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Efficacy and Safety of Evolocumab in Chronic Kidney Disease in the FOURIER Trial

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ABSTRACT

BACKGROUND Data on PCSK9 inhibition in chronic kidney disease (CKD) is limited.

OBJECTIVES The purpose of this study was to compare outcomes with evolocumab and placebo according to kidney function.

METHODS The FOURIER (Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk) trial randomized individuals with clinically evident atherosclerosis and low-density lipoprotein cholesterol (LDL-C) ≥70 mg/dl or non-high-density lipoprotein cholesterol ≥100 mg/dl to evolocumab or placebo. The primary endpoint (cardiovascular death, myocardial infarction, stroke, hospitalization for unstable angina, or coronary revascularization), key secondary endpoint (cardiovascular death, myocardial infarction, or stroke), and safety were analyzed according to chronic kidney disease (CKD) stage estimated from CKD-epidemiology estimated glomerular filtration rate.

RESULTS There were 8,077 patients with preserved kidney function, 15,034 with stage 2 CKD, and 4,443 with ≥stage 3 CKD. LDL-C reduction with evolocumab compared with placebo at 48 weeks was similar across CKD groups at 59%, 59%, and 58%, respectively. Relative risk reduction for the primary endpoint was similar for preserved function (hazard ratio [HR]: 0.82; 95% CI: 0.71 to 0.94), stage 2 (HR: 0.85; 95% CI: 0.77 to 0.94), and stage ≥3 CKD (HR: 0.89; 95% CI: 0.76 to 1.05); $p_{int} = 0.77$. Relative risk reduction for the secondary endpoint was similar across CKD stages ($p_{int} = 0.75$)—preserved function (HR: 0.75; 95% CI: 0.62 to 0.90), stage 2 (HR: 0.82; 95% CI: 0.72 to 0.93), stage ≥3 (HR: 0.79; 95% CI: 0.65 to 0.95). Absolute RRs at 30 months for the secondary endpoint were −2.5% (95% CI: −0.4% to −4.7%) for stage ≥3 CKD compared with −1.7% (95% CI: 0.5% to −2.8%) with preserved kidney function. Adverse events, including estimated glomerular filtration rate decline, were infrequent and similar regardless of CKD stage.

CONCLUSIONS LDL-C lowering and relative clinical efficacy and safety of evolocumab versus placebo were consistent across CKD groups. Absolute reduction in the composite of cardiovascular death, MI, or stroke with evolocumab was numerically greater with more advanced CKD. (Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk [FOURIER]; NCT01764633) (J Am Coll Cardiol 2019;73:2961–70) © 2019 by the American College of Cardiology Foundation.

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ABBREVIATIONS AND ACRONYMS

ARR = absolute risk reduction

CKD = chronic kidney disease

eGFR = estimated glomerular filtration rate

HR = hazard ratio

LDL-C = low-density lipoprotein cholesterol

NNT = number needed to treat

PCSK9 = proprotein convertase subtilisin-kexin type 9

Kidney function is strongly associated with cardiovascular disease, and the risk of cardiovascular events increases as estimated glomerular filtration rate (eGFR) declines (1,2). Given this high risk of cardiovascular events, there has been a great interest in the use of cholesterol-lowering therapies to treat and prevent cardiovascular disease in the setting of chronic kidney disease (CKD). However, the risk of cardiovascular outcomes remains high in individuals with CKD even among those receiving lipid-lowering therapy, whereas the ability of statins, the most widely used agents, to lower the risk of cardiovascular death appears to be attenuated in those with severe CKD requiring renal replacement therapy (3–6).

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Recently, biological agents targeting the proprotein convertase subtilisin-kexin type 9 (PCSK9) have been shown to reduce low-density lipoprotein cholesterol (LDL-C) by 50% to 60% in addition to background statin and reduce cardiovascular events (7–10). The FOURIER (Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk) (NCT01764633) trial demonstrated that evolocumab, a fully-human monoclonal antibody targeting PCSK9, reduces the incidence of cardiovascular outcomes when added to high- or moderate-intensity statin therapy in patients with clinically evident atherosclerosis (7). Similar benefits for alirocumab were confirmed in the ODYSSEY OUTCOMES (Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab) (NCT01663402) trial (10). However, the safety and efficacy of PCSK9 inhibitors in the setting of CKD remains uncertain. Furthermore, no information is available regarding their effect on progression of CKD. We therefore analyzed cardiovascular and renal outcomes of evolocumab therapy according to kidney function at baseline among 27,554 individuals enrolled in the FOURIER trial who were randomized to evolocumab or placebo.

METHODS

STUDY POPULATION. The FOURIER trial has been described previously (7,11). In brief, patients between ages 40 and 85 years with atherosclerotic cardiovascular disease and additional cardiovascular risk factors were eligible. Clinically evident atherosclerotic cardiovascular disease was defined as prior myocardial infarction (MI), prior nonhemorrhagic stroke, or symptomatic peripheral arterial disease. A fasting LDL-C level ≥70 mg/dl or non-high-density lipoprotein cholesterol ≥100 mg/dl while on a high- or moderate-intensity statin (defined as equivalent to a dose of atorvastatin ≥20 mg daily) was also required. Patients with an eGFR <20 ml/min/1.73 m^2 or a history of renal transplantation were excluded. Enrolled patients were randomized to receive double-blind evolocumab (140 mg every 2 weeks or 420 mg monthly) or matching placebo in a 1:1 ratio. All subjects signed a written informed consent prior to enrollment, and local institutional review boards approved the study.

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ENDPOINTS AND FOLLOW-UP. The primary endpoint was defined as the composite of cardiovascular death, MI, stroke, hospitalization for unstable angina, or coronary revascularization. The composite of cardiovascular death, MI, or stroke was the key secondary endpoint. Cardiovascular events and new-onset diabetes were adjudicated by the blinded TIMI (Thrombolysis In Myocardial Infarction) clinical events committee using standard definitions. Safety was assessed by central laboratory monitoring and investigator-reported adverse events. Study visits were conducted at weeks 2, 4, and 12 and then at 12-week intervals thereafter. Patients were assessed for adverse events at each visit and had central laboratory monitoring of blood and urine every 6 months. In addition, for this post hoc analysis, we examined the change in eGFR over time as the primary renal endpoint of interest. Secondary renal endpoints included a decline of 30%, 40%, or 50% in eGFR defined as present on the basis of sustained changes meeting the threshold from baseline or when the last available measurement met the criteria.

ASSESSMENT OF KIDNEY FUNCTION. The eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation (12), based on baseline or follow-up creatinine measured at a central laboratory. We classified individuals according to standard CKD stages (13) based on the level of eGFR as preserved kidney function, mild impairment/stage 2 CKD, or stage ≥3 CKD (≥90, 60 to <90, and <60 ml/min/1.73 m^2). A secondary analysis subdivided stage 3 CKD into stage 3a (eGFR 45 to <60 ml/min/1.73 m^2) and 3b (eGFR <45 ml/min/1.73 m^2). Urinary albumin to creatinine ratios were not available.

STATISTICAL ANALYSES. Baseline data were reported as n (%), mean ± SD, or medians and interquartile range according to the distribution. Baseline patient characteristics were compared across groups using the Jonckheere-Terpstra trend test for continuous variables and Cochran-Armitage trend test for categorical variables. All efficacy endpoints were analyzed using Cox proportional hazard regression adjusted for randomization strata (LDL-C ≥85 mg/dl and region) and stratified by kidney function group. Proportional hazards assumptions were tested using Schoenfeld residuals. We specifically tested for interaction between CKD stage and treatment. The complements of Kaplan-Meier estimates were reported for the event rate at 30 months. The number needed to treat (NNT) at 30 months was calculated as the inverse of the absolute risk reduction, and Mann-Kendall nonparametric trend tests (1-sided) were used for post hoc testing of positive trend of absolute risk across treatment group and CKD stage.

Associations of kidney function with event rates were analyzed using proportional hazard regression adjusted for randomization strata, age, sex, race, prior MI, prior ischemic stroke, history of peripheral vascular disease, hypertension, diabetes, current cigarette use, statin intensity, baseline triglycerides, and baseline CKD category. In a secondary analysis, we plotted the relationship between baseline eGFR as a continuous function and outcomes by using a smoothing function applied to the averages of estimated event rates at each CKD-EPI level based on the adjusted Cox model.

Changes in LDL-C and eGFR over time were assessed using linear mixed effects models with repeated measures including model terms with treatment, visit, visit by treatment interaction, and randomization strata. When necessary, log-transformation was used for continuous variables to meet the modeling assumptions. The association between primary and secondary endpoints and achieved LDL-C was examined by CKD stage utilizing the models previously developed for the purpose of analyzing the association between achieved LDL-C and outcomes in Fourier (14). This was performed using a smoothing function applied to the averages of estimated event probabilities of individuals (group prognosis method) (15) at each LDL-C level based on the adjusted Cox model, which included CKD class, LDL-C concentration at baseline, age, sex, race, body mass index, geographical region, and baseline medication use. A value of $p < 0.05$ was considered significant. All data were analyzed using SAS software version 9.4 (SAS Institute, Cary, North Carolina).

RESULTS

BASELINE CHARACTERISTICS. Of the 27,564 patients enrolled in the trial, 27,554 had data to calculate eGFR. There were 8,077 individuals with preserved kidney function (eGFR ≥90 ml/min/1.73 m^2), 15,034 with mild impairment/stage 2 CKD (eGFR 60 to <90 ml/min/1.73 m^2), and 4,443 with stage ≥3 CKD (eGFR <60 ml/min/1.73 m^2), including 1,064 with stage 3b CKD (GFR <45 ml/min/1.73 m^2) and 208 with stage 4 CKD (eGFR ≤30 ml/min/1.73 m^2). As shown in **Table 1**, individuals with more severe kidney impairment tended to be older and were more likely to have hypertension, diabetes, and a history of nonhemorrhagic stroke or peripheral arterial disease, and were less likely to have a history of myocardial infarction.

TABLE 1 Baseline Characteristics of the Study Population, by eGFR (ml/min/1.73 m^2) Category at Baseline

	Stage ≥3 CKD (n = 4,443)	Stage 2 CKD (n = 15,034)	Preserved Kidney Function (n = 8,077)	p Value Trend
Age, yrs	68.7 ± 7.8	64.0 ± 8.2	56.3 ± 7.4	<0.001
Male	2,889 (65.0)	11,386 (75.7)	6,511 (80.6)	<0.001
Race				
Black	140 (3.2)	303 (2.0)	226 (2.8)	0.89
Other	524 (11.8)	1,750 (11.6)	1,162 (14.4)	<0.001
White	3,779 (85.1)	12,981 (86.3)	6,689 (82.8)	<0.001
Weight, kg	84.4 ± 17.5	84.9 ± 16.9	86.4 ± 18.2	<0.001
Region				
Asia Pacific and South Africa	543 (12.2)	2,014 (13.4)	1,278 (15.8)	<0.001
Europe	2,487 (56.0)	9,572 (63.7)	5,268 (65.2)	<0.001
Latin America	380 (8.6)	954 (6.3)	488 (6.0)	<0.001
North America	1,033 (23.3)	2,494 (16.6)	1,043 (12.9)	<0.001
Type of atherosclerosis				
Myocardial infarction	3,419 (77.0)	12,223 (81.3)	6,701 (83.0)	<0.001
Median time from most recent previous MI	4.1 (1.3–9.0)	3.6 (1.1–8.1)	2.5 (0.6–6.0)	<0.001
Nonhemorrhagic stroke	1,110 (25.0)	2,907 (19.3)	1,317 (16.3)	<0.001
Median time from most recent previous stroke	3.5 (1.2–7.7)	3.4 (1.1–7.3)	2.9 (1.0–6.7)	0.001
Peripheral artery disease	773 (17.4)	1,888 (12.6)	980 (12.1)	<0.001
Cardiovascular risk factors				
Hypertension	3,968/4,443 (89.3)	12,008/15,034 (79.9)	6,101/8,076 (75.5)	<0.001
Diabetes mellitus	2,062 (46.4)	4,958 (33.0)	3,056 (37.8)	<0.001
Current cigarette use	704/4,443 (15.8)	3,679/15,033 (24.5)	3,393/8,076 (42.0)	<0.001
Statin use				
High intensity	2,947 (66.3)	10,362 (68.9)	5,785 (71.6)	<0.001
Moderate intensity	1,480 (33.3)	4,635 (30.8)	2,276 (28.2)	<0.001
Ezetimibe	222 (5.0)	776 (5.2)	441 (5.5)	0.23
Other cardiovascular medications				
Aspirin, $P2Y_{12}$ inhibitor, or both	3,916/4,439 (88.2)	13,855/15,019 (92.2)	7651/8,071 (94.8)	<0.001
Beta-blocker	3,440/4,439 (77.5)	11,278/15,019 (75.1)	6,089/8,071 (75.4)	0.04
ACEi, ARB, or AA antagonist	3,649/4,439 (82.2)	11,731/15,019 (78.1)	6,145/8,071 (76.1)	<0.001
Lipid measures				
LDL cholesterol, mg/dl	91.0 (79.0–107.5)	91.5 (79.5–107.5)	92.5 (80.0–111.5)	<0.001
Total cholesterol, mg/dl	168.0 (151.5–188.5)	167.5 (151.0–187.5)	167.5 (150.5–190.0)	0.93
HDL cholesterol, mg/dl	43.5 (36.0–52.5)	44.5 (37.5–53.5)	43.0 (36.0–51.0)	<0.001
Triglycerides, mg/dl	141.0 (107.0–195.5)	130.5 (98.5–178.0)	133.5 (99.0–183.5)	<0.001
Lipoprotein(a), nmol/l	40.0 (14.0–172.0)	37.0 (13.0–166.0)	35.0 (12.0–159.0)	<0.001
Kidney function tests				
Serum creatinine, mg/dl	1.3 (1.2–1.5)	1.0 (0.9–1.1)	0.8 (0.7–0.9)	–
eGFR, mg/dl	51.1 (43.6–56.2)	76.6 (69.3–83.5)	97.1 (93.3–101.8)	–

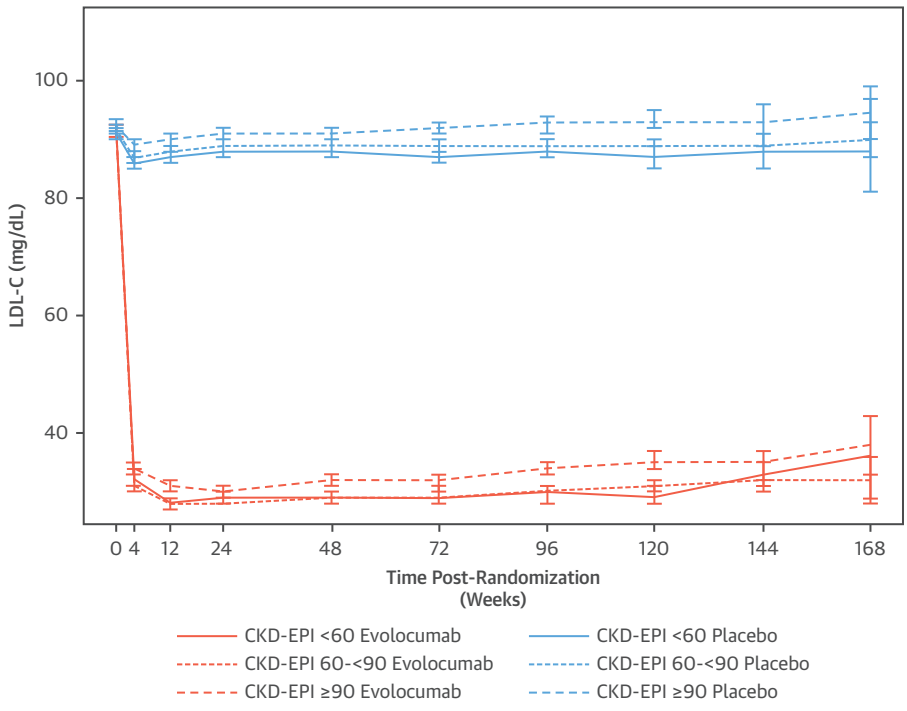
Values are mean ± SD, n (%), median (interquartile range), or n/N (%). Baseline characteristics of the study population according to kidney function. Among stage 3 CKD patients, there were 3,171 with stage 3a CKD and 1,272 with stage ≥3b CKD.

AA = aldosterone antagonist; ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin-receptor blocker; eGFR = estimated glomerular filtration rate; HDL = high-density lipoprotein; LDL = low-density lipoprotein; MI = myocardial infarction; P2Y = platelet P2Y inhibitor.

LIPIDS. Median LDL-C levels at baseline were clinically comparable albeit statistically lower with worse CKD stage (91.0, 91.5, and 92.5 mg/dl in stage ≥3 CKD, stage 2 CKD, and preserved kidney function groups, respectively; p_{trend} <0.001) (Table 1). In contrast, lipoprotein(a) and triglyceride levels were higher in individuals with more severe CKD. Evolocumab significantly and robustly reduced LDL-C levels regardless of baseline kidney function (Figure 1). At 48 weeks among evolocumab-treated patients, LDL-C had decreased by 58%, 59%, and 59%, compared with placebo among individuals with stage ≥3 CKD, stage 2 CKD, and preserved kidney function, respectively. Changes in other lipid parameters were consistently larger with evolocumab compared with placebo at each stage of CKD (Online Table 1).

CARDIOVASCULAR OUTCOMES AND SAFETY. The overall rates of the primary composite endpoint at 30 months for the pooled treatment group were 15.3%, 11.1%, and 11.1% in the stage ≥3 CKD, stage 2

FIGURE 1 **LDL-C Levels Over Time**



Low-density lipoprotein cholesterol (LDL-C) levels over time according to chronic kidney disease (CKD) category and treatment group. **Red** indicates evolocumab-treated; **blue** indicates placebo. **Solid, dotted, and dashed lines** represent subjects in the estimated glomerular filtration rate <60, 60 to <90, and ≥90 ml/min/1.73 m^2 groups, respectively.

CKD, and preserved kidney function groups, respectively. Compared with preserved kidney function, stage ≥3 CKD was a significant risk factor for the primary endpoint (adjusted hazard ratio [HR]: 1.36; 95% CI: 1.20 to 1.54; $p < 0.001$); stage 2 CKD was not (adjusted HR: 1.04; 95% CI: 0.94 to 1.14; $p = 0.46$). There was no gradient for unstable angina by CKD stage, nor, as expected, was coronary revascularization undertaken more often in patients with worse renal function. Thus, for the key secondary endpoint of cardiovascular death, MI, or stroke, the corresponding rates were 11.5%, 7.0%, and 6.2%. In adjusted analyses, both stage ≥3 CKD (HR: 1.65; 95% CI: 1.41 to 1.92; $p < 0.001$) and stage 2 CKD (HR: 1.14; 95% CI: 1.01 to 1.29; $p = 0.04$) were associated with increased risk compared with patients with preserved kidney function.

As shown in **Table 2**, relative risk reduction with evolocumab compared with placebo for the primary endpoint was similar in stage ≥3 CKD (HR: 0.89; 95% CI: 0.76 to 1.05), stage 2 CKD (HR: 0.85; 95% CI: 0.77 to 0.94), and preserved kidney function (HR: 0.82; 95% CI: 0.71 to 0.94; $p_{interaction} = 0.77$). Absolute risk reduction (ARR) at 30 months for the primary endpoint was 1.5% (95% CI: −0.8% to 3.8%; NNT at 30 months = 66; $p = 0.20$) with stage ≥3 CKD, 1.8% (95% CI: 0.8% to 2.8%; NNT at 30 months = 56; $p < 0.001$) with stage 2 CKD, and 2.2% (95% CI: 0.7% to 3.6%; NNT at 30 months = 48; $p = 0.003$) with preserved kidney function (**Table 2, Central Illustration**). Trends across CKD stage were consistent with more robust risk reduction for the hard components of the primary endpoint (cardiovascular death, MI, and stroke) than for hospitalization for unstable angina or coronary revascularization (**Table 2**). Relative risk reductions with evolocumab for the key secondary endpoint were similar across CKD stages ($p_{interaction} = 0.75$)—stage ≥3 CKD (HR: 0.79; 95% CI: 0.65 to 0.95), stage 2 CKD (HR: 0.82; 95% CI: 0.72 to 0.93), and preserved kidney function (HR: 0.75; 95% CI: 0.62 to 0.90). However, the ARRs for the key secondary endpoint were numerically larger among those with stage ≥3 CKD (2.5%; 95% CI: 0.4% to 4.7%; NNT = 39; $p = 0.02$) compared with individuals with stage 2 CKD (1.5%; 95% CI: 0.7% to 2.3%; NNT = 68; $p = 0.004$) and preserved kidney function (1.7%; 95% CI: 0.5% to 2.8%; NNT = 60; $p = 0.01$).

TABLE 2 Primary, Key Secondary, and Component Endpoints According to Baseline Kidney Function and Randomized Therapy

		Evolocumab (n = 13,782)		Placebo (n = 13,772)		Evolocumab vs. Placebo (n = 27,554)	
	CKD Subgroup	Events	KM (%)	Events	KM (%)	HR (95% CI)	ARR (%) (95% CI)
Primary	Stage ≥3	296	14.6	303	16.1	0.89 (0.76 to 1.05)	−1.5 (−3.8 to 0.8)
	Stage 2	688	10.2	818	12.0	0.85 (0.77 to 0.94)	−1.8 (−2.8 to −0.8)
	Preserved function	360	10.0	439	12.2	0.82 (0.71 to 0.94)	−2.2 (−3.6 to −0.7)
Key secondary	Stage ≥3	205	10.3	236	12.8	0.79 (0.65 to 0.95)	−2.5 (−4.7 to −0.4)
	Stage 2	423	6.2	523	7.7	0.82 (0.72 to 0.93)	−1.5 (−2.3 to −0.7)
	Preserved function	188	5.4	252	7.1	0.75 (0.62 to 0.90)	−1.7 (−2.8 to 0.5)
Cardiovascular death	stage ≥3	78	4.0	82	4.7	0.88 (0.64 to 1.20)	−0.7 (−2.1 to 0.7)
	Stage 2	120	1.8	105	1.6	1.16 (0.89 to 1.51)	0.3 (−0.2 to 0.7)
	Preserved function	53	1.6	52	1.3	1.03 (0.70 to 1.51)	0.2 (−0.4 to 0.8)
Myocardial infarction	Stage ≥3	107	5.5	138	7.4	0.70 (0.55 to 0.91)	−2.0 (−3.6 to −0.3)
	Stage 2	252	3.8	330	4.8	0.78 (0.66 to 0.91)	−1.1 (−1.8 to −0.4)
	Preserved function	109	3.0	171	4.9	0.64 (0.50 to 0.81)	−1.9 (−2.8 to −0.9)
Hospitalization for unstable angina	Stage ≥3	43	2.2	33	1.8	1.20 (0.76 to 1.89)	0.4 (−0.6 to 1.4)
	Stage 2	117	1.7	125	1.9	0.96 (0.74 to 1.23)	−0.1 (−0.6 to 0.3)
	Preserved function	76	2.1	80	2.1	0.95 (0.70 to 1.31)	−0.04 (−0.7 to 0.6)
Coronary revascularization	Stage ≥3	137	6.8	147	7.7	0.85 (0.68 to 1.08)	−1.0 (−2.7 to 0.7)
	Stage 2	399	6.0	514	7.6	0.79 (0.69 to 0.90)	−1.6 (−2.4 to −0.8)
	Preserved function	223	6.1	303	8.6	0.74 (0.62 to 0.87)	−2.5 (−3.7 to −1.3)
Stroke	Stage ≥3	56	3.0	64	3.3	0.79 (0.55 to 1.14)	−0.4 (−1.6 to 0.8)
	Stage 2	105	1.5	142	2.1	0.75 (0.58 to 0.97)	−0.6 (−1.1 to −0.1)
	Preserved function	46	1.3	55	1.6	0.84 (0.56 to 1.24)	−0.3 (−0.9 to 0.4)
All-cause death	Stage ≥3	128	6.2	143	7.9	0.82 (0.65 to 1.04)	−1.7 (−3.4 to 0.01)
	Stage 2	219	3.2	189	2.7	1.18 (0.97 to 1.43)	0.5 (−0.1 to 1.1)
	Preserved function	97	2.9	93	2.5	1.06 (0.80 to 1.41)	0.4 (−0.4 to 1.2)

Event rate for primary endpoint, key secondary endpoint, and components of the endpoints. The primary endpoint included cardiovascular death, myocardial infarction, stroke, hospitalization for unstable angina, or coronary revascularization. The key secondary endpoint included cardiovascular death, myocardial infarction, or stroke. $p_{interaction} = 0.77$ and 0.75 for the HR for the primary and key secondary endpoints, respectively. $p_{trend} = 0.03$ and 0.01 for the ARR in the primary and key secondary endpoints, respectively. Evolocumab: n = 2,302, 7,456, and 4,024 for stage ≥3 CKD, stage 2 CKD, and preserved kidney function, respectively. Placebo: n = 2,141, 7,578, and 4,053 for stage ≥3 CKD, stage 2 CKD, and preserved kidney function, respectively.

ARR = absolute risk reduction; CI = confidence interval; CKD = chronic kidney disease; HR = hazard ratio; KM% = Kaplan Meier event rates at 30 months.

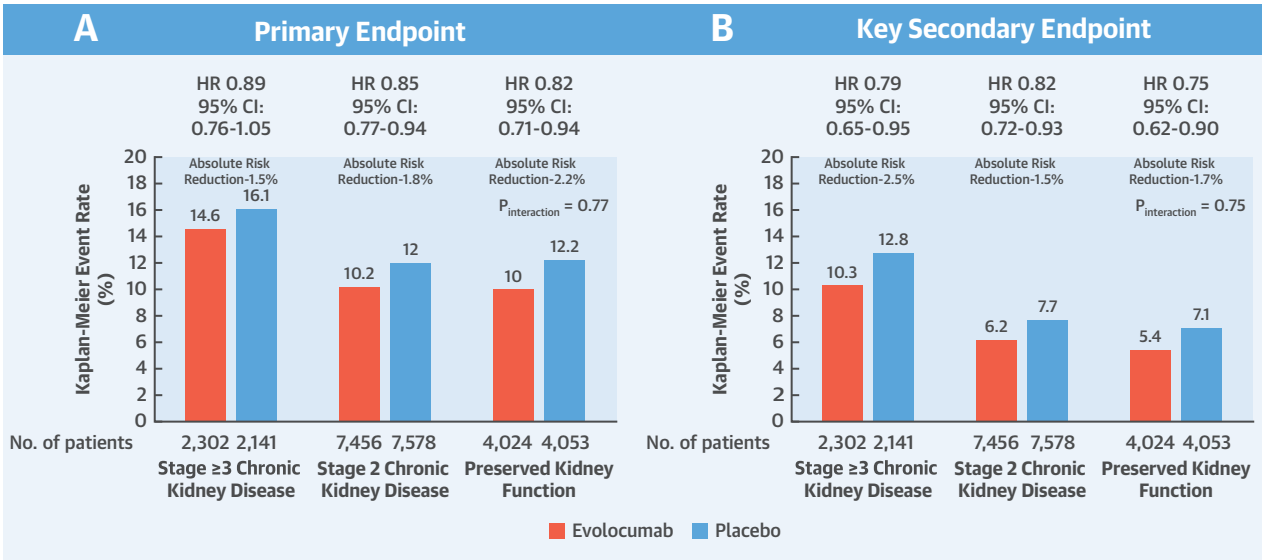
Analyses of eGFR as a continuous variable were qualitatively similar and consistent with preserved reductions in absolute risk with evolocumab compared with placebo for the both the primary endpoint and key secondary endpoint as eGFR declined. Absolute risk reduction was numerically greater in individuals with the late stage 3 and 4 CKD (**Figure 2**), but tests of interaction between treatment and eGFR for the primary ($p_{interaction} = 0.42$) and key secondary endpoint ($p_{interaction} = 0.28$) were nonsignificant. The incidence of the primary endpoint and the key secondary endpoint decreased as the achieved LDL-C concentration at 1 month decreased both in individuals with stage ≥3 CKD and those with stage 2 CKD or preserved kidney function. There was no evidence in either group for a threshold below which the benefits of further LDL-C lowering diminished (Online Figure 1).

Results were qualitatively similar across most of the secondary endpoints and for the individual components of the primary and key secondary endpoints (**Table 2**, Online Table 2). Among the 1,272 individuals with stage ≥3b CKD, results for the primary endpoint (HR: 0.74; 95% CI: 0.56 to 0.97) and the key secondary endpoint (HR: 0.66; 95% CI: 0.48 to 0.90) were consistent with the overall findings and showed absolute risk reductions of 5.4% and 7.4%, respectively.

Discontinuation rates for placebo compared with evolocumab were similar within each category of baseline kidney function—preserved kidney function (placebo: 511 [12.6%], evolocumab: 461 [11.5%]; p = 0.17), stage 2 CKD (placebo: 909 [12.0%], evolocumab: 887 [11.9%]; p = 0.21), stage ≥3 CKD (placebo: 325 [15.2%], evolocumab: 334 [14.5%]; p = 0.36).

Adverse events leading to treatment discontinuation, serious adverse events, muscle-related events, allergic reactions, new-onset diabetes, and neurocognitive changes occurred with a numerically higher frequency in those with stage ≥3 CKD than in individuals with less severe kidney impairment (Online Table 3). However, among those with stage ≥3 CKD,

CENTRAL ILLUSTRATION **PCSK9 Inhibition in Chronic Kidney Disease**



Charytan, D.M. et al. J Am Coll Cardiol. 2019;73(23):2961–70.

Relative and absolute risk of the **(A)** primary endpoint (combined cardiovascular death, myocardial infarction, stroke, hospitalization for unstable angina, or coronary revascularization) and **(B)** key secondary endpoint (cardiovascular death, myocardial infarction, or stroke), according to CKD stage. Kaplan-Meier event rates at 30 months are provided according to treatment group with placebo in **blue** and evolocumab in **red**. CI = confidence interval; HR = hazard ratio.

there was no evidence of an increase in the risk of adverse events in those taking evolocumab compared with those receiving placebo.

EFFECT ON KIDNEY FUNCTION. Kidney function was analyzed as both a binary endpoint and rate of decline. The Kaplan-Meier event rate for ≥50% decline at 30 months was 0.5% and 0.6% (p = 0.86) in the evolocumab and placebo groups, respectively. Results were similar and did not show a significant difference between the evolocumab and placebo groups when thresholds of ≥30% or ≥40% decline in eGFR were used (Table 3). Exploratory analyses did not demonstrate significant effect modification according to baseline CKD stage or the presence of diabetes.

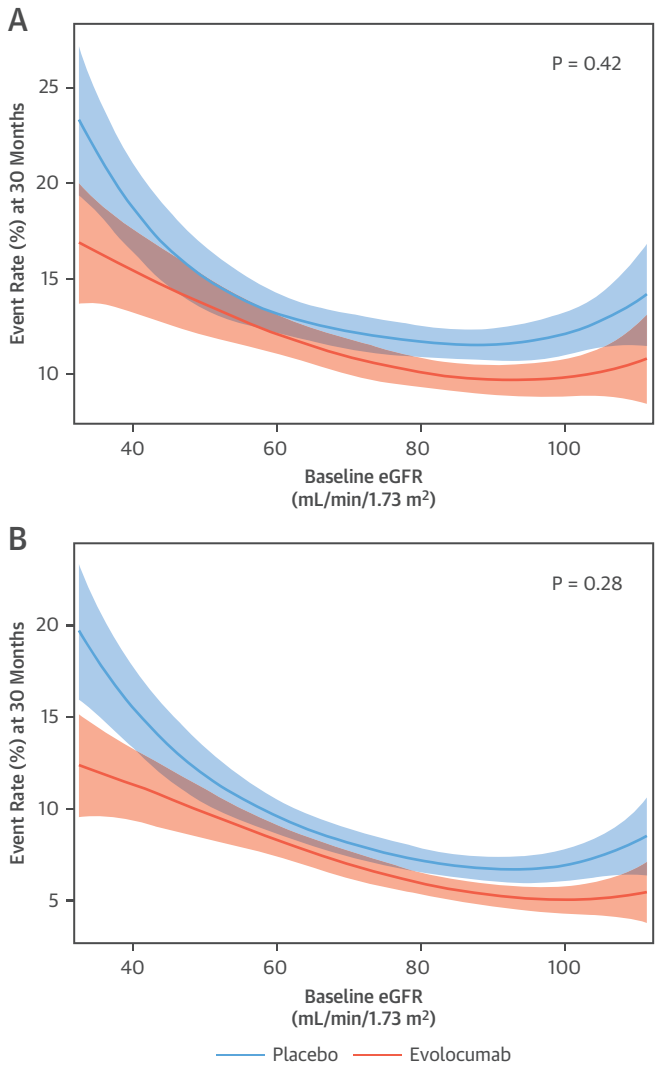
When eGFR was analyzed as a continuous variable (Online Figure 2), differences in eGFR between placebo and evolocumab-treated patients over time were minimal and nonsignificant (p = 0.15). There was no significant evidence of effect modification by baseline CKD stage (p = 0.52) or diabetes (p = 0.72).

DISCUSSION

In this analysis of 27,554 patients enrolled in the FOURIER trial, we investigated outcomes in patients with clinically evident atherosclerosis and hyperlipidemia on statin therapy randomized to placebo or evolocumab therapy. We found that compared with placebo, evolocumab demonstrates a similar potency for LDL-C lowering and a similar safety profile both in individuals with preserved kidney function and those with mild or moderate kidney impairment. Relative risk reductions for the primary endpoint and key secondary cardiovascular outcomes were similar regardless of CKD stage. However, given the higher event rates at lower eGFR, the absolute reduction in cardiovascular death, MI, or stroke with evolocumab was more robust with more advanced CKD.

Although several sizeable randomized trials have raised questions about the benefits of statins among individuals with severe CKD requiring maintenance dialysis (3–5), they do appear to provide significant cardioprotective benefits among those with less severe kidney impairment (4,16). Nevertheless, work by the Cholesterol Treatment Trialists' collaboration highlights several important limitations of statin therapy in the setting of CKD. First, similar to individuals with preserved kidney function, among individuals with CKD, the benefits appear to be related to the degree of cholesterol lowering, with a 21% relative risk reduction for each mmol/l reduction in LDL-C. Second, their benefits are attenuated as CKD

FIGURE 2 Event Rates With Evolocumab and Placebo According to eGFR at Baseline



Event rates for primary endpoint **(A)** and key secondary endpoint **(B)** according to randomized therapy and baseline estimated glomerular filtration rate (eGFR). **Red** indicates evolocumab; and **blue** indicates placebo. **Light blue and light red shading** shows the 95% confidence bands.

becomes more severe, perhaps due to a high risk of death from nonatherosclerotic causes of death such as arrhythmia and infection (17). Most importantly, the absolute incidence of all-cause mortality and cardiovascular events remains quite high among patients with CKD (4,16,17) and suggests a clear need for additional therapies in this high-risk population.

These data suggest that individuals with CKD and cardiovascular disease might particularly benefit from potent lipid-lowering agents such as the PCSK9 inhibitors, which were recently proven to reduce the risk of cardiovascular events among patients with cardiovascular disease who are already receiving statins (7-10). Although a recent pooled analysis of 8 randomized trials demonstrated good safety and equivalent lipid-lowering efficacy with alirocumab compared to placebo among 4,629 patients with and without CKD (18), to our knowledge, a detailed description of the effect of PCSK9 inhibitors on survival and cardiovascular outcomes in the setting of CKD has not been previously evaluated. Our analysis of 27,554 randomized patients in the FOURIER trial confirmed the excellent safety profile of this medication by demonstrating that the relative risks of adverse events with placebo compared with evolocumab, another agent within this class, were similar across the spectrum of CKD. Furthermore, our results extend these findings by providing evidence that PCSK9 inhibition reduces the risk of cardiovascular events among individuals with mild or moderate CKD. Although relative risk reduction for both the primary and key secondary outcomes was similar regardless of baseline kidney function, absolute risk reduction was particularly robust among individuals with more severe CKD, particularly for the key secondary endpoint. This may reflect inclusion in the key secondary endpoint of only objective cardiovascular endpoints of cardiovascular death, MI, and stroke. Relative risk reduction with evolocumab in individuals with stage ≥3 CKD was more robust for these endpoints than for the additional endpoints included in the primary endpoint—hospitalization for unstable angina or coronary revascularization, which may both be susceptible to differential symptoms of and recognition of cardiovascular disease and differential clinical decision making in the setting of CKD (19,20). Furthermore, analyses of the limited number of individuals with stage 3b and 4 CKD were consistent with the overall findings, and demonstrated significant reduction in the risk of cardiovascular events among evolocumab-treated patients. Further studies would be welcome, but these observations suggest that evolocumab may be particularly suited for the treatment of individuals with CKD.

Although the cardiovascular and survival benefits of cholesterol-lowering medications, particularly statins, are well-established, their impact on kidney function is less well understood. In the 4S (Scandinavian Simvastatin Study), simvastatin was associated with a 32% reduction in the incidence of a ≥25% decline in eGFR (21). However, more recent analyses of the CRIC (Chronic Renal Insufficiency Cohort) were unable to confirm an association between total or LDL-C concentrations and CKD progression in a large cohort of patients with confirmed CKD (22), while

TABLE 3 Change in Kidney Function Over Time According to Treatment Group

	Evolocumab (n = 13,782)		Placebo (n = 13,772)		Evolocumab vs. Placebo (n = 27,554)		
	Events	KM (%)	Events	KM (%)	HR (95% CI)	p Value	p Interaction
Overall							
≥30% decline in eGFR	367	3.2	373	3.3	0.99 (0.86–1.14)	0.90	–
≥40% decline in eGFR	159	1.4	152	1.4	1.05 (0.84–1.31)	0.66	–
≥50% decline in eGFR	63	0.5	65	0.6	0.97 (0.69–1.37)	0.86	–
≥50% decline in subgroups							
Diabetes							0.15
No diabetes (evolocumab n = 8,728, placebo n = 8,750)	16	0.2	24	0.3	0.67 (0.36–1.27)	0.22	–
Diabetes (evolocumab n = 5,054, placebo n = 5,022)	47	1.0	41	1.0	1.17 (0.77–1.78)	0.46	–
Baseline eGFR							0.09
Stage ≥ 3 CKD (evolocumab n = 2,302, placebo n = 2,141)	24	1.1	26	1.2	0.87 (0.50–1.52)	0.62	–
Stage 2 CKD (evolocumab n = 7,456, placebo n = 7,578)	32	0.5	23	0.4	1.39 (0.82–2.38)	0.23	–
Preserved kidney function (evolocumab n = 4,024, placebo n = 4,053)	7	0.2	16	0.5	0.45 (0.19–1.10)	0.07	–

Event rate for binary changes in eGFR overall (≥30%, 40%, or 50% decline in eGFR) or in subgroups defined by diabetes or baseline CKD stage. Calculations were based on Cox proportional hazards models adjusted for randomization strata (LDL-C ≥85 mg/dl and region).

eGFR = estimated glomerular filtration rate; other abbreviations as in Table 2.

subgroup analyses of the SHARP (Study of Heart and Renal Protection) were unable to confirm a significant effect on the rate of CKD progression of the combination simvastatin and ezetimibe compared with placebo therapy (23). It remains unclear whether these differential findings relate to the duration of the follow-up, differences in baseline risk, or the biology of the agents studied.

We did not find a significant effect of evolocumab therapy on the currently accepted standard endpoint used to define kidney function decline by the U.S. Food and Drug Administration (≥50% decline in eGFR) or when less strict binary definitions of kidney function decline were utilized. In this context, the absence of a significant effect of evolocumab compared with placebo in our analysis is consistent with results seen by Toth et al. (18) in their analysis of a much smaller number of alirocumab-treated patients. Given the lipid-lowering potency of the PCKS9 class of agents compared with statins alone, our data suggests that cholesterol-lowering therapy in general is unlikely to be associated with kidney-specific benefits in the short- to medium-term, and that future efforts to slow CKD progression should focus on other pathways. In addition, exploratory analyses in subgroups defined by CKD stage and diabetes as well as those using a continuous measure of kidney function also failed to identify definitive signals of a treatment effect in the included population. However, given that follow-up was relatively short and kidney function decline may occur over a long time frame, data on baseline albuminuria was unavailable, and the number of patients with advanced CKD at high risk of progression was limited, we cannot definitively rule out the potential for kidney-specific benefits of evolocumab, particularly beyond 3 years.

STUDY LIMITATIONS. There were few patients with stage 4 or 5 CKD enrolled in FOURIER, and individuals with eGFR <20 ml/min/1.73 m^2 were excluded from enrollment. It is unclear how our data apply to patients with albuminuric kidney disease, and our results may not be generalizable to individuals with the most severe stages of CKD or patients without stable atherosclerosis and LDL-C ≥70 mg/dl (or non-high-density lipoprotein ≥100 mg/dl). Our analyses were post hoc, and the trial was not specifically powered to examine interactions with CKD stage. However, point-estimates were consistent with a preserved effect in moderate CKD, and there were more than 4,400 individuals with stage ≥3 CKD and more than 23,000 with stage 2 CKD or preserved kidney function enrolled in the FOURIER study. Thus, it is unlikely that qualitative effect modification was missed by our analysis. Additionally, overall follow-up was short (2.2 years), which limited the ability to detect a significant effect on outcomes, particularly for CKD progression. Finally, CKD progression did not require confirmation at ≥30 days and was not specifically adjudicated. Given the relatively small number of patients at risk for CKD progression during the trial time frame, our analysis of these endpoints should be interpreted cautiously.

CONCLUSIONS

In stable individuals with moderate CKD and clinically evident atherosclerosis, ACS, and

hyperlipidemia despite statin therapy, PCSK9 inhibition with evolocumab was safe and more effective than statin monotherapy in reducing LDL-C and the risk of cardiovascular events. Further cardiovascular outcomes trials examining the benefits of evolocumab in individuals with CKD are needed, especially among those with more severe reductions in eGFR.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: In statin-treated patients with clinical atherosclerosis, evolocumab reduces the risk of cardiovascular events without adversely affecting kidney function, and its efficacy and safety are consistent across the spectrum of renal impairment.

TRANSLATIONAL OUTLOOK: Additional trials are needed to assess the renal effects of evolocumab in individuals at high risk of disease progression and in those with the most advanced degrees of renal dysfunction.

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KEY WORDS atherosclerosis, cardiovascular disease, cardiovascular risk, chronic kidney disease, lipids, PCSK9

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

Supplementary Table 1. Change in additional lipid parameters at week 48 according to treatment and kidney function

Lipid Parameter		Placebo			Evolocumab			Treatment Difference Evolocumab-Placebo		
		% Change from Baseline			% Change from Baseline			% Change from Baseline		
	CKD Stage	Mean	95% CI	P Value	Mean	95% CI	P Value	Mean	95% CI	P Value
Total Cholesterol										
	≥Stage 3	-1.1	-2.0, -0.2	0.02	-36.2	-37.0, -35.3	<0.001	-35.1	-36.2, -33.9	<0.001
	Stage 2	-0.8	-1.3, -0.3	0.002	-36.2	-36.7, -35.7	<0.001	-35.4	-36.0, -34.8	<0.001
	Preserved Function	0.9	0.2, 1.6	0.01	-34.9	-35.6, -34.2	<0.001	-35.8	-36.7, -34.9	<0.001
Non-HDL Cholesterol										
	≥Stage 3	-0.7	-1.9, 0.5	0.26	-51.4	-52.7, -50.3	<0.001	-50.8	-52.4, -49.2	<0.001
	Stage 2	-0.3	-0.9, 0.4	0.42	-52.2	-52.9, -51.5	<0.001	-51.9	-52.8, -51.1	<0.001
	Preserved Function	1.7	0.8, 2.7	<0.001	-49.7	-50.7, -48.7	<0.001	-51.4	-52.6, -50.2	<0.001
HDL Cholesterol										
	≥Stage 3	-0.6	-1.4, 0.2	0.16	7.8	7.1, 8.6	<0.001	8.4	7.4, 9.5	<0.001
	Stage 2	-0.4	-0.8, 0.1	0.09	7.8	7.3, 8.2	<0.001	8.1	7.6, 8.6	<0.001
	Preserved Function	0.2	-0.4, 0.8	0.52	8.1	7.4, 8.7	<0.001	7.9	7.1, 8.7	<0.001
Triglycerides										
	≥Stage 3	4.6	2.9, 6.3	<0.001	-12.7	-14.3, -11.0	<0.001	-17.3	-19.5, -15.1	<0.001
	Stage 2	5.7	4.7, 6.7	<0.001	-.9.9	-10.9, -8.9	<0.001	-15.5	-16,8, -14.2	<0.001
	Preserved Function	9.6	7.9, 11.2	<0.001	-5.8	-7.5, -4.2	<0.001	-15.4	-17.6, -13.3	<0.001
ApoB										
	≥Stage 3	0.7	-0.6, 2.0	0.27	-47.4	-48.6, -46.1	<0.001	-48.1	-49.7, -46.5	<0.001
	Stage 2	2.2	1.5, 2.9	<0.001	-47.1	-47.8, -46.4	<0.001	-49.3	-50.1, -48.4	<0.001
	Preserved Function	3.5	2.5, 4.5	<0.001	-44.3	-45.3, -43.3	<0.001	-47.8	-49.1, -46.6	<0.001
apoA1										
	≥Stage 3	0.4	-0.3, 1.09	0.23	5.1	4.4, 5.7	<0.001	4.7	3.8, 5.5	<0.001
	Stage 2	1.2	0.8, 1.6	<0.001	5.7	5.3, 6.1	<0.001	4.5	4.0, 5.0	<0.001
	Preserved Function	2.1	1.6, 2.7	<0.001	6.8	6.3, 7.4	<0.001	4.7	4.0, 5.4	<0.001
Lp(a)*										
	≥Stage 3	0.96	(0.94, 0.98)	<0.001	0.67	(0.65, 0.68)	<0.001	0.70	(0.68, 0.72)	<0.001

Stage 2	0.95	(0.94, 0.96)	<0.001	0.66	(0.65, 0.67)	<0.001	0.69	(0.68, 0.70)	<0.001
Preserved Function	0.94	(0.93, 0.96)	<0.001	0.66	(0.65, 0.67)	<0.001	0.70	(0.69, 0.72)	<0.001

Least squares mean (adjusted mean) is based on a repeated measures ANCOVA model including treatment, randomization strata (LDL >= 85 mg/dL and region), visit and the interaction of treatment-by-visit interaction with the baseline value. 95% CI-95% confidence interval. HDL-high density lipoprotein. Lp(a)-lipoprotein (a). apoB-apolipoprotein B. *For Lp(a), the estimated treatment effect is provided in terms of ratios of geometric means (as a ratio to baseline rather than as % change), which was calculated by exponentially back transforming the LS means based on the ANCOVA model above. If this value is < 1, it means a reduction from baseline

Supplementary Table 2. Additional cardiovascular endpoints according to baseline kidney function and randomized therapy

Endpoints	CKD Subgroup	Evolocumab (N=13782) Events (N)	Evolocumab (N=13782) KM %	Placebo (N=13772) Events (N)	Placebo (N=13772) KM %	Evolocumab vs Placebo (N=27554) HR (95% CI)
CTT (CHD/MI/Stroke/Coronary Revascularization	≥Stage 3	280	13.8	291	15.5	0.87 (0.74, 1.03)
	Stage 2	653	9.7	789	11.6	0.84 (0.75, 0.93)
	Preserved Function	338	9.4	429	12.0	0.78 (0.68, 0.90)
Urgent Coronary Revascularization	≥Stage 3	77	3.8	98	5.1	0.72 (0.54, 0.97)
	Stage 2	213	3.1	287	4.3	0.76 (0.63, 0.90)
	Preserved Function	113	3.1	161	4.5	0.70 (0.55, 0.89)
Elective Coronary Revascularization	≥Stage 3	72	3.6	63	3.2	1.04 (0.74, 1.46)
	Stage 2	219	3.3	276	4.0	0.81 (0.68, 0.96)
	Preserved Function	129	3.6	164	4.6	0.79 (0.63, 1.00)
Hosp for Worsening HF	≥Stage 3	68	3.4	80	4.6	0.78 (0.56, 1.07)
	Stage 2	94	1.5	84	1.3	1.14 (0.85, 1.53)
	Preserved Function	31	0.9	36	1.2	0.88 (0.54, 1.42)
Ischemic Stroke	≥Stage 3	45	2.4	51	2.5	0.80 (0.53, 1.19)
	Stage 2	91	1.3	125	1.8	0.74 (0.56, 0.97)
	Preserved Function	35	1.0	49	1.4	0.71 (0.46, 1.10)

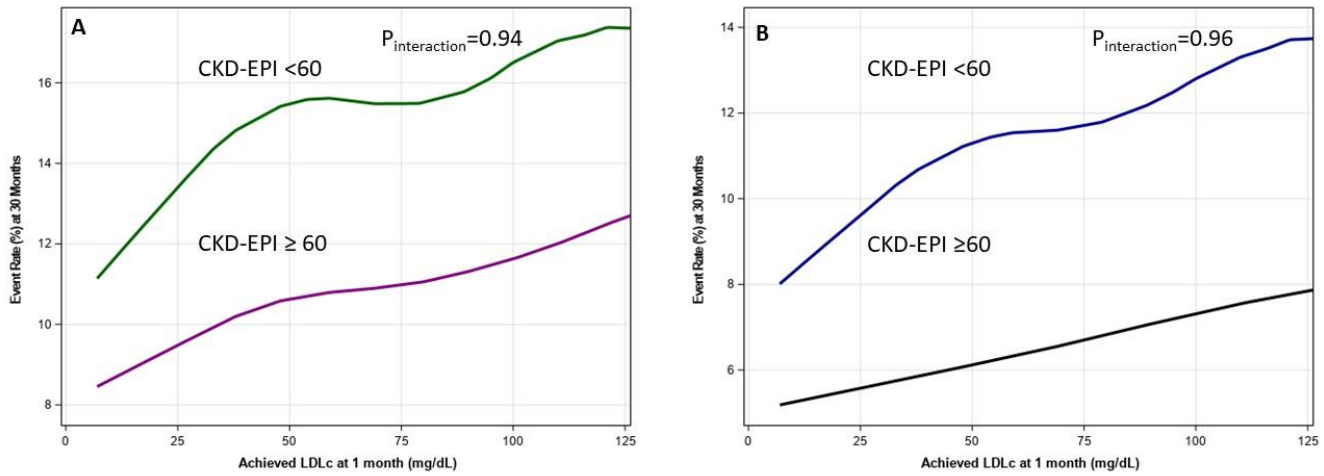
Event rates for additional endpoints. KM% = Kaplan Meier event rates at 30 months. HR = hazard ratio. CI = confidence interval. Evolocumab: N=2302, 7456, and 4024 for ≥Stage 3 CKD, Stage 2 CKD, and Preserved Kidney Function, respectively. Placebo: N=2141, 7578, and 4053 for ≥Stage 3 CKD, Stage 2 CKD, and Preserved Kidney Function, respectively. CHD=coronary heart death. CVD=cardiovascular disease hospitalization. CTT=cholesterol treatment trialists. HF=heart failure. Hosp=hospitalization. MI=myocardial infarction.

Supplementary Table 3. Adverse events according to CKD stage and treatment

	≥Stage 3 CKD (N=4443)		Stage 2 CKD (N=15034)		Preserved Kidney Function (N=8077)	
	Evolocumab (N=2302)	Placebo (N=2141)	Evolocumab (N=7456)	Placebo (N=7578)	Evolocumab (N=4024)	Placebo (N=4053)
Any adverse event	1901/2299(82.7%)	1747/2138(81.7%)	5746/7450(77.1%)	5806/7565(76.8%)	3015/4018(75.0%)	3086/4047(76.3%)
Serious adverse event	750/2299(32.6%)	712/2138(33.3%)	1801/7450(24.2%)	1817/7565(24.0%)	858/4018(21.4%)	874/4047(21.6%)
AE leading to discontinuation	140/2299(6.1%)	126/2138(5.9%)	331/7450(4.4%)	312/7565(4.1%)	137/4018(3.4%)	133/4047(3.3%)
Related to therapy AND leading to discontinuation	44/2299(1.9%)	42/2138(2.0%)	124/7450(1.7%)	114/7565(1.5%)	58/4018(1.4%)	44/4047(1.1%)
Allergic reaction	145/2299(6.3%)	119/2138(5.6%)	479/7450(6.4%)	454/7565(6.0%)	231/4018(5.8%)	206/4047(5.1%)
Muscle-related	312/2299(13.6%)	303/2138(14.2%)	1024/7450(13.7%)	1043/7565(13.8%)	481/4018(12.0%)	488/4047(12.1%)
Rhabdomyolysis	0/2299(0.0%)	4/2138(0.2%)	6/7450(0.1%)	6/7565(0.1%)	2/4018(0.1%)	1/4047(0.0%)
Cataract	66/2299(2.9%)	61/2138(2.9%)	128/7450(1.7%)	139/7565(1.8%)	42/4018(1.1%)	43/4047(1.1%)
New onset diabetes	102/1164(8.8%)	99/1091(9.1%)	394/4739(8.3%)	379/4886(7.8%)	180/2432(7.4%)	166/2360(7.0%)
Neurocognitive	57/2299(2.5%)	58/2138(2.7%)	142/7450(1.9%)	129/7565(1.7%)	62/4018(1.5%)	54/4047(1.3%)
Aminotransferase >3xULN	37/2247(1.7%)	30/2097(1.4%)	114/7344(1.6%)	116/7450(1.6%)	89/3950(2.3%)	96/3970(2.4%)
CK >5x ULN at any post baseline visit	12/2247(0.5%)	19/2097(0.9%)	55/7344(0.8%)	53/7450(0.7%)	28/3950(0.71%)	27/3970(0.7%)

AE=adverse event. ULN=upper limit of normal. CK=creatinine kinase. Comparison of evolocumab with placebo were non-significant within each CKD stage (P≥0.15) for all comparisons except for rhabdomyolysis in ≥stage 3 CKD (P=0.04).

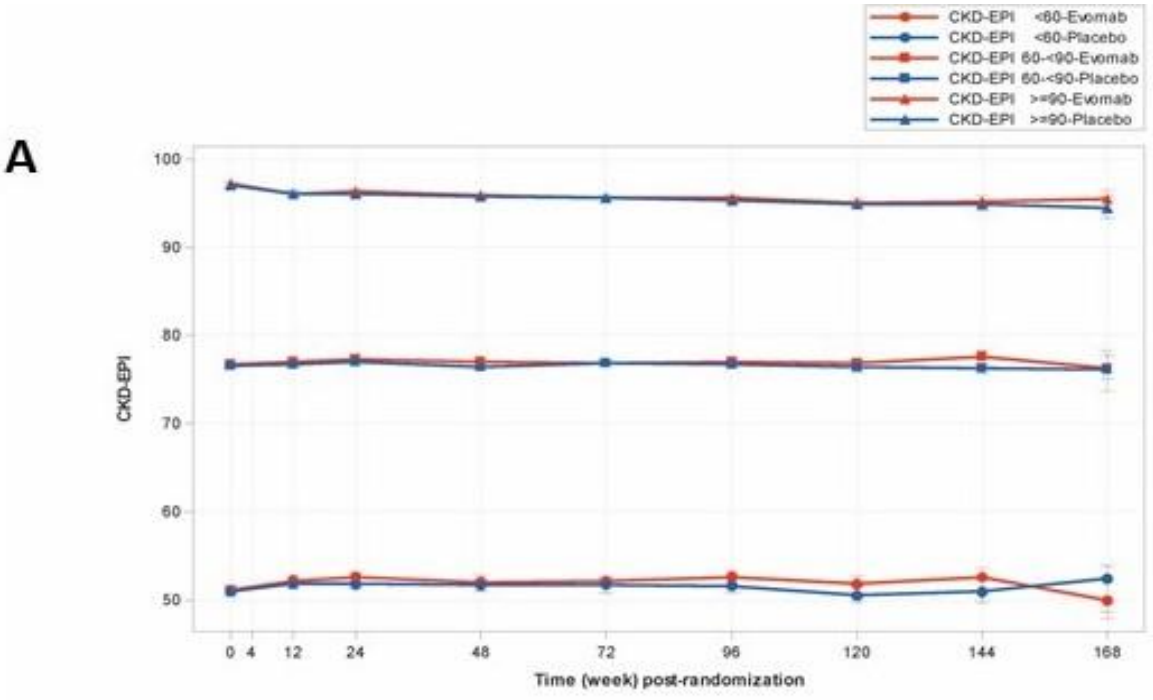
Supplementary Figure 1. Outcomes according CKD and achieved LDL cholesterol concentration at one month.



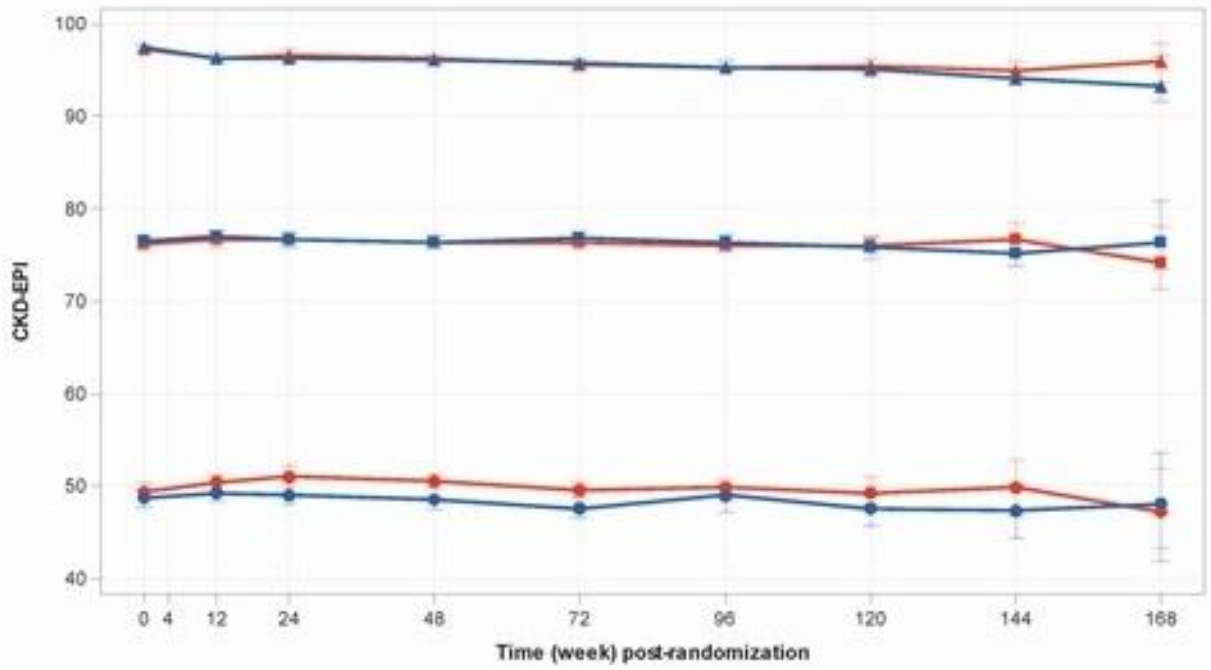
Adjusted event probability for the primary endpoint (A) or key secondary endpoint (B) according the achieved LDL cholesterol concentration at one month and baseline estimated glomerular filtration rate according to the CKD-EPI equation. P values are provided for the interaction between achieved LDL concentration and CKD stage.

Supplementary Figure 2. eGFR over time according to baseline kidney function and CKD group.

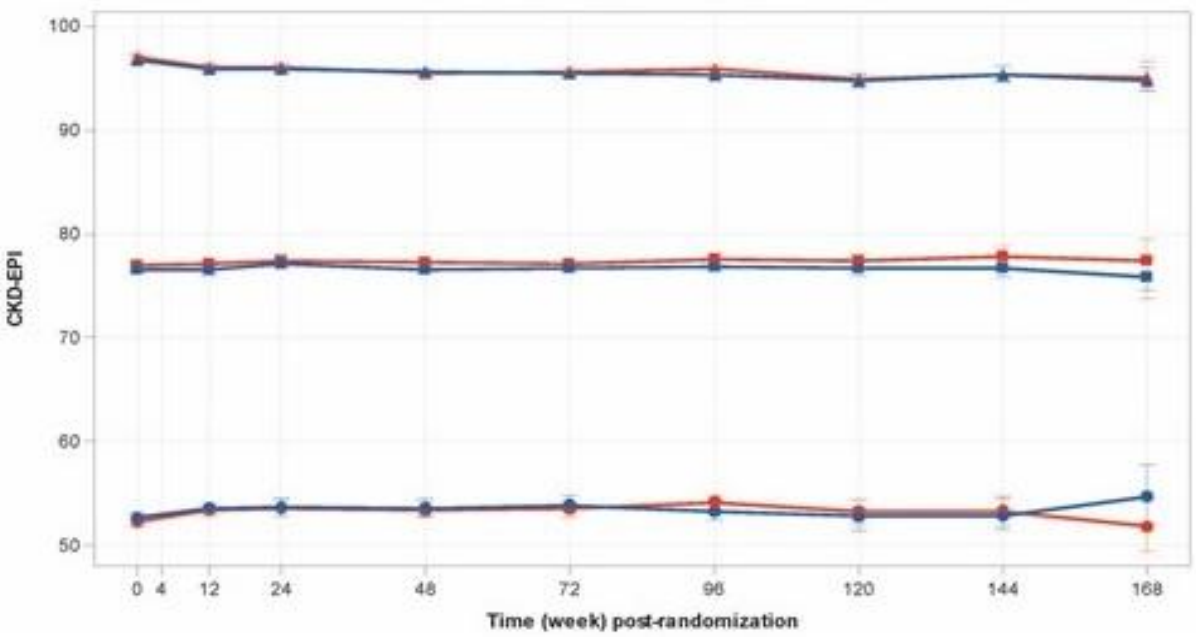
Legend—Estimated glomerular filtration rate (eGFR) over time according to baseline kidney function in the overall population (A), individuals with diabetes (B) and individuals without diabetes at baseline (C). Evomab-evolocumab. Evolocumab treated subjects are shown in red and placebo-treated patients are shown in blue. Circles, squares and triangles represent, patients in the eGFR ≤60, 60-<90, and ≥90 mL/min/1.73m^2 groups, respectively.



B


100
90
80
70
60
50
40
CKD-EPI
0
4
12
24
48
72
96
120
144
168
Time (week) post-randomization

C


100
90
80
70
60
50
CKD-EPI
0 4 12 24 48 72 96 120 144 168
Time (week) post-randomization