverse events, including more frequent blood transfusions, major arrhythmias, infections, sternal wound dehiscence, and unplanned surgical and radiologic procedures (Online Table 3). In addition, the rate of ARF was ~6× greater in patients with CKD compared to those without (5.0% vs. 0.8%; p < 0.0001). The 3-year primary composite endpoint of death, stroke, or MI was increased in patients with compared to those without CKD (**Figure 2**) (20.8% vs. 13.5%; HR: 1.60; 95% CI: 1.22 to 2.09; p = 0.0005), driven by greater cardiac and noncardiac mortality (**Table 3**). The rates of adverse outcomes incrementally increased as renal function worsened from eGFR >60 ml/min/1.73 m^2 (no CKD) to eGFR 45 to 60 ml/min/1.73 m^2 (Stage 3A CKD) to eGFR <45 ml/min/1.73 m^2 (Stage 3B, 4, or 5 CKD) (Online Table 4). When modeled as a continuous variable, progressively lower eGFR was associated with a steadily greater 3-year risk of death, stroke, or MI (HR per 10 ml/min/1.73 m^2 decrease: 1.09; 95% CI: 1.03 to 1.15; p = 0.004) and all-cause death (HR per 10 ml/min/1.73 m^2 decrease: 1.23; 95% CI: 1.14 to 1.34; p < 0.0001) (**Figures 3A and 3B**). Results were consistent using the MDRD and the Cockcroft-Gault equations (Online Tables 5 and 6).

PCI VERSUS CABG IN PATIENTS WITH AND WITHOUT CKD. PCI was associated with lower 30-day rates of major adverse events compared with CABG, in patients with and without CKD (**Table 4**). PCI was also associated with shorter in-hospital stay

TABLE 2 Angiographic and Procedural Characteristics in Patients With Versus Without CKD

	Chronic Kidney Disease (n = 361)	No Chronic Kidney Disease (n = 1,508)	p Value
Baseline angiographic characteristics			
SYNTAX score, site-reported	21.0 ± 6.0	20.4 ± 6.2	0.11
Low complexity (<23)	211/361 (58.4)	917/1,506 (60.9)	
Intermediate complexity (23–32)	150/361 (41.6)	589/1,506 (39.1)	
SYNTAX score, core laboratory assessed	26.5 ± 8.7	26.5 ± 9.4	0.63
Low complexity (<23)	111/348 (31.9)	534/1,457 (36.7)	
Intermediate complexity (23–32)	157/348 (45.1)	568/1,457 (39.0)	
High complexity (>32)	80/348 (23.0)	355/1,457 (24.4)	
Left main diameter stenosis,	75.7 ± 12.4	75.3 ± 12.0	0.60
Bifurcation or trifurcation disease of the distal left main segment	275/352 (78.1)	1,212/1,491 (81.3)	0.18
Number of non-left main diseased vessels			
0	49/352 (13.9)	276/1,491 (18.5)	0.04
1	117/352 (33.2)	455/1,491 (30.5)	0.32
2	122/352 (34.7)	491/1,491 (32.9)	0.54
3	64/352 (18.2)	269/1,491 (18.0)	0.95
Diffuse or small vessel disease	36/356 (10.1)	76/1,482 (5.1)	0.0004
PCI characteristics			
Non-left main lesions stented per patient			
Left anterior descending artery	57/172 (33.1)	207/750 (27.6)	0.15
Left circumflex artery	31/172 (18.0)	122/750 (16.3)	0.58
Right coronary artery	41/172 (23.8)	203/750 (27.1)	0.39
Number of any stented lesions per patient	2.0 ± 1.1	1.9 ± 1.1	0.34
Number of any stented vessels per patient	1.7 ± 0.8	1.7 ± 0.8	0.55
Number of stents implanted per patient	2.6 ± 1.5	2.4 ± 1.5	0.09
Total stent length, per patient	50.9 ± 35.6	48.8 ± 35.8	0.27
Intravascular imaging used	133/172 (77.3)	579/750 (77.2)	0.97
Fractional flow reserve used	13/171 (7.6)	70/750 (9.3)	0.48
Time in the catheterization laboratory, min	112.6 ± 53.1	111.0 ± 52.5	0.81
CABG characteristics			
Coronary segments of distal anastomosis (CASS)			
Left anterior descending artery	174/176 (98.9)	718/727 (98.8)	1.00
Left circumflex artery	154/176 (87.5)	644/727 (88.6)	0.69
Right coronary artery	73/176 (41.5)	268/727 (36.9)	0.26
Number of vessels bypassed per patient	2.3 ± 0.6	2.2 ± 0.5	0.41
Number of conduits per patient	2.6 ± 0.8	2.6 ± 0.8	0.16
Number of arterial conduits per patient	1.3 ± 0.6	1.4 ± 0.6	0.31
Number of venous conduits per patient	1.3 ± 0.9	1.2 ± 1.0	0.10
Bypass duration, min	77.2 ± 33.1	85.3 ± 48.1	0.17
Time in the operating room, min	291.0 ± 76.6	282.9 ± 75.0	0.11

Values are mean ± SD or n/N (%), as appropriate.
CASS = Coronary Artery Surgery Study.

compared with CABG both in patients with CKD (6.7 ± 7.0 days vs. 16.1 ± 15.2 days; p < 0.0001) and without CKD (5.2 ± 4.7 days vs. 11.9 ± 7.4 days; p < 0.0001). At 30 days, PCI compared with CABG resulted in lower rates of the composite endpoint of death, MI, or stroke both in patients with CKD (6.2% vs. 9.3%; HR: 0.68; 95% CI: 0.32 to 1.45) and without CKD (4.5% vs. 7.4%; HR: 0.61; 95% CI: 0.40 to 0.93) ($p_{interaction}$ = 0.80). At 3 years (Figure 4), there were no significant differences in the rates of the primary composite endpoint of death, MI, or stroke after PCI versus CABG, an effect that was consistent in patients with and without CKD ($p_{interaction}$ = 0.36) (Table 5). The 3-year relative rates of the components of the primary endpoint as well as revascularization and bleeding after PCI versus CABG were also consistent in patients with and without CKD (Table 5). CABG was associated with less ischemia-driven revascularization during follow-up, the risk of which was consistent across varying levels of baseline renal function (Online Table 7). In the CKD group, 3-year mortality was increased after PCI compared with CABG, due to greater noncardiac deaths, specifically due to sepsis (5.4% vs. 1.1%; p = 0.02), which occurred more than 30 days post-procedure. There was no significant difference in cardiac mortality after PCI versus CABG either in patients with or without CKD. The comparative effectiveness of PCI versus CABG on the risk of death, MI, or stroke at 30 days and 3 years was consistent across varying definitions of CKD (Figure 5).

ARF AND OUTCOMES AFTER LM REVASCULARIZATION. Baseline clinical and procedural characteristics that were associated with the development of ARF within 30 days are reported in Online Table 8. Compared with CABG, PCI was associated with significantly lower rates of ARF at 30 days in both patients with CKD (2.3% vs. 7.6%; HR: 0.28; 95% CI: 0.09 to 0.87) and in those without CKD (0.3% vs. 1.3%; HR: 0.20; 95% CI: 0.04 to 0.90; $p_{interaction}$ = 0.71) (Table 6). Dialysis was also required more frequently after CABG compared with PCI, regardless of baseline CKD status ($p_{interaction}$ = 0.87). Outcomes at 3 years in patients with versus without ARF within 30 days are reported in Online Table 9. The occurrence of ARF was strongly associated with increased 3-year risk of death, stroke, or MI at 3 years (50.7% vs. 14.4%; HR: 4.59; 95% CI: 2.73 to 7.73; p < 0.0001).

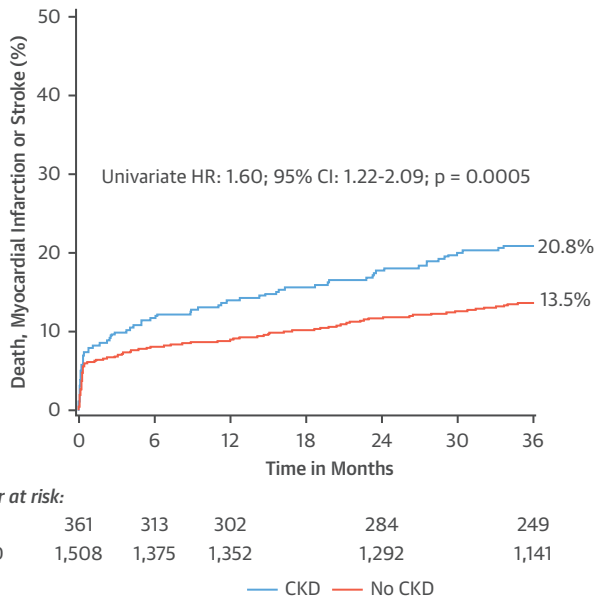
DISCUSSION

The Central Illustration demonstrates the major findings of the present pre-specified analysis from the EXCEL trial, in which we explored the relative effects of PCI with EES versus CABG in patients with LMCAD and low or intermediate SYNTAX scores according to baseline renal function. Progressively worse renal impairment in patients undergoing LM revascularization was associated with steadily increasing rates of cardiovascular and hemorrhagic adverse events and mortality during 3 years of follow-up. Compared with

CABG, PCI was associated with lower rates of ARF, including dialysis, and 30-day major adverse events in both patients with and without CKD. The occurrence of ARF at 30 days was strongly associated with increased risk of adverse events and mortality over 3 years of follow-up. At 3 years, however, there were no significant differences in the rates of death, MI, or stroke between PCI-treated and CABG-treated patients, regardless of baseline CKD. Despite the fact that definite stent thrombosis occurred less frequently than symptomatic graft failure, ischemia-driven revascularization rates at 3 years were lower after CABG compared with PCI, an effect that was consistent in patients with preserved or reduced renal function. Finally, the impact of CKD and the comparative outcomes of PCI versus CABG in patients with and without CKD were consistent irrespective of the definition of renal dysfunction.

Evidence from prior randomized trials to inform revascularization decisions in patients with CKD is scarce, especially in LMCAD. Among diabetic patients with CKD and non-LM multivessel disease enrolled in the FREEDOM (Future Revascularization Evaluation in Patients with Diabetes Mellitus: Optimal Management of Multivessel Disease) trial, CABG compared with PCI with paclitaxel-eluting stents resulted in a 27% relative risk reduction in major adverse cardiovascular and cerebrovascular events (MACCE) at a median follow-up of 3.8 years (7). Among CKD patients with non-LM multivessel disease enrolled in the New York State outcomes registries, PCI with EES was associated with lower rates of MACCE at 30 days than CABG, but higher rates of MI and repeat revascularization at 4 years, with similar rates of death (19). In a pooled analysis from the PRECOMBAT (Bypass Surgery Versus Angioplasty Using Sirolimus-Eluting Stent in Patients With Left Main Coronary Artery Disease) and SYNTAX trials, PCI with first-generation paclitaxel-eluting and sirolimus-eluting stents was associated with comparable 5-year rates of MACCE and death compared with CABG in patients with LMCAD with and without CKD, without significant interaction (8).

FIGURE 2 3-Year Outcomes in Patients With Versus Without CKD



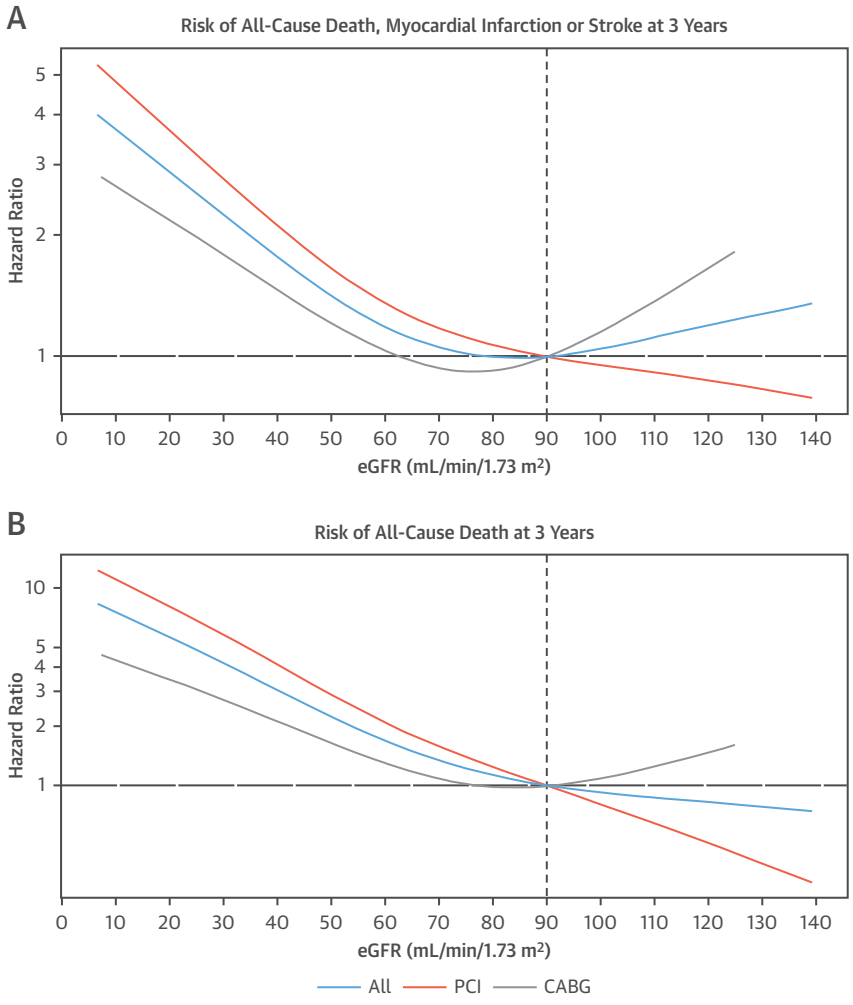
Kaplan-Meier time-to-first event curves for death, myocardial infarction, or stroke during 3 years of follow-up in patients with and without chronic kidney disease (CKD). CKD estimated with the CKD-EPI equation. CI = confidence interval; HR = hazard ratio.

TABLE 3 3-Year Outcomes in Patients With Versus Without Chronic Kidney Disease

	Chronic Kidney Disease (n = 361)	No Chronic Kidney Disease (n = 1,508)	Hazard Ratio (95% Confidence Interval)	p Value
Death, stroke, or myocardial infarction	20.8 (73)	13.5 (200)	1.60 (1.22–2.09)	0.0005
Death	12.9 (45)	5.4 (80)	2.48 (1.72–3.57)	<0.0001
Cardiac death	7.3 (25)	3.3 (48)	2.27 (1.40–3.69)	0.0006
Noncardiac death	6.0 (20)	2.2 (32)	2.78 (1.59–4.86)	0.0002
Stroke	3.6 (12)	2.5 (36)	1.46 (0.76–2.80)	0.26
Myocardial infarction	9.0 (31)	8.0 (118)	1.13 (0.76–1.68)	0.54
Death, stroke, myocardial infarction, or ischemia-driven revascularization	24.2 (85)	19.9 (296)	1.25 (0.98–1.59)	0.07
Ischemia-driven revascularization	8.6 (29)	10.3 (149)	0.85 (0.57–1.26)	0.42
Stent thrombosis, definite or probable	1.1 (4)	0.6 (9)	1.93 (0.59–6.26)	0.27
Graft stenosis or occlusion	2.3 (8)	2.7 (39)	0.89 (0.42–1.90)	0.76
Definite stent thrombosis or symptomatic graft occlusion	2.6 (9)	3.1 (45)	0.87 (0.42–1.78)	0.70
TIMI major or minor bleeding	11.1 (39)	6.9 (103)	1.61 (1.12–2.33)	0.01

Values are Kaplan-Meier estimate (number of events) unless otherwise indicated.
TIMI = Thrombolysis In Myocardial Infarction.

FIGURE 3 Risk of Adverse Events According to Baseline Renal Function



Smooth hazard function for the risk of **(A)** death, myocardial infarction, or stroke; and **(B)** death at 3 years according to baseline renal function estimated with the CKD-EPI equation. CABG = coronary artery bypass grafting; PCI = percutaneous coronary intervention; other abbreviations as in Figures 1 and 2.

The present large-scale study in which contemporary DES and revascularization techniques were used confirms and extends these prior findings to patients with LMCAD. Patients with CKD constituted ~25% of the EXCEL trial population, in whom the mean eGFR was 48.5 ± 9.9 ml/min/1.73 m^2, representing predominantly moderate CKD. PCI with EES in patients with LMCAD reduced 30-day periprocedural adverse events and the 30-day composite rate of death, stroke, or MI consistently in both CKD and non-CKD cohorts. Specifically, PCI resulted in reduced bleeding, need for transfusions, arrhythmias, and less ARF (including the need for dialysis) compared with CABG in patients with CKD, adverse events which have been associated with long-term mortality (20-26). In this regard, ARF in the EXCEL trial was defined as an increase in serum creatinine ≥5 mg/dl or a new requirement for dialysis, corresponding to acute kidney injury of stage III or greater in the most recent KDIGO (Kidney Disease: Improving Global Outcomes) classification (27). ARF as so defined was strongly associated with worse outcomes over 3 years of follow-up. The reduced rate of ARF after PCI compared with CABG in both the CKD and non-CKD cohorts is 1 factor that should be considered when deciding between revascularization strategies to avoid further declines in renal function in patients with CKD. However,

TABLE 4 30-Day Major Adverse Events After PCI Versus CABG in Patients With Versus Without Chronic Kidney Disease

	Chronic Kidney Disease (n = 361)				No Chronic Kidney Disease (n = 1,508)			
	PCI (n = 177)	CABG (n = 184)	Hazard Ratio (95% CI)	p Value	PCI (n = 757)	CABG (n = 751)	Hazard Ratio (95% CI)	p Value
Major adverse events, any	10.9 (19)	29.8 (54)	0.36 (0.23–0.59)	<0.0001	6.2 (47)	21.5 (160)	0.29 (0.21–0.39)	<0.0001
Death	1.1 (2)	1.7 (3)	0.69 (0.12–4.08)	1.00	0.3 (2)	1.1 (8)	0.25 (0.05–1.16)	0.06
Myocardial infarction	4.0 (7)	6.6 (12)	0.60 (0.24–1.50)	0.27	3.4 (26)	5.9 (44)	0.58 (0.36–0.94)	0.02
Stroke	1.1 (2)	1.7 (3)	0.69 (0.12–4.08)	1.00	0.3 (2)	1.3 (10)	0.20 (0.04–0.90)	0.02
Transfusion of ≥2 U blood	6.3 (11)	24.3 (44)	0.26 (0.14–0.48)	<0.0001	2.7 (20)	15.6 (116)	0.17 (0.11–0.27)	<0.0001
TIMI major or minor bleeding	3.4 (6)	12.2 (22)	0.28 (0.12–0.68)	0.002	2.7 (20)	8.7 (65)	0.30 (0.19–0.50)	<0.0001
Major arrhythmia	2.3 (4)	19.9 (36)	0.11 (0.04–0.32)	<0.0001	1.7 (13)	13.6 (101)	0.13 (0.07–0.22)	<0.0001
Unplanned coronary revascularization for ischemia	1.1 (2)	2.2 (4)	0.52 (0.10–2.79)	0.69	0.1 (1)	1.1 (8)	0.12 (0.02–0.98)	0.02
Any unplanned surgery or therapeutic radiological procedure	0.6 (1)	8.3 (15)	0.07 (0.01–0.52)	0.0004	0.9 (7)	2.7 (20)	0.34 (0.15–0.81)	0.01
Acute renal failure*	2.3 (4)	7.7 (14)	0.30 (0.10–0.88)	0.02	0.3 (2)	1.2 (9)	0.22 (0.05–1.01)	0.03
Sternal wound dehiscence	0.0 (0)	3.3 (6)	0.08 (0.00–1.40)	0.03	0.0 (0)	0.4 (3)	0.14 (0.01–2.72)	0.12
Infection requiring antibiotics	2.3 (4)	11.6 (21)	0.20 (0.07–0.56)	0.0006	0.8 (6)	8.2 (61)	0.10 (0.04–0.22)	<0.0001
Intubation for >48 h	0.6 (1)	3.9 (7)	0.15 (0.02–1.19)	0.07	0.4 (3)	2.4 (18)	0.16 (0.05–0.56)	0.0009
Post-pericardiotomy syndrome	0.0 (0)	0.0 (0)	–	–	0.0 (0)	0.3 (2)	0.20 (0.01–4.10)	0.25

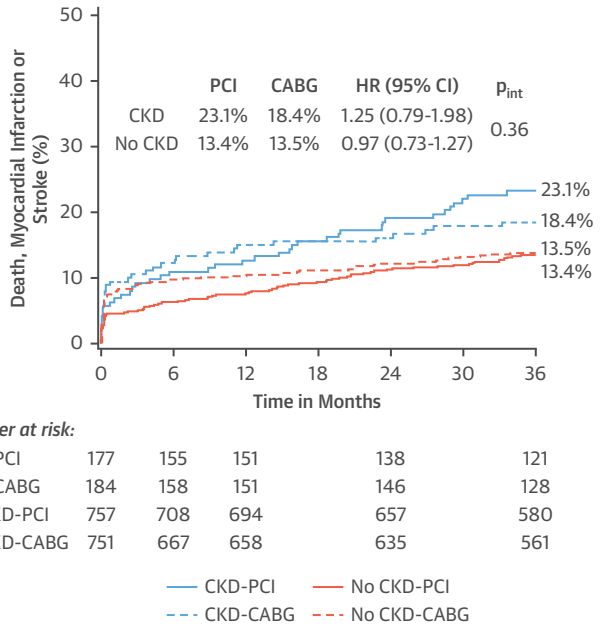
Values are % (N) unless otherwise indicated. *Defined as a serum creatinine increase ≥5.0 mg/dl from baseline or a new requirement for dialysis.
CABG = coronary artery bypass graft; CI = confidence interval; PCI = percutaneous coronary intervention; TIMI = Thrombolysis In Myocardial Infarction.

the composite 3-year primary endpoint rate of death, MI, or stroke was similar after PCI and CABG, a finding that was consistent in patients with and without CKD. The lower rates of MI and revascularization during the follow-up period after CABG compared with PCI as initially described in EXCEL (7) may have offset the deleterious effects of ARF and surgical complications in the CKD cohort.

Renal dysfunction has been associated with late DES failure (28–30). Nonetheless, the 3-year rates of definite EES thrombosis were lower than the rates of symptomatic graft occlusion in patients with and without CKD, and ischemia-driven revascularization after EES within 3 years was required in only 10.9% of patients with CKD compared with 13.0% of patients without CKD. These observations demonstrate that the antithrombotic and antirestenotic properties of EES are preserved in higher-risk CKD patients and lesions (31,32). It thus follows that improved chronic medical therapy regimens are required to slow progressive atherosclerosis if the long-term prognosis of high-risk CKD patients is to be improved after coronary revascularization. Toward this end, insights may be gained from the ongoing ISCHEMIA-CKD (International Study of Comparative Health Effectiveness With Medical and Invasive Approaches-Chronic Kidney Disease) trial (NCT01985360), in which patients with stable ischemic heart disease and advanced CKD (eGFR <30 ml/min/1.73 m^2 or dialysis) are being assigned to an invasive revascularization strategy versus initial medical management.

STUDY LIMITATIONS. First, although the present study was pre-specified, the CKD and non-CKD subgroups were not individually powered to draw

FIGURE 4 3-Year Outcomes for PCI Versus CABG in Patients With or Without CKD



Kaplan-Meier time-to-first event curves for death, myocardial infarction, or stroke during 3 years of follow-up according to randomized treatment with PCI versus CABG in patients with and without CKD. CKD estimated with the CKD-EPI equation. Abbreviations as in Figure 2 and 3.

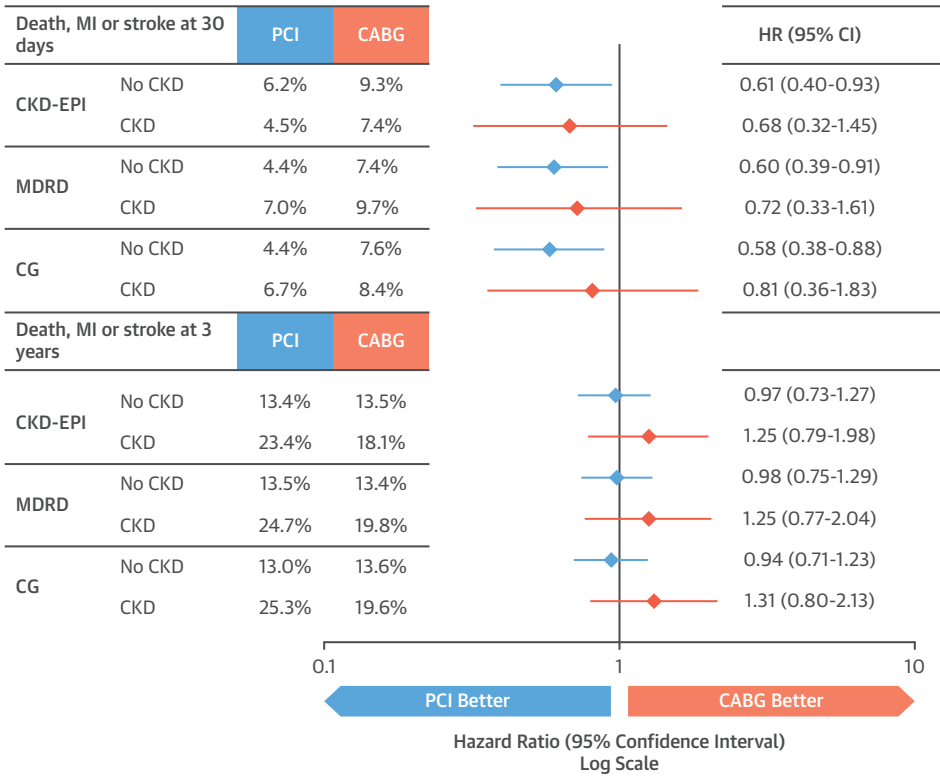
TABLE 5 3-Year Outcomes for PCI Versus CABG in Patients With or Without Chronic Kidney Disease

	Chronic Kidney Disease (n = 361)			No Chronic Kidney Disease (n = 1,508)			
	PCI (n = 177)	CABG (n = 184)	Hazard Ratio (95% CI)	PCI (n = 757)	CABG (n = 751)	Hazard Ratio (95% CI)	$p_{interaction}$
Death, stroke, or myocardial infarction	23.1 (40)	18.4 (33)	1.25 (0.79–1.98)	13.4 (100)	13.5 (100)	0.97 (0.73–1.27)	0.36
Death	16.9 (29)	9.0 (16)	1.91 (1.04–3.52)	5.9 (44)	4.9 (36)	1.19 (0.77–1.85)	0.22
Cardiac	8.3 (14)	6.2 (11)	1.34 (0.61–2.94)	3.5 (26)	3.0 (22)	1.15 (0.65–2.04)	0.77
Noncardiac	9.2 (15)	2.9 (5)	3.15 (1.15–8.68)	2.5 (18)	2.0 (14)	1.25 (0.62–2.52)	0.14
Stroke	3.1 (5)	4.0 (7)	0.75 (0.24–2.36)	2.2 (16)	2.8 (20)	0.78 (0.40–1.50)	0.95
Myocardial infarction	9.5 (16)	8.4 (15)	1.11 (0.55–2.24)	7.7 (57)	8.3 (61)	0.91 (0.63–1.30)	0.62
Death, stroke, myocardial infarction, or IDR	27.2 (47)	21.2 (38)	1.28 (0.84–1.97)	21.8 (163)	18.0 (133)	1.20 (0.95–1.50)	0.77
IDR	10.9 (18)	6.4 (11)	1.74 (0.82–3.68)	13.0 (95)	7.5 (54)	1.75 (1.25–2.44)	0.96
Stent thrombosis, definite or probable	2.3 (4)	–	–	1.2 (9)	–	–	–
Graft occlusion, symptomatic	–	4.5 (8)	–	–	5.4 (39)	–	–
Definite stent thrombosis or symptomatic graft occlusion	0.6 (1)	4.5 (8)	0.13 (0.02–1.03)	0.8 (6)	5.4 (39)	0.15 (0.06–0.35)	0.91
TIMI major or minor bleeding	8.3 (14)	13.8 (25)	0.57 (0.29–1.09)	4.8 (36)	9.0 (67)	0.52 (0.35–0.78)	0.80

Values are Kaplan-Meier estimate (number of events).
CKD = chronic kidney disease; IDR = ischemia-driven revascularization; other abbreviations as in Table 4.

definitive conclusions as to whether PCI or CABG should be favored. Randomization was not stratified by renal function, and the role of unmeasured confounders cannot be excluded. Our findings should thus be considered hypothesis-generating. Second, while some patients with severe CKD were included, the majority had moderate renal impairment. Therefore, our findings cannot be extrapolated to a severe

FIGURE 5 30-Day and 3-Year Outcomes for PCI Versus CABG Using Alternative CKD Equations



CG = Cockcroft-Gault; MDRD = Modification of Diet in Renal Disease; MI = myocardial infarction; other abbreviations as in Figures 1 to 3.

TABLE 6 Acute Renal Failure at 30 Days in Patients With or Without CKD Undergoing PCI Versus CABG

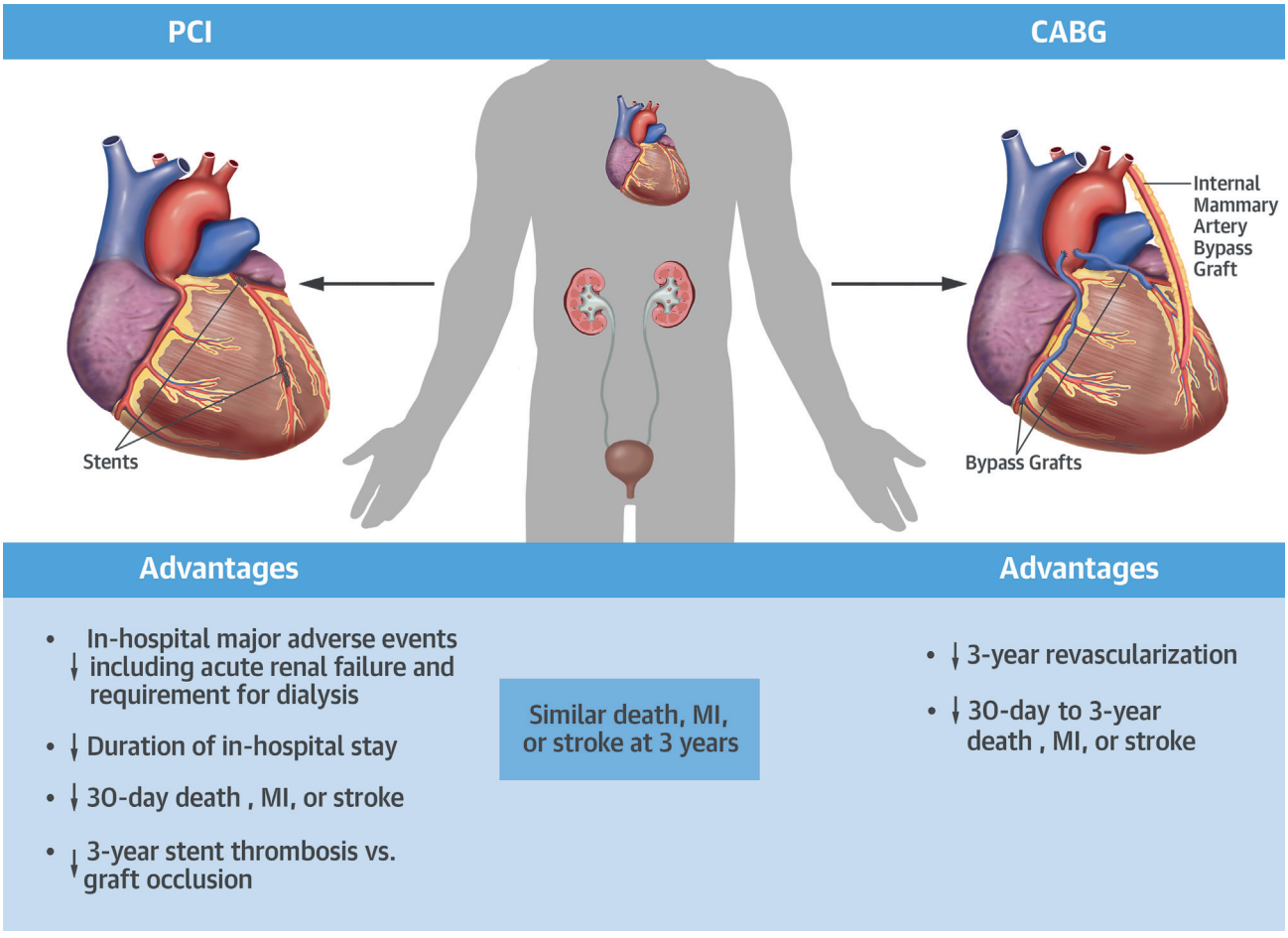
	Chronic Kidney Disease (n = 361)			No Chronic Kidney Disease (n = 1,508)			
	PCI (n = 177)	CABG (n = 184)	Hazard Ratio (95% CI)	PCI (n = 757)	CABG (n = 751)	Hazard Ratio (95% CI)	$p_{interaction}$
Acute renal failure*	2.3 (4)	7.6 (14)	0.28 (0.09–0.87)	0.3 (2)	1.3 (10)	0.20 (0.04–0.90)	0.71
New requirement for dialysis	1.1 (2)	5.4 (10)	0.20 (0.04–0.92)	0.1 (1)	0.5 (4)	0.25 (0.03–2.22)	0.87
Hemodialysis	0.6 (1)	2.7 (5)	0.20 (0.02–1.76)	0.1 (1)†	0.4 (3)	0.33 (0.03–3.18)	0.76
CVVH	0.6 (1)	2.7 (5)	0.20 (0.02–1.76)	0.1 (1)†	0.1 (1)	0.99 (0.06–15.89)	0.38

Values are % (n) unless otherwise indicated. *Defined as the rise in serum creatinine >5 mg/dl or a new requirement for dialysis. †One patient in the no chronic kidney disease group had both CVVH and hemodialysis.

CVVH = continuous venovenous hemofiltration; other abbreviations as in Table 4.

CKD and end-stage renal disease population. Third, EXCEL enrolled patients with LMCAD and site-assessed low and intermediate anatomical complexity. Our findings therefore do not apply to patients with CAD and extreme anatomic complexity. Nonetheless, the mean core laboratory-assessed SYNTAX score in the EXCEL trial of 26.5 was roughly comparable to that from the FREEDOM trial

CENTRAL ILLUSTRATION Left Main Revascularization and Chronic Kidney Disease



Giustino, G. et al. J Am Coll Cardiol. 2018;72(7):754–65.

Risk and benefits of percutaneous coronary intervention (PCI) versus coronary artery bypass graft surgery (CABG) in patients with chronic kidney disease and left main coronary artery disease with site-assessed low or intermediate SYNTAX (Synergy between PCI with Taxus and Cardiac Surgery) scores. MI = myocardial infarction.

(mean 26.2) and the SYNTAX trial (mean 28.8), implying that the present results may inform outcomes in patients with more extensive CAD. Finally, follow-up in EXCEL is complete through only 3 years. Longer-term follow-up (currently planned for 5 years) is required to determine whether additional late differences between PCI and CABG emerge.

CONCLUSIONS

In patients with LMCAD and site-assessed low or intermediate SYNTAX scores undergoing revascularization, the presence of CKD was associated with a substantially greater risk of periprocedural adverse events and mortality during 3-year follow-up. Although PCI with EES was associated with significantly lower 30-day rates of ARF and major adverse events compared with CABG, there were no significant differences between the revascularization modalities for the primary composite endpoint or components of death, MI, or stroke at 3 years, with no interaction according to baseline CKD status. Both PCI and CABG are thus acceptable revascularization approaches in selected high-risk patients with LMCAD and CKD. Individual patient comorbidities, the likelihood to safely obtain complete revascularization, and patient preferences as to the early benefits of PCI versus the late benefits of CABG should thus be factored into the heart team decision-making process in high-risk patients with LMCAD and CKD.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Patients with CKD and LMCAD undergoing revascularization are at substantially greater risk of acute renal failure, periprocedural adverse events, and mortality during 3 years of follow-up. Those with low or intermediate anatomical complexity undergoing PCI with EES exhibit lower 30-day rates of adverse events including ARF, major bleeding, and arrhythmias compared with those undergoing CABG. Over 3 years of follow-up, however, PCI and CABG were associated with similar rates of death, MI, and stroke, irrespective of baseline renal function.

TRANSLATIONAL OUTLOOK: Future studies should evaluate enhanced medical therapies that reduce the progression of atherosclerosis to improve the long-term prognosis of high-risk patients with CKD undergoing coronary revascularization.

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KEY WORDS chronic kidney disease, coronary artery bypass grafting, coronary artery disease, left main, percutaneous coronary intervention

APPENDIX For supplemental tables, please see the online version of this paper.