HDL Cholesterol Is Not Associated with Lower Mortality in Patients with Kidney Dysfunction

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ABSTRACT

In the general population, HDL cholesterol (HDL-C) is associated with reduced cardiovascular events. However, recent experimental data suggest that the vascular effects of HDL can be heterogeneous. We examined the association of HDL-C with all-cause and cardiovascular mortality in the Ludwigshafen Risk and Cardiovascular Health study comprising 3307 patients undergoing coronary angiography. Patients were followed for a median of 9.9 years. Estimated GFR (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration eGFR creatinine-cystatin C ($eGFR_{creat-cys}$) equation. The effect of increasing HDL-C serum levels was assessed using Cox proportional hazard models. In participants with normal kidney function (eGFR>90 ml/min per 1.73 m^2), higher HDL-C was associated with reduced risk of all-cause and cardiovascular mortality and coronary artery disease severity (hazard ratio [HR], 0.51, 95% confidence interval [95% CI], 0.26–0.92 [*P*=0.03]; HR, 0.30, 95% CI, 0.13–0.73 [*P*=0.01]). Conversely, in patients with mild (eGFR=60–89 ml/min per 1.73 m^2) and more advanced reduced kidney function (eGFR<60 ml/min per 1.73 m^2), higher HDL-C did not associate with lower risk for mortality (eGFR=60–89 ml/min per 1.73 m^2: HR, 0.68, 95% CI, 0.45–1.04 [*P*=0.07]; HR, 0.84, 95% CI, 0.50–1.40 [*P*=0.50]; eGFR<60 ml/min per 1.73 m^2: HR, 1.18, 95% CI, 0.60–1.81 [*P*=0.88]; HR, 0.82, 95% CI, 0.40–1.69 [*P*=0.60]). Moreover, Cox regression analyses revealed interaction between HDL-C and eGFR in predicting all-cause and cardiovascular mortality (*P*=0.04 and *P*=0.02, respectively). We confirmed a lack of association between higher HDL-C and lower mortality in an independent cohort of patients with definite CKD (*P*=0.63). In summary, higher HDL-C levels did not associate with reduced mortality risk and coronary artery disease severity in patients with reduced kidney function. Indeed, abnormal HDL function might confound the outcome of HDL-targeted therapies in these patients.

J Am Soc Nephrol 25: 1073–1082, 2014. doi: 10.1681/ASN.2013050482

Cardiovascular disease (CVD) represents the leading cause of death in Western society. In 2009, coronary artery disease (CAD) was responsible for approximately 400,000 deaths and an estimated >600,000 cardiovascular events among United States inhabitants.[1] In addition to traditional risk factors, such as arterial hypertension, smoking, dyslipidemia, obesity, and diabetes, CKD was identified as a potent and independent risk factor for CVD.[2–4] Two related meta-analyses that included

Received May 13, 2013. Accepted September 8, 2013.

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Published online ahead of print. Publication date available at www.jasn.org.

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>1 million individuals recently demonstrated a strong association between estimated GFR (eGFR) or albuminuria and mortality in patients with arterial hypertension as well as diabetes.[5,6] Moreover, it was previously documented that even mildly reduced kidney function represents a major risk factor for atherosclerotic CVD.[7,8] Recent reports indicate a 14.0% prevalence of CKD in the general population, which underscores the importance to accurately identify patients with impaired kidney function and to examine the mechanisms underlying the high cardiovascular burden in these patients.[9]

LDL and HDL are crucially involved in the pathogenesis of atherosclerotic CVD. It is well known that LDL may promote the formation of vascular atherosclerotic lesions. In contrast, HDL has commonly been thought to act as a vasoprotective agent mainly by preventing endothelial dysfunction that reflects the initial step of atherosclerosis.[10] However, there is a growing body of experimental evidence indicating that HDL may lose its vasoprotective properties in certain clinical conditions (*e.g.*, diabetes, CAD).[11] In line with these findings, our group recently showed that even in patients with incipient CKD, HDL is transformed into a noxious particle inducing endothelial dysfunction and arterial hypertension.[12] Interestingly, a recent study failed to demonstrate a beneficial effect of genetically elevated HDL cholesterol (HDL-C) serum levels on the rate of cardiovascular events.[13] Moreover, increasing HDL-C serum levels using pharmacologic inhibitors of the cholesterol-ester transfer protein did not reduce the rate of cardiovascular events.[10,14] In addition, a recent study showed that higher levels of HDL-C were not significantly associated with reduced carotid intima media thickness in patients with more advanced CKD.[15]

This study aimed to prospectively evaluate the effect of a reduced kidney function on long-term outcome of patients undergoing coronary angiography and to assess the effect of HDL-C levels on the outcome in patients with normal and reduced kidney function.

RESULTS

Table 1 shows characteristics of Ludwigshafen Risk and Cardiovascular Health (LURIC) study participants (*N*=3307). Patients were classified into three categories by their estimated GFR using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) creatinine-cystatin C equation ($eGFR_{creat\text{-}cys}$). Patients with advanced kidney failure (eGFR <60 ml/min per

Table 1. Baseline characteristics of LURIC study participants

Characteristics	Overall (*N*=3307)	eGFR (ml/min per 1.73 m^2)			*P* Value[a]
		≥90 (*n*=1209)	60–89 (*n*=1642)	<60 (*n*=456)	
All-cause mortality (%)	995 (30.0)	209 (17.3)	514 (31.3)	272 (59.6)	<0.001
Cardiovascular mortality (%)	622 (18.8)	121 (10.0)	317 (19.9)	184 (40.4)	<0.001
Age (yr)	62.7±10.6	55.8±10.2	65.5±8.4	70.8±8.4	<0.001
Sex (% male)	69.6	78.2	66.5	58.1	<0.001
Body mass index (kg/m^2)	27.5±4.1	27.2±4.0	27.7±4.0	27.5±4.4	0.02
Systolic BP (mmHg)	141.1±23.6	136.4±21.8	143.4±23.8	145.4±25.5	<0.001
Diastolic BP (mmHg)	81.0±11.5	80.5±10.9	81.8±11.6	79.2±11.9	<0.001
Total cholesterol (mg/dl)	192.4±39.1	194.1±40.5	192.6±37.4	186.7±40.4	0.002
Triglycerides (mg/dl)	147.0±92.0	144.0±93.0	145.0±91.0	159.0±91.0	0.07
HDL-C (mg/dl)	38.7±10.8	39.1±10.7	39.0±10.8	36.8±11.0	<0.001
LDL-C (mg/dl)	116.6±34.3	117.3±35.2	117.4±33.6	111.3±34.2	0.002
Glycated hemoglobin (%)	6.3±1.2	6.1±1.2	6.4±1.2	6.7±1.4	<0.001
Creatinine (mg/dl)	1.0±0.4	0.8±0.1	1.0±0.1	1.4±0.8	<0.001
Cystatin C (mg/L)	1.0±0.4	0.8±0.1	1.0±0.1	1.6±0.7	<0.001
eGFR (ml/min per 1.73 m^2)	81.7±20.1	101.5±8.0	77.1±8.5	46.2±11.5	<0.001
hsCRP (mg/L)	3.4 (7.3)	2.4 (5.7)	3.5 (7.3)	6.5 (12.4)	<0.001
sICAM-1 (mg/L)	258.2±98.7	244.7±73.2	260.4±106.1	294.9±129.3	<0.001
IL-6 (ng/L)	5.2 (6.1)	4.1 (4.8)	5.3 (6.1)	7.7 (7.8)	<0.001
CAD (%)	77.9	72.9	79.9	83.8	<0.001
Friesinger score	5.4±3.9	4.9±3.9	5.6±3.9	6.2±3.9	<0.001
Acute coronary syndrome (%)	31.3	28.7	32.0	35.5	0.02
Statin use (%)	46.9	45.9	48.0	45.8	0.48
Lipid-lowering therapy (%)[b]	48.6	48.2	49.3	46.9	0.63
Diabetes (%)	39.9	30.4	42.4	56.4	<0.001
Smoking (%)	64.0	70.6	61.0	57.2	<0.001
Hypertension (%)	72.7	61.9	77.6	84.0	<0.001

Values are presented as the mean±SD, median (interquartile range) or *n* (%). LDL-C, LDL cholesterol.
[a]Comparison between patients with an eGFR≥90, eGFR 60–89 ml/min per 1.73 m^2, and <60 ml/min per 1.73 m^2. $P<0.05$ was considered significant.
[b]Comprises usage of statins, niacin, fibrates, and selective cholesterol absorption inhibitors.

1.73 m^2) showed typical features of uremic dyslipidemia characterized by significantly reduced concentrations of total cholesterol, LDL cholesterol, and HDL-C, whereas triglycerides were elevated. Moreover, inflammatory markers such as high-sensitivity C-reactive protein (hsCRP), soluble intercellular adhesion molecule-1 (sICAM-1), and IL-6 were already significantly elevated in patients with mildly reduced eGFR. Traditional cardiovascular risk factors such as diabetes and hypertension were more prevalent in patients with an eGFR of 60–90 ml/min per 1.73 m^2 compared with patients with normal eGFR.

After a median follow-up time of 9.9 years, 995 (30.0%) of the study participants died; 622 deaths (66.5%) were caused by cardiovascular or cerebrovascular events. Compared with patients with normal kidney function, the age- and sex-adjusted hazard ratios (HRs) for all-cause mortality were 2.0 (95% confidence interval [95% CI], 1.7 to 2.3) in patients with an eGFR of 60–89 ml/min per 1.73 m^2 and 4.9 (95% CI, 4.1 to 5.9) in patients with an eGFR<60 ml/min per 1.73 m^2 (Supplemental Table 1). This effect was still present after further adjustment for potential confounders. Notably, compared with all-cause mortality, the effect of a reduced eGFR<90 ml/min per 1.73 m^2 on cardiovascular mortality was even more pronounced.

To unravel potential causes underlying the effects of an impaired kidney function on all-cause and cardiovascular mortality, we focused our analyses on HDL-C. First we determined the association of increasing HDL-C serum levels with mortality in the whole study cohort. Figure 1 shows all-cause and cardiovascular mortality according to categories of HDL-C serum levels. The log-rank test identified a significant inverse association between the categories of HDL-C and all-cause as well as cardiovascular mortality ($P<0.001$ and $P<0.001$, respectively).

We next performed subgroup analyses to determine the effect of HDL-C serum levels on mortality in patients stratified into three categories of their eGFR. Baseline characteristics of the study participants according to categories of HDL-C are shown in Supplemental Table 2. The HRs for the categories of HDL-C serum levels calculated using Cox regression analysis in a crude model, as well as adjusted for age, sex, glycated hemoglobin, systolic BP, body mass index, acute coronary syndrome, Friesinger score (as a measure for CAD severity), lipid-lowering therapy, smoking status, and hsCRP are shown in Figure 2 and Table 2, respectively. Whereas HDL-C categories remained significantly associated with a lower HR for all-cause and cardiovascular mortality in patients with normal kidney function ($P=0.04$ and $P=0.03$, respectively), higher concentrations of HDL-C lost their beneficial effect on all-cause and cardiovascular mortality in patients with an eGFR <60 ml/min per 1.73 m^2 ($P=0.25$ and $P=0.09$, respectively). Interestingly, in patients with mildly reduced kidney function (eGFR=60–89 ml/min per 1.73 m^2), categories of HDL-C were not associated with a significantly reduced HR for all-cause and cardiovascular mortality ($P=0.33$ and $P=0.93$, respectively). In addition, subgroup analyses revealed that the predictive value of HDL-C in patients with eGFR<60 ml/min per 1.73 m^2 did actually not depend on the intake of lipid-lowering medication (Supplemental Table 3). Notably, in a validation cohort consisting of 246 patients with definite CKD (Supplemental Table 4), HDL-C divided in two categories according to the median value was not significantly associated with all-cause mortality ($P=0.63$; Figure 3), confirming the results of the LURIC study.

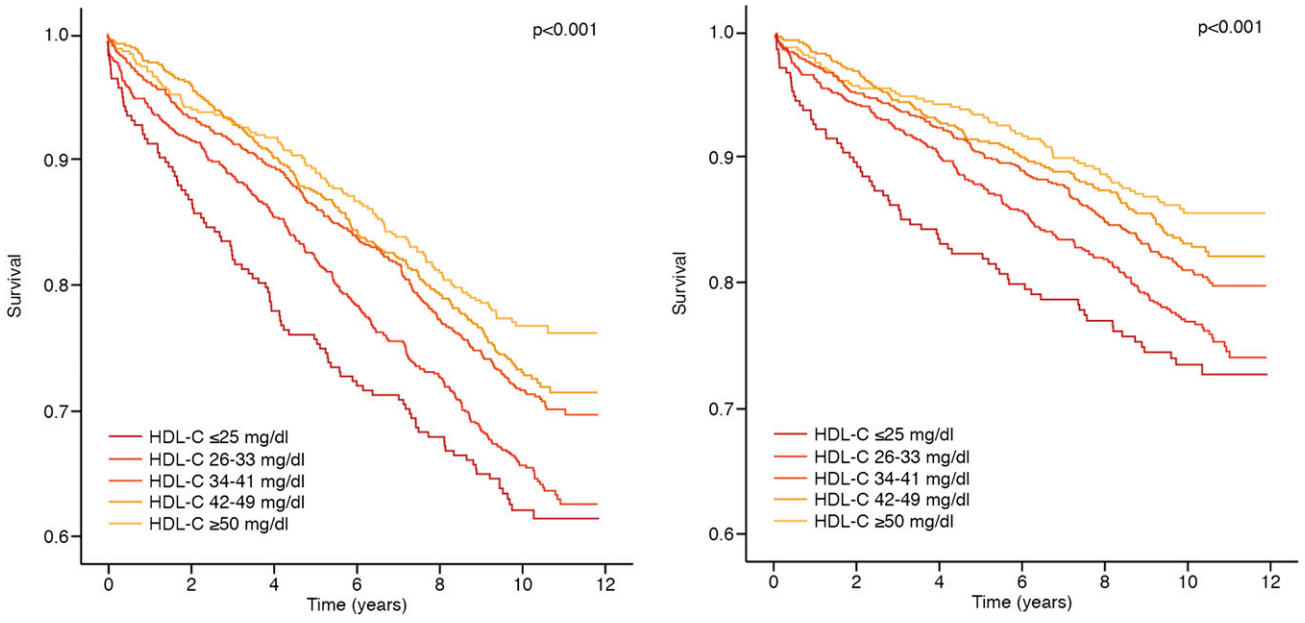

Figure 1. All-cause and cardiovascular mortality according to categories of HDL-C in all participants in the LURIC study.

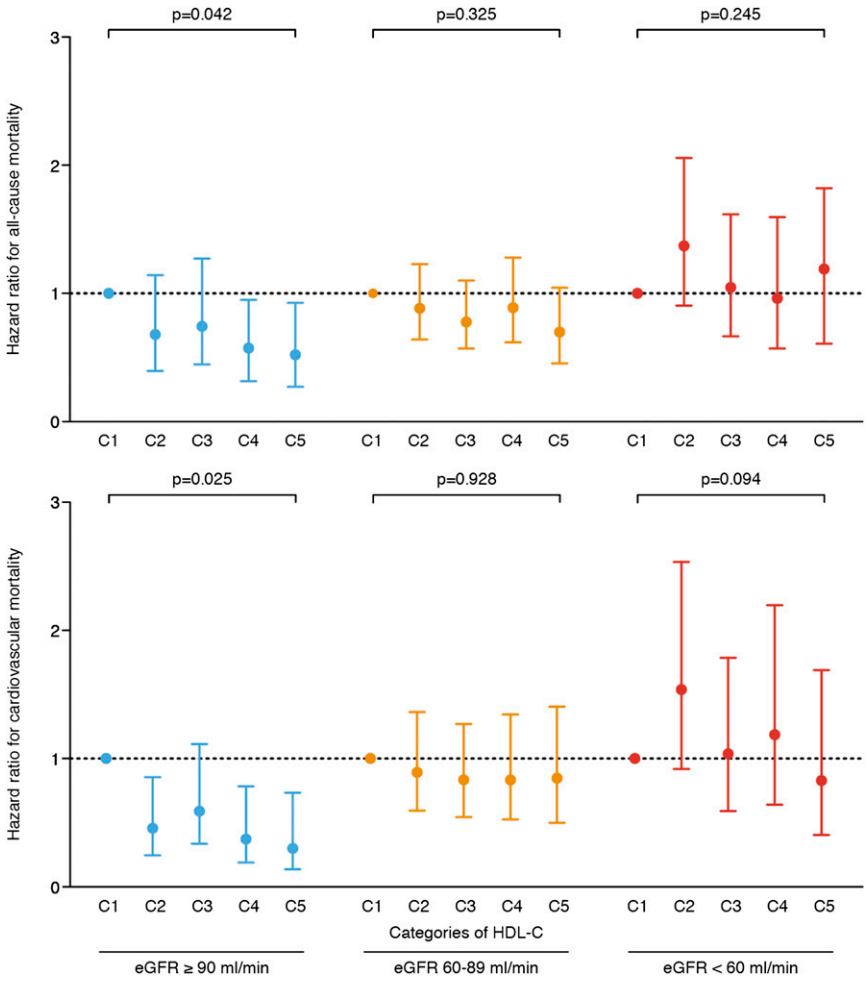

Figure 2. HRs for all-cause and cardiovascular mortality in patients from the LURIC study according to categories of eGFR and HDL-C. The HDL-C categories are as follows: C1, ≤25 mg/dl; C2, 26–33 mg/dl; C3, 34–41 mg/dl; C4, 42–49 mg/dl; and C5, ≥50 mg/dl. Category 1 is used as the reference. HRs have been calculated using a multivariable Cox proportional hazard model adjusted for age, sex, glycated hemoglobin, systolic BP, body mass index, acute coronary syndrome, Friesinger score, lipid-lowering therapy, smoking status, and hsCRP.

Because the composition of HDL is known to be a critical determinant of the vasoprotective properties of HDL,[16,17] we next determined the lipid composition of HDL in patients with different eGFR categories (Table 3). Here we found that the concentrations of cholesterol, phospholipids, free cholesterol, as well as cholesterol in the HDL fraction were significantly reduced in patients with impaired kidney function. In contrast, triglycerides significantly accumulated in the HDL fraction when kidney function was impaired. Moreover, the concentration of apoA1, the prevailing protein constituent of HDL, was significantly reduced in HDL from patients with impaired kidney function. Notably, Cox regression analyses revealed that higher levels of apoA1 were associated with a reduced risk of all-cause and cardiovascular mortality in patients with normal kidney function and in patients with eGFR=60–89 ml/min per 1.73 m^2, but not in patients with eGFR<60 ml/min per 1.73 m^2 (Supplemental Table 5).

To prove that the predictive value of HDL-C serum levels actually depends on eGFR, we included HDL-C and eGFR as continuous variables as well as a first-order interaction term between both parameters into a Cox proportional model (Supplemental Table 6). Notably, in fully adjusted models, there was a significant interaction between HDL-C and eGFR for all-cause (P=0.04) and cardiovascular mortality (P=0.02), indicating that HDL-C was a more powerful predictor of mortality in patients with normal eGFR than in those with reduced eGFR.

We next analyzed whether HDL-C serum levels might also have an effect on CAD disease severity. In linear regression analyses (Table 4), we found HDL-C to be significantly associated with a reduced Friesinger score in patients with an eGFR≥90 ml/min per 1.73 m^2 (P<0.001) and patients with an eGFR of 60–89 ml/min per 1.73 m^2 (P<0.001). Importantly, in patients with an eGFR<60 ml/min per 1.73 m^2, the association of HDL-C with the Friesinger score did not reach statistical significance (P=0.30) after adjustment for potential confounders.

Because the baseline characteristics of the study cohort (Table 1) revealed a significant difference of HDL-C serum levels between participants with normal and reduced kidney function, we calculated the estimated marginal means of HDL-C according to the categories of eGFR using a general linear model (Supplemental Table 7). These studies revealed a significant reduction of HDL-C levels already in patients with an eGFR of 60–89 ml/min per 1.73 m^2 compared with participants with normal kidney function after adjustment for potential confounders. Interestingly, reduced kidney function was also associated with higher levels of proinflammatory markers such as hsCRP, sICAM-1, and IL-6 at baseline (Table 1), which have been shown to reduce HDL-C levels in experimental models of inflammation.[18] Indeed, we could confirm that higher concentrations of hsCRP, sICAM-1, and IL-6 were associated with significantly reduced HDL-C levels. In addition, we could show that higher levels of these proinflammatory markers were associated with increased all-cause and cardiovascular mortality in patients with normal and mildly reduced kidney function (eGFR=60–89 ml/min per 1.73 m^2) as well as partially in patients with an eGFR<60 ml/min per 1.73 m^2 (Supplemental Table 8).

Table 2. Cox regression for all-cause and cardiovascular mortality in the LURIC study according to categories of HDL-C serum levels

Model	eGFR (ml/min per 1.73 m^2)	HDL Category	All-Cause Mortality			Cardiovascular Mortality		
			Events (%)	HR (95% CI)	*P* Value	Events (%)	HR (95% CI)	*P* Value
Crude	≥90	C1	22.2	1	—	18.0	1	—
		C2	16.8	0.71 (0.42 to 1.20)	0.20	9.3	0.49 (0.27 to 0.91)	0.03
		C3	19.5	0.84 (0.52 to 1.37)	0.49	12.4	0.66 (0.38 to 1.17)	0.15
		C4	15.6	0.65 (0.38 to 1.11)	0.11	7.9	0.41 (0.21 to 0.79)	0.01
		C5	13.0	0.54 (0.30 to 0.97)	0.04	5.4	0.28 (0.13 to 0.62)	0.002
	60–89	C1	40.0	1	—	25.6	1	—
		C2	35.5	0.80 (0.58 to 1.11)	0.18	22.2	0.78 (0.52 to 1.17)	0.23
		C3	30.2	0.66 (0.48 to 0.91)	0.01	19.0	0.65 (0.44 to 0.97)	0.04
		C4	30.7	0.68 (0.48 to 0.95)	0.02	17.0	0.59 (0.38 to 0.91)	0.02
		C5	23.2	0.50 (0.34 to 0.73)	< 0.001	15.9	0.54 (0.38 to 0.86)	0.01
	<60	C1	58.5	1	—	37.7	1	—
		C2	69.2	1.29 (0.86 to 1.93)	0.21	51.0	1.46 (0.89 to 2.40)	0.13
		C3	54.0	0.87 (0.57 to 1.33)	0.52	34.7	0.86 (0.51 to 1.47)	0.59
		C4	50.7	0.82 (0.51 to 1.33)	0.43	42.0	1.03 (0.59 to 1.83)	0.91
		C5	56.9	0.94 (0.57 to 1.53)	0.79	29.3	0.75 (0.39 to 1.42)	0.38
Adjusted 1[a]	≥90	C1	22.2	1	—	18.0	1	—
		C2	16.8	0.65 (0.38 to 1.09)	0.10	9.3	0.45 (0.24 to 0.84)	0.01
		C3	19.5	0.70 (0.43 to 1.15)	0.16	12.4	0.57 (0.32 to 1.01)	0.05
		C4	15.6	0.51 (0.30 to 0.89)	0.02	7.9	0.34 (0.18 to 0.67)	0.002
		C5	13.0	0.43 (0.24 to 0.79)	0.01	5.4	0.25 (0.11 to 0.55)	0.001
	60–89	C1	40.0	1	—	25.6	1	—
		C2	35.5	0.76 (0.55 to 1.05)	0.10	22.2	0.74 (0.50 to 1.11)	0.15
		C3	30.2	0.62 (0.45 to 0.86)	0.004	19.0	0.62 (0.41 to 0.92)	0.02
		C4	30.7	0.65 (0.46 to 0.92)	0.01	17.0	0.56 (0.36 to 0.87)	0.01
		C5	23.2	0.47 (0.32 to 0.69)	<0.001	15.9	0.50 (0.31 to 0.81)	0.01
	<60	C1	58.5	1	—	37.7	1	—
		C2	69.2	1.27 (0.85 to 1.90)	0.25	51.0	1.46 (0.89 to 2.40)	0.13
		C3	54.0	0.91 (0.59 to 1.40)	0.67	34.7	0.86 (0.51 to 1.47)	0.59
		C4	50.7	0.85 (0.52 to 1.39)	0.53	42.0	1.03 (0.59 to 1.83)	0.91
		C5	56.9	0.96 (0.58 to 1.61)	0.88	29.3	0.75 (0.39 to 1.43)	0.38
Adjusted 2[b]	≥90	C1	22.2	1	—	18.0	1	—
		C2	16.8	0.67 (0.39 to 1.14)	0.13	9.3	0.45 (0.24 to 0.85)	0.01
		C3	19.5	0.75 (0.44 to 1.27)	0.23	12.4	0.60 (0.32 to 1.11)	0.10
		C4	15.6	0.57 (0.31 to 0.94)	0.04	7.9	0.37 (0.17 to 0.78)	0.01
		C5	13.0	0.51 (0.26 to 0.92)	0.03	5.4	0.30 (0.13 to 0.73)	0.01
	60–89	C1	40.0	1	—	25.6	1	—
		C2	35.5	0.88 (0.63 to 1.22)	0.44	22.2	0.90 (0.59 to 1.36)	0.61
		C3	30.2	0.78 (0.56 to 1.09)	0.15	19.0	0.83 (0.54 to 1.27)	0.39
		C4	30.7	0.88 (0.61 to 1.27)	0.50	17.0	0.84 (0.52 to 1.34)	0.46
		C5	23.2	0.68 (0.45 to 1.04)	0.07	15.9	0.84 (0.50 to 1.40)	0.50
	<60	C1	58.5	1	—	37.7	1	—
		C2	69.2	1.36 (0.90 to 2.05)	0.15	51.0	1.52 (0.92 to 2.53)	0.11
		C3	54.0	1.03 (0.66 to 1.61)	0.90	34.7	1.02 (0.59 to 1.78)	0.94
		C4	50.7	0.95 (0.56 to 1.59)	0.83	42.0	1.18 (0.64 to 2.19)	0.60
		C5	56.9	1.18 (0.60 to 1.81)	0.88	29.3	0.82 (0.40 to 1.69)	0.60

The categories are as follows: C1, ≤25 mg/dl; C2, 26–33 mg/dl; C3, 34–41 mg/dl; C4, 42–49 mg/dl; and C5, ≥50 mg/dl. Category 1 is used as the reference.
[a]Adjusted for age and sex.
[b]Adjusted for age, sex, glycated hemoglobin, systolic BP, body mass index, acute coronary syndrome, Friesinger score, lipid-lowering therapy, smoking status, and hsCRP.

DISCUSSION

The results of this study confirmed that reduced kidney function—as determined by the novel and validated $eGFR_{creat\text{-}cys}$—is a strong risk factor for all-cause and cardiovascular mortality in a large cohort of patients at intermediate to high cardiovascular risk during long-term follow-up. Moreover, our findings indicate that high concentrations of

HDL-C are associated with a lower risk of mortality in this population. However, HDL-C lost its association with lower mortality in patients with even minor impairment of kidney function, whereas higher HDL-C levels almost turned into a potential cardiovascular risk factor in patients with more advanced kidney failure (*i.e.*, the HR reached almost statistical significance).

For many years, reduced kidney function has been known to be associated with an elevated risk for cardiovascular events and mortality. An eGFR<60 ml/min per 1.73 m^2 has been identified to increase the risk for mortality, cardiovascular events, and hospitalization in large study populations,[7] mainly because of a high prevalence of traditional and nontraditional cardiovascular risk factors in these patients.[19] These studies led to recognition of CKD patients as a population with an exceptionally high cardiovascular risk. The presence of nontraditional cardiovascular risk factors (*e.g.*, oxidative stress, anemia, and calcium-phosphate disturbances) in this population results in pathophysiologic mechanisms for cardiovascular disease that differ from the general population.

To identify potential causes contributing to the elevated risk of mortality in patients with reduced kidney function, we focused on HDL-C. Our group recently showed that HDL transforms from a vasoprotective into a noxious particle inducing endothelial dysfunction and hypertension in CKD patients.[12] These observations are in marked contrast to studies reporting only a moderate diminution of the beneficial vascular properties under disease conditions such as CAD or diabetes.[20,21] Moreover, we identified the accumulation of symmetric dimethylarginine in the HDL fraction of CKD patients as the culprit inverting its vascular function. In this study, we show for the first time that higher levels of HDL-C or its major protein constituent apoA1 do not reduce the risk for all-cause and cardiovascular mortality in patients with reduced kidney function in a large population during a long follow-up period. Importantly, analyses of an independent data set of patients with proven CKD confirmed these observations. These findings are in marked contrast to patients with normal kidney function, in whom higher HDL-C levels were significantly associated with reduced risk for all-cause and cardiovascular mortality. Notably, in patients with an already mildly reduced eGFR, higher levels of HDL-C were not associated with a reduced risk of death. Importantly, for all-cause and cardiovascular mortality, we

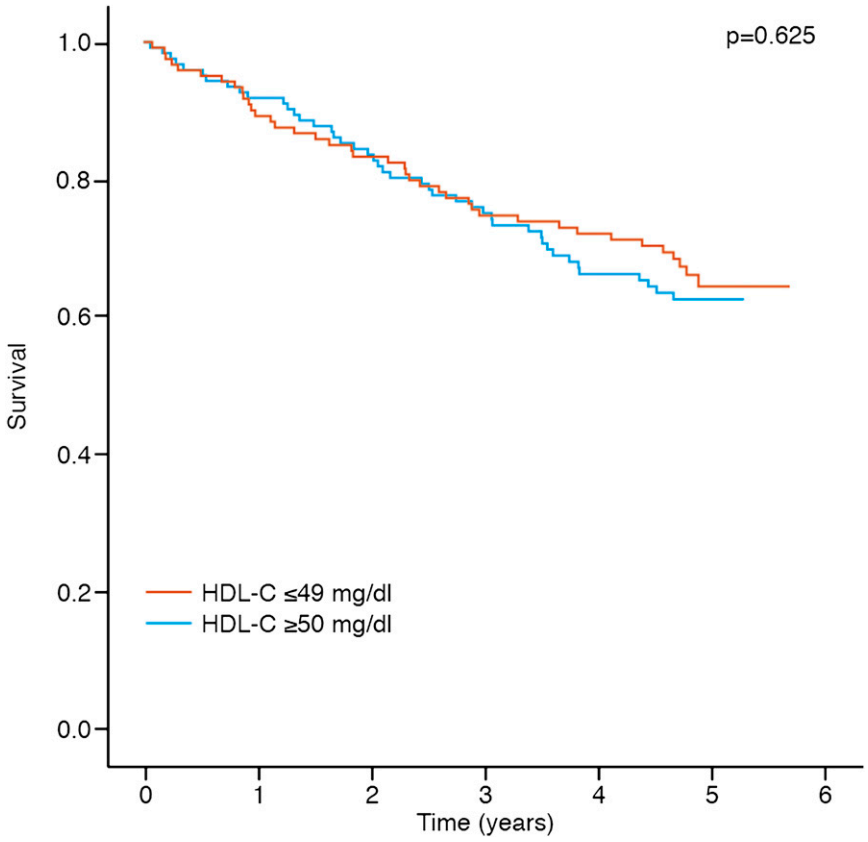

Figure 3. All-cause mortality in CKD patients in the validation cohort stratified into two groups by the median of HDL-C.

Table 3. HDL composition in LURIC study participants

HDL Composition (mg/dl)	Overall (*N*=3307)	eGFR (ml/min per 1.73 m^2)			*P* Value[a]
		≥90 (*n*=1209)	60–89 (*n*=1642)	<60 (*n*=456)	
HDL cholesterol	38.7±10.8	39.1±10.7	39.0±10.8	36.8±11.0	<0.001
HDL triglycerides	15.9±7.0	14.6±6.5	16.2±6.9	18.5±7.7	<0.001
HDL phospholipids	91.2±20.5	92.8±20.6	91.4±20.1	86.7±21.2	<0.001
HDL free cholesterol	9.0±2.8	9.0±2.7	9.1±2.8	8.6±2.9	0.01
HDL cholesteryl ester	30.1±8.4	30.5±8.3	30.3±8.3	28.3±8.6	<0.001
apoA1 (mg/dl)	129.4±25.0	130.0±25.0	130.3±24.7	124.7±25.9	<0.001

[a]Comparison between patients with an eGFR≥90 ml/min per 1.73 m^2, eGFR 60–89=ml/min per 1.73 m^2, and eGFR<60 ml/min per 1.73 m^2. $P<0.05$ was considered significant. Data are presented as the mean±SD.

Table 4. Association between HDL-C and Friesinger score in the LURIC study as a measure of CAD severity according to eGFR calculated by using CKD-EPI $eGFR_{creat-cys}$ equation

Model	eGFR (ml/min per 1.73 m^2)	β	*P* Value[a]
Crude	≥90	−0.250	<0.001
	60–89	−0.242	<0.001
	<60	−0.178	<0.001
Adjusted 1[b]	≥90	−0.223	<0.001
	60–89	−0.190	<0.001
	<60	−0.136	0.004
Adjusted 2[c]	≥90	−0.116	<0.001
	60–89	−0.111	<0.001
	<60	−0.073	0.30

[a] $P<0.001$ for the interaction between eGFR and HDL-C as continuous variables.
[b] Adjusted for age and sex.
[c] Adjusted for age, sex, glycated hemoglobin, body mass index, mean systolic BP, lipid-lowering therapy, acute coronary syndrome, smoking status, and hsCRP.

observed a significant interaction between HDL-C and eGFR, which indicates that the predictive value of HDL-C is indeed modulated by eGFR. In addition, we documented that higher HDL-C is associated with significantly reduced severity of CAD, but only in patients with normal kidney function. These findings ideally confirm our recent experimental observations, in which HDL from patients with mildly reduced eGFR already promoted endothelial dysfunction *in vitro* and in several animal models. Thus, this study points to a pivotal role of reduced kidney function in the modification of traditional factors involved in cardiovascular risk.

Pharmacologically increasing HDL-C concentrations has been considered a promising tool to improve survival in patients with high cardiovascular risk. Although observational studies suggested a beneficial effect of high HDL-C concentrations on cardiovascular mortality and morbidity, two recent interventional trials failed to reveal any beneficial effect of elevated HDL-C levels on cardiovascular outcome.[14,22] Notably, the dal-OUTCOMES study included patients with serum creatinine levels<2.2 mg/dl and even 11% of all participants had an eGFR<60 ml/min per 1.73 m^2. Given the fact that CKD is highly prevalent in patients with CAD,[23] our results suggest that the presence of even mildly reduced kidney function may serve as an explanation, at least in part, as to why increasing HDL-C levels may not improve cardiovascular outcome. It is obvious that increasing dysfunctional or even noxious HDL may not reduce cardiovascular morbidity and mortality. In contrast, the function of HDL (*e.g.,* reverse cholesterol transport) and not its serum concentrations has been demonstrated to greatly associate with subclinical atherosclerosis.[24] Moreover, we could show that HDL-C serum levels are strongly influenced by markers of oxidative and inflammatory stress. These findings support experimental evidence suggesting that proinflammatory activation affects HDL metabolism and composition[18] providing a link between HDL and inflammation. However, it cannot be deduced whether HDL itself or kidney dysfunction induces proinflammatory vascular activation. Therefore, the development and validation of novel laboratory assays to quantify biologic function, rather than measuring serum concentrations of HDL-C, is mandatory.

The main strengths of this study are the large study population and the long follow-up period. Thus, we were able to reliably document that minor impairment of kidney function strongly affects long-term all-cause and cardiovascular mortality and abolishes the beneficial effect of HDL-C. Accurate and comprehensive clinical characterization of the participants made it possible to adjust for potential confounding variables. In addition, the availability of cystatin C and creatinine values in all study participants allowed for the use of the CKD-EPI $eGFR_{creat-cys}$ equation as the present state-of-the-art method to estimate kidney function. However, results of urinalyses (*e.g.*, albuminuria) were not available, which did not allow for identification of patients with albuminuria but normal eGFR. Moreover, in the observational LURIC study, we have not examined the functionality of HDL, which has been previously linked to a worsened outcome in patients with ESRD.[25] Nonetheless, our findings clearly document that quantitative measures of HDL such as HDL-C or apoA-I, which are commonly used in clinical practice, are not associated with better outcome in patients with impaired kidney function. Furthermore, the LURIC study mainly enrolled patients with preexisting CAD. Therefore, from the present data, one cannot deduce that HDL-C reduces cardiovascular events *per se*. Even more important is that HDL-C associates with improved long-term outcome in patients with prevalent CAD as long as kidney function is normal. The fact that only Caucasian patients were included limits the generalization of the results to other races. Although a recent study found lower HDL-C levels to be associated with enhanced mortality during short-term outcome in CKD patients with metabolic syndrome,[26] our data, rather, confirm recent experimental evidence revealing dysfunctional HDL in a variety of *in vitro* and *in vivo* assays under CKD conditions.[27] Nonetheless, additional interventional studies are necessary to definitely confirm a divergent effect of increasing HDL-C on cardiovascular mortality in participants with normal and reduced kidney function.

In summary, our results confirmed that even mildly reduced kidney function is a potent cardiovascular risk factor and documented the usefulness of the recent CKD-EPI $eGFR_{creat-cys}$ equation to estimate kidney function and predict outcome. Moreover, one explanation for this finding might be the fact that the presence of even a mildly reduced eGFR deteriorates the beneficial vascular effect of HDL-C and abolishes its favorable effect on cardiovascular outcome.

CONCISE METHODS

Participants

The LURIC study included 3307 patients undergoing coronary angiography between 1997 and 2000. Study design and baseline examinations were previously described in detail.[28] Briefly, we enrolled Caucasian patients who were clinically stable except for acute coronary syndromes and available for coronary angiogram. Patients with acute illness other than acute coronary syndromes, chronic noncardiac diseases, or malignancy within the past 5 years were excluded. The study was approved by the local ethics committee in accordance with the Declaration of Helsinki and written consent was obtained from all participants.

To validate the findings of the LURIC study in patients with CKD, we additionally analyzed data from a prospective cohort of 246 patients with CKD and ESRD. Details of the study protocol and patient characteristics were previously described in detail.[29] Briefly, the study included stable ambulatory patients with CKD Kidney Disease Improving Global Outcomes GFR stages 1–5 (n=151) as well as stable patients with ESRD on dialysis (n=95).

Measures

CAD was examined by determining the maximal luminal narrowing estimated by visual analysis using coronary angiography. Clinically relevant CAD was defined as the presence of ≥1 stenosis of ≥20% in ≥1 of 15 coronary segments. The Friesinger score was used to assess the severity of CAD.[30] Details are provided in the Supplemental Methods. Acute coronary syndrome was defined as the occurrence of symptoms of unstable angina within 7 days before coronary angiography, non-ST segment elevation myocardial infarction, or ST segment elevation myocardial infarction. Systolic and diastolic aortic BP was measured during coronary angiography. Diabetes was defined as a fasting plasma glucose>1.25 g/L or >2.00 g/L after oral administration of a glucose dose, glycated hemoglobin≥6.5% or patients receiving oral antidiabetics or insulin.

For laboratory analyses, fasting blood samples were obtained before angiography. The LDL was separated from HDL by precipitation with PTA/$MgCl_2$ and very low-density lipoprotein was floated by ultracentrifugation. Cholesterol, triglycerides, free cholesterol, phospholipids, and free fatty acids were all determined enzymatically using Wako reagents on a Wako 30R analyzer (Neuss, Germany). The assays were calibrated by multicalibrators, which were double-checked before use against primary standards. The interassay coefficients of variations for all lipid determinations varied between 1% and 3%.

A turbidimetry assay (Rolf Greiner Biochemica, Flacht, Germany) was used to measure apoA1. Serum creatinine was determined using the Jaffé method with CREA test kits (Roche, Mannheim, Germany) on a Hitachi 717 Analyzer and cystatin C concentrations were determined using a nephelometric assay (N LATEX Cystatin C) on a Behring nephelometer II (Dade Behring GmbH, Marburg, Germany). Measurements of creatinine were calibrated against an international standard. For cystatin C, no international standard was available at the time of determination. GFR was estimated by using the 2012 CKD-EPI $eGFR_{creat\text{-}cys}$ equation as previously described.[31] hsCRP was measured by immunonephelometry on a Behring nephelometer II (N High Sensitivity CRP; Dade Behring GmbH). IL-6 was determined using ELISA (Quantikine High-Sensitivity ELISA kit for human IL-6; R&D Systems GmbH, Wiesbaden, Germany) and ICAM-1 was measured using an immunoenzymometric assay (human soluble ICAM-1; R&D Systems GmbH, Wiesbaden, Germany) on a Rosys Plato. Glycated hemoglobin was determined by high-performance liquid chromatography (Diamat; Chromsystems Instruments & Chemicals GmbH, Martinsried, Germany).

Follow-Up

Information on death during follow-up was obtained from local person registries. During a median follow-up time of 9.9 years (range, 8.5–10.7 years), 995 patients of the LURIC study died (30.0%). Two experienced clinicians blinded for the study data independently performed classification into cardiovascular and noncardiovascular mortality. Cardiovascular mortality was defined as sudden cardiac death, fatal myocardial infarction, death due to congestive heart failure, and death immediately after intervention to treat CAD and fatal stroke.

CKD patients in the validation cohort were followed for median of 4.7 years (range, 2.5–4.9 years). During this follow-up period, 84 patients (34.1%) died.

Statistical Analyses

Patients were stratified into categories of their $eGFR_{creat\text{-}cys}$ (eGFR≥90 ml/min per 1.73 m^2, 60–89 ml/min per 1.73 m^2, and <60 ml/min per 1.73 m^2). Continuous data are presented as the mean±SD when normally distributed or as the median and interquartile range for variables with skewed distribution. Categorical data are presented as percentages. Statistical differences between continuous variables were determined using one-way ANOVA or the Kruskal–Wallis test or the chi-squared test for categorical variables.

Cox proportional hazard models were built to assess the effect of categories of $eGFR_{creat\text{-}cys}$, HDL-C, apoA1, and proinflammatory markers (hsCRP, IL-6, sICAM-1) on all-cause and cardiovascular mortality. Crude models included categories of $eGFR_{creat\text{-}cys}$, HDL-C, apoA1, or inflammatory markers (hsCRP, IL-6, sICAM-1) as single categorical variables. In addition, adjusted models further included age, sex, glycated hemoglobin, systolic BP, body mass index, acute coronary syndrome, Friesinger score, and lipid-lowering therapy (approximately 97% statins). HRs±95% CIs are reported. Moreover, survival curves were used to determine the effect of categories of HDL-C on all-cause and cardiovascular mortality. To assess whether the beneficial effect of HDL-C on all-cause and cardiovascular mortality depends on eGFR, we built Cox proportional hazard models including HDL-C and eGFR as well as the first-order interaction term between both as continuous variables. In addition, adjustments were performed for age, sex, glycated hemoglobin, systolic BP, body mass index, acute coronary syndrome, Friesinger score, lipid-lowering therapy, smoking status, and hsCRP.

To examine the association between HDL-C and Friesinger score, we performed linear regression analyses including HDL-C as a continuous variable and Friesinger score as a dependent variable. Adjustments were made for age, sex, glycated hemoglobin, systolic

BP, body mass index, acute coronary syndrome, Friesinger score, and lipid-lowering therapy.

To examine the relationship between hsCRP, IL-6, and sICAM-1 and HDL-C, hsCRP was divided into tertiles and IL-6 and sICAM-1 into quartiles. A general linear model was used to calculate the estimated marginal means of HDL-C according to categories of $eGFR_{creat-cys}$, hsCRP, IL-6, or sICAM-1, including age, sex, glycated hemoglobin, systolic BP, body mass index, acute coronary syndrome, Friesinger score, and lipid-lowering therapy for multivariable adjustment.

A P value<0.05 was considered statistically significant. All analyses were carried out using the SPSS 20.0 statistical package (SPSS, Chicago, IL).

ACKNOWLEDGMENTS

The authors thank all of the LURIC study participants, the LURIC study team, and the laboratory staff at Ludwigshafen General Hospital.

LURIC has received funding through the Sixth Framework Program (integrated project Bloodomics; Grant LSHM-CT-2004-503485) and the Seventh Framework Program (integrated project Atheroremo; Grant 201668), and the RiskyCAD project (Project Number 305739) of the European Union. T.S. was supported by the Deutsche Forschungsgemeinschaft and Deutsche Hochdruckliga.

DISCLOSURES

None.

REFERENCES

1. Roger VL, Go AS, Lloyd-Jones DM, Adams RJ, Berry JD, Brown TM, Carnethon MR, Dai S, de Simone G, Ford ES, Fox CS, Fullerton HJ, Gillespie C, Greenlund KJ, Hailpern SM, Heit JA, Ho PM, Howard VJ, Kissela BM, Kittner SJ, Lackland DT, Lichtman JH, Lisabeth LD, Makuc DM, Marcus GM, Marelli A, Matchar DB, McDermott MM, Meigs JB, Moy CS, Mozaffarian D, Mussolino ME, Nichol G, Paynter NP, Rosamond WD, Sorlie PD, Stafford RS, Turan TN, Turner MB, Wong ND, Wylie-Rosett J; American Heart Association Statistics Committee and Stroke Statistics Subcommittee: Heart disease and stroke statistics—2011 update: A report from the American Heart Association. *Circulation* 123: e18–e209, 2011
2. Tonelli M, Muntner P, Lloyd A, Manns BJ, Klarenbach S, Pannu N, James MT, Hemmelgarn BR; Alberta Kidney Disease Network: Risk of coronary events in people with chronic kidney disease compared with those with diabetes: A population-level cohort study. *Lancet* 380: 807–814, 2012
3. Schiffrin EL, Lipman ML, Mann JF: Chronic kidney disease: Effects on the cardiovascular system. *Circulation* 116: 85–97, 2007
4. Wilson PW, D'Agostino RB, Levy D, Belanger AM, Silbershatz H, Kannel WB: Prediction of coronary heart disease using risk factor categories. *Circulation* 97: 1837–1847, 1998
5. Fox CS, Matsushita K, Woodward M, Bilo HJ, Chalmers J, Heerspink HJ, Lee BJ, Perkins RM, Rossing P, Sairenchi T, Tonelli M, Vassalotti JA, Yamagishi K, Coresh J, de Jong PE, Wen CP, Nelson RG; Chronic Kidney Disease Prognosis Consortium: Associations of kidney disease measures with mortality and end-stage renal disease in individuals with and without diabetes: A meta-analysis. *Lancet* 380: 1662–1673, 2012
6. Mahmoodi BK, Matsushita K, Woodward M, Blankestijn PJ, Cirillo M, Ohkubo T, Rossing P, Sarnak MJ, Stengel B, Yamagishi K, Yamashita K, Zhang L, Coresh J, de Jong PE, Astor BC; Chronic Kidney Disease Prognosis Consortium: Associations of kidney disease measures with mortality and end-stage renal disease in individuals with and without hypertension: A meta-analysis. *Lancet* 380: 1649–1661, 2012
7. Go AS, Chertow GM, Fan D, McCulloch CE, Hsu CY: Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. *N Engl J Med* 351: 1296–1305, 2004
8. Sarnak MJ, Levey AS, Schoolwerth AC, Coresh J, Culleton B, Hamm LL, McCullough PA, Kasiske BL, Kelepouris E, Klag MJ, Parfrey P, Pfeffer M, Raij L, Spinosa DJ, Wilson PW; American Heart Association Councils on Kidney in Cardiovascular Disease, High Blood Pressure Research, Clinical Cardiology, and Epidemiology and Prevention: Kidney disease as a risk factor for development of cardiovascular disease: A statement from the American Heart Association Councils on Kidney in Cardiovascular Disease, High Blood Pressure Research, Clinical Cardiology, and Epidemiology and Prevention. *Circulation* 108: 2154–2169, 2003
9. US Renal Data System: *USRDS 2012 Annual Data Report: Atlas of Chronic Kidney Disease and End-Stage Renal Disease in the United States*, Bethesda, MD, National Institutes of Health National Institute of Diabetes and Digestive and Kidney Diseases, 2012
10. Barter P, Gotto AM, LaRosa JC, Maroni J, Szarek M, Grundy SM, Kastelein JJ, Bittner V, Fruchart JC; Treating to New Targets Investigators: HDL cholesterol, very low levels of LDL cholesterol, and cardiovascular events. *N Engl J Med* 357: 1301–1310, 2007
11. Mineo C, Shaul PW: Novel biological functions of high-density lipoprotein cholesterol. *Circ Res* 111: 1079–1090, 2012
12. Speer T, Rohrer L, Blyszczuk P, Shroff R, Kuschnerus K, Kränkel N, Kania G, Zewinger S, Akhmedov A, Shi Y, Martin T, Perisa D, Winnik S, Müller MF, Sester U, Wernicke G, Jung A, Gutteck U, Eriksson U, Geisel J, Deanfield J, von Eckardstein A, Lüscher TF, Fliser D, Bahlmann FH, Landmesser U: Abnormal high-density lipoprotein induces endothelial dysfunction via activation of Toll-like receptor-2. *Immunity* 38: 754–768, 2013
13. Voight BF, Peloso GM, Orho-Melander M, Frikke-Schmidt R, Barbalic M, Jensen MK, Hindy G, Hólm H, Ding EL, Johnson T, Schunkert H, Samani NJ, Clarke R, Hopewell JC, Thompson JF, Li M, Thorleifsson G, Newton-Cheh C, Musunuru K, Pirruccello JP, Saleheen D, Chen L, Stewart A, Schillert A, Thorsteinsdottir U, Thorgeirsson G, Anand S, Engert JC, Morgan T, Spertus J, Stoll M, Berger K, Martinelli N, Girelli D, McKeown PP, Patterson CC, Epstein SE, Devaney J, Burnett MS, Mooser V, Ripatti S, Surakka I, Nieminen MS, Sinisalo J, Lokki ML, Perola M, Havulinna A, de Faire U, Gigante B, Ingelsson E, Zeller T, Wild P, de Bakker PI, Klungel OH, Maitland-van der Zee AH, Peters BJ, de Boer A, Grobbee DE, Kamphuisen PW, Deneer VH, Elbers CC, Onland-Moret NC, Hofker MH, Wijmenga C, Verschuren WM, Boer JM, van der Schouw YT, Rasheed A, Frossard P, Demissie S, Willer C, Do R, Ordovas JM, Abecasis GR, Boehnke M, Mohlke KL, Daly MJ, Guiducci C, Burtt NP, Surti A, Gonzalez E, Purcell S, Gabriel S, Marrugat J, Peden J, Erdmann J, Diemert P, Willenborg C, König IR, Fischer M, Hengstenberg C, Ziegler A, Buysschaert I, Lambrechts D, Van de Werf F, Fox KA, El Mokhtari NE, Rubin D, Schrezenmeir J, Schreiber S, Schäfer A, Danesh J, Blankenberg S, Roberts R, McPherson R, Watkins H, Hall AS, Overvad K, Rimm E, Boerwinkle E, Tybjaerg-Hansen A, Cupples LA, Reilly MP, Melander O, Mannucci PM, Ardissino D, Siscovick D, Elosua R, Stefansson K, O'Donnell CJ, Salomaa V, Rader DJ, Peltonen L, Schwartz SM, Altshuler D, Kathiresan S: Plasma HDL cholesterol and risk of myocardial infarction: A mendelian randomisation study. *Lancet* 380: 572–580, 2012
14. Schwartz GG, Olsson AG, Abt M, Ballantyne CM, Barter PJ, Brumm J, Chaitman BR, Holme IM, Kallend D, Leiter LA, Leitersdorf E, McMurray JJ, Mundl H, Nicholls SJ, Shah PK, Tardif JC, Wright RS; dal-OUTCOMES

Investigators: Effects of dalcetrapib in patients with a recent acute coronary syndrome. *N Engl J Med* 367: 2089–2099, 2012
15. Lamprea-Montealegre JA, Astor BC, McClelland RL, de Boer IH, Burke GL, Sibley CT, O'Leary D, Sharrett AR, Szklo M: CKD, plasma lipids, and common carotid intima-media thickness: Results from the multi-ethnic study of atherosclerosis. *Clin J Am Soc Nephrol* 7: 1777–1785, 2012
16. Holzer M, Birner-Gruenberger R, Stojakovic T, El-Gamal D, Binder V, Wadsack C, Heinemann A, Marsche G: Uremia alters HDL composition and function. *J Am Soc Nephrol* 22: 1631–1641, 2011
17. Weichhart T, Kopecky C, Kubicek M, Haidinger M, Döller D, Katholnig K, Suarna C, Eller P, Tölle M, Gerner C, Zlabinger GJ, van der Giet M, Hörl WH, Stocker R, Säemann MD: Serum amyloid A in uremic HDL promotes inflammation. *J Am Soc Nephrol* 23: 934–947, 2012
18. Han CY, Chiba T, Campbell JS, Fausto N, Chaisson M, Orasanu G, Plutzky J, Chait A: Reciprocal and coordinate regulation of serum amyloid A versus apolipoprotein A-I and paraoxonase-1 by inflammation in murine hepatocytes. *Arterioscler Thromb Vasc Biol* 26: 1806–1813, 2006
19. Shlipak MG, Fried LF, Cushman M, Manolio TA, Peterson D, Stehman-Breen C, Bleyer A, Newman A, Siscovick D, Psaty B: Cardiovascular mortality risk in chronic kidney disease: Comparison of traditional and novel risk factors. *JAMA* 293: 1737–1745, 2005
20. Charakida M, Besler C, Batuca JR, Sangle S, Marques S, Sousa M, Wang G, Tousoulis D, Delgado Alves J, Loukogeorgakis SP, Mackworth-Young C, D'Cruz D, Luscher T, Landmesser U, Deanfield JE: Vascular abnormalities, paraoxonase activity, and dysfunctional HDL in primary antiphospholipid syndrome. *JAMA* 302: 1210–1217, 2009
21. Sorrentino SA, Besler C, Rohrer L, Meyer M, Heinrich K, Bahlmann FH, Mueller M, Horváth T, Doerries C, Heinemann M, Flemmer S, Markowski A, Manes C, Bahr MJ, Haller H, von Eckardstein A, Drexler H, Landmesser U: Endothelial-vasoprotective effects of high-density lipoprotein are impaired in patients with type 2 diabetes mellitus but are improved after extended-release niacin therapy. *Circulation* 121: 110–122, 2010
22. Barter PJ, Caulfield M, Eriksson M, Grundy SM, Kastelein JJ, Komajda M, Lopez-Sendon J, Mosca L, Tardif JC, Waters DD, Shear CL, Revkin JH, Buhr KA, Fisher MR, Tall AR, Brewer B; ILLUMINATE Investigators: Effects of torcetrapib in patients at high risk for coronary events. *N Engl J Med* 357: 2109–2122, 2007
23. Shlipak MG, Simon JA, Grady D, Lin F, Wenger NK, Furberg CD; Heart and Estrogen/progestin Replacement Study (HERS) Investigators: Renal insufficiency and cardiovascular events in postmenopausal women with coronary heart disease. *J Am Coll Cardiol* 38: 705–711, 2001
24. Khera AV, Cuchel M, de la Llera-Moya M, Rodrigues A, Burke MF, Jafri K, French BC, Phillips JA, Mucksavage ML, Wilensky RL, Mohler ER, Rothblat GH, Rader DJ: Cholesterol efflux capacity, high-density lipoprotein function, and atherosclerosis. *N Engl J Med* 364: 127–135, 2011
25. Kalantar-Zadeh K, Kopple JD, Kamranpour N, Fogelman AM, Navab M: HDL-inflammatory index correlates with poor outcome in hemodialysis patients. *Kidney Int* 72: 1149–1156, 2007
26. Navaneethan SD, Schold JD, Kirwan JP, Arrigain S, Jolly SE, Poggio ED, Beddhu S, Nally JV Jr: Metabolic syndrome, ESRD, and death in CKD. *Clin J Am Soc Nephrol* 8: 945–952, 2013
27. Speer T, Zewinger S, Fliser D: Uraemic dyslipidaemia revisited: Role of high-density lipoprotein. *Nephrol Dial Transplant* 28: 2456–2463, 2013
28. Winkelmann BR, März W, Boehm BO, Zotz R, Hager J, Hellstern P, Senges J; LURIC Study Group (LUdwigshafen RIsk and Cardiovascular Health): Rationale and design of the LURIC study—a resource for functional genomics, pharmacogenomics and long-term prognosis of cardiovascular disease. *Pharmacogenomics* 2[Suppl 1]: S1–S73, 2001
29. Rogacev KS, Seiler S, Zawada AM, Reichart B, Herath E, Roth D, Ulrich C, Fliser D, Heine GH: CD14++CD16+ monocytes and cardiovascular outcome in patients with chronic kidney disease. *Eur Heart J* 32: 84–92, 2011
30. Friesinger GC, Page EE, Ross RS: Prognostic significance of coronary arteriography. *Trans Assoc Am Physicians* 83: 78–92, 1970
31. Inker LA, Schmid CH, Tighiouart H, Eckfeldt JH, Feldman HI, Greene T, Kusek JW, Manzi J, Van Lente F, Zhang YL, Coresh J, Levey AS; CKD-EPI Investigators: Estimating glomerular filtration rate from serum creatinine and cystatin C. *N Engl J Med* 367: 20–29, 2012

See related editorial, "HDL in CKD: How Good Is the "Good Cholesterol?"," on pages 871–874.

This article contains supplemental material online at http://jasn.asnjournals.org/lookup/suppl/doi:10.1681/ASN.2013050482/-/DCSupplemental.