Malnutrition-Inflammation Modifies the Relationship of Cholesterol with Cardiovascular Disease

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ABSTRACT

In moderate and severe CKD, the association of cholesterol with subsequent cardiovascular disease (CVD) is weak. We examined whether malnutrition or inflammation (M-I) modifies the risk relationship between cholesterol levels and CVD events in African Americans with hypertensive CKD and a GFR between 20 and 65 ml/min per 1.73 m^2. We stratified 990 participants by the presence or absence of M-I, defined as body mass index <23 kg/m^2 or C-reactive protein >10 mg/L at baseline. The primary composite outcome included cardiovascular death or first hospitalization for coronary artery disease, stroke, or congestive heart failure occurring during a median follow-up of 77 months. Baseline total cholesterol (212 $\pm$ 48 *versus* 212 $\pm$ 44 mg/dl) and overall incidence of the primary CVD outcome (19 *versus* 21%) were similar in participants with ($n = 304$) and without ($n = 686$) M-I. In adjusted analyses, the CVD composite outcome exhibited a significantly stronger relationship with total cholesterol for participants without M-I than for participants with M-I at baseline ($P < 0.02$). In the non–M-I group, the cholesterol-adjusted hazard ratio (HR) for CVD increased progressively across cholesterol levels: HR = 1.19 [95% CI; 0.77, 1.84] and 2.18 [1.43, 3.33] in participants with cholesterol 200 to 239 and $\geq$240 mg/dl, respectively (reference: cholesterol <200). In the M-I group, the corresponding HRs did not vary significantly by cholesterol level. In conclusion, the presence of M-I modifies the risk relationship between cholesterol level and CVD in African Americans with hypertensive CKD.

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The role of hypercholesterolemia as a risk factor for the development of cardiovascular disease (CVD) in moderate and severe chronic kidney disease (CKD) is actively debated, in large part, because of the inconsistent and often paradoxical relationships reported in observational studies.[1–5] Evidence from interventional trials in end-stage renal disease (ESRD) likewise highlights the uncertain relationship. In two randomized clinical trials conducted in maintenance dialysis participants, hepatic hydroxymethyl glutaryl-CoA reductase inhibitors (statins) therapies had no beneficial effects on CVD events, despite substantial reductions in serum cholesterol levels.[6,7]

A recent study[8] provided a potential explanation for the contradictory results of the epidemiologic studies. In the observational study by Liu *et al.*,[8] the presence of malnutrition or systemic inflammation (M-I) modified the risk relationship between baseline cholesterol level and overall mortality in maintenance dialysis participants. Whereas elevated cholesterol levels were associated with higher mortality risk in the group of participants without M-I, elevated cholesterol levels were associated with lower mortality risk in the M-I group. Whether M-I modifies the risk relationship of cholesterol with CVD in patients with CKD who have not reached ESRD is unknown.[5] Most studies have examined associations of M-I with CVD in ESRD populations.[1,2,4,8–12] Few studies have examined associations of CVD with these risk factors in CKD populations not on maintenance dialysis,[5,13–15] and there are no studies in African Americans with hypertensive CKD.

The African-American Study of Kidney Disease and Hypertension (AASK)[16–20] provides a unique opportunity to study the relationship among cholesterol level, M-I, and the development of CVD events in African Americans with hypertensive CKD. The AASK participants were well characterized for relevant risk factors at baseline, and CVD events were prospectively ascertained over an extended follow-up period. Body mass index (BMI) and high sensitivity C-reactive protein (hs-CRP) levels, markers of M-I, were measured at baseline in the trial.[15,16] Additionally, the prevalence of hyperlipidemia in AASK participants was very high; however, in prospective analyses, elevated baseline cholesterol was only weakly associated with CVD events.[19] In this study, we assessed the prevalence of M-I and its modifying effects on the risk relationship of cholesterol level with subsequent CVD events in African Americans with hypertensive CKD.

RESULTS

Cross-Sectional Analyses at Baseline

This report is based on 990 of the 1094 randomized AASK participants who provided baseline total cholesterol, M-I status, and the other factors included as covariates in the Cox regression models (see Statistical Analysis). Baseline demographic and comorbid characteristics were similar between the 990 included and 104 excluded participants (Table 1). Three hundred four (31%) participants had M-I, defined as BMI of <23 kg/m^2 ($n = 115$) or hs-CRP of >10 mg/L ($n = 206$), of whom 17 participants fulfilled both criteria. Compared with participants without M-I, participants with M-I were more likely women or current tobacco smokers and they had lower serum albumin, lower iodine 125-iothalamate GFR, lower urinary urea nitrogen excretion, higher proteinuria, and higher serum phosphate (Table 1). Four hundred twenty-nine (43%), 297 (30%), and 264 (27%) participants had total cholesterol levels <200, 200 to 239, and ≥ 240 mg/dl, respectively. A total of 368 participants used statins during the course of the study, including 96 (22%), 127 (43%), and 145 (55%) in the total cholesterol categories of <200, 200 to 239, and ≥ 240 mg/dl, respectively. Table 2 shows baseline demographic and clinical characteristics stratified both by cholesterol categories and M-I status. The positive relationships of M-I with female gender and current smoking and the inverse relationship of M-I with urinary urea nitrogen all persisted within each cholesterol category.

CVD Events

A total of 202 participants experienced the primary composite CVD outcome over a median follow-up of 77 (interquartile range: 43, 113) months, including 58 (19%) and 144 (21%) participants with and without M-I at baseline, respectively. The events leading to the CVD composite outcome included 61 congestive heart failure (CHF) hospitalizations, 64 strokes, 53 coronary artery disease (CAD) hospitalizations, and 24 cardiovascular deaths.

Interaction of M-I with Total Cholesterol

Figure 1A and the top of Table 3 summarize the results of the multivariable Cox regression models relating the primary CVD outcome jointly to baseline total cholesterol and M-I status while adjusting for the covariates. Under the cubic spline model (Figure 1A), the association of the adjusted hazard ratio (HR) for the primary CVD outcome with total cholesterol was significantly nonlinear ($P = 0.008$) and differed significantly between participants with and without M-I (interaction, $P = 0.002$). As shown in Figure 1A, the HR for the primary CVD outcome increased as total cholesterol increased in participants without M-I, whereas the HR for the primary CVD outcome with total cholesterol tended to decrease in participants with M-I.

M-I was also found to modify the risk relationship between total cholesterol and the primary CVD outcome in the Cox regressions treating total cholesterol as a categorical variable (interaction, $P = 0.016$). In the non–M-I group, the adjusted HR of total cholesterol level for the primary CVD outcome progressively increased across successively higher cholesterol categories: HR = 1.0, 1.19 [95% confidence interval, 0.77, 1.84] and 2.18 [1.43, 3.33] for participants with total cholesterol <200 (reference), 200 to 239, and ≥ 240 mg/dl, respec-

Table 1. Baseline characteristics of the African-American study of kidney disease and hypertension participants included in this study stratified by the absence or presence of malnutrition-inflammation and participants excluded from this study

Baseline Variables	Included Group (n = 990)	Non-M-I Group (n = 686)	M-I Group (n = 304)	Excluded Group (n = 104)
Age, years ± SD	55 ± 11	55 ± 11	55 ± 10	54 ± 12
Women, *n* (%)	387 (39)	235 (34)	152 (50)[a]	38 (37)
Pre-existing cardiovascular disease, *n* (%)	515 (52)	348 (51)	167 (55)	49 (47)
Years with hypertension[b]	14 ± 10	14 ± 10	14 ± 10	14 ± 11
Tobacco use, *n* (%)				
current	290 (29)	164 (24)	126 (41)[a]	31 (30)
past	284 (29)	206 (30)	78 (26)	28 (27)
never	416 (42)	316 (46)	100 (33)	45 (43)
Body mass index, kg/m^2 ± SD	30.6 ± 6.6	31.3 ± 5.7	29.0 ± 8.1[a]	30.1 ± 6.2
Clinic systolic blood pressure, mmHg ± SD	150 ± 24	150 ± 24	151 ± 23	150 ± 22
Clinic diastolic blood pressure, mmHg ± SD	95 ± 14	95 ± 15	95 ± 14	97 ± 12
Alcohol use, *n* (%)[c]				
yes	279 (28)	196 (29)	83 (28)	24 (23)
no	706 (72)	488 (71)	218 (72)	80 (77)
Total cholesterol, mg/dl ± SD	212 ± 46	212 ± 44	212 ± 48	209 ± 45
Women HDL cholesterol, mg/dl ± SD	55 ± 15	55 ± 16	55 ± 16	51 ± 15
Men HDL cholesterol, mg/dl ± SD	44 ± 15	43 ± 13	48 ± 21[d]	43 ± 12
Non-HDL cholesterol, mg/dl ± SD	163 ± 45	164 ± 44	161 ± 47	163 ± 45
GFR, ml/min per 1.73 m^2 ± SD	46 ± 14	47 ± 13	44 ± 14[a]	47 ± 13
Urinary urea nitrogen, g/day ± SD	8.3 ± 3.8	8.6 ± 3.9	7.5 ± 3.4[a]	8.2 ± 3.7
Serum creatinine, mg/dl ± SD	2.02 ± 0.71	2.03 ± 0.73	1.99 ± 0.64	2.06 ± 0.64
Blood urea nitrogen, mg/dl ± SD	24 ± 10	24 ± 9	25 ± 10	25 ± 10
UP/Cr, g/g [interquartile range]	0.08 [0.03 to 0.36]	0.08 [0.03 to 0.34]	0.10 [0.03 to 0.47][d]	0.10 [0.03 to 0.30]
Urine sodium to potassium ratio, g/g ± SD	2.3 ± 1.2	2.2 ± 1.2	2.3 ± 1.1	2.3 ± 1.2
Phosphate, mg/dl ± SD	3.5 ± 0.6	3.5 ± 0.6	3.6 ± 0.5[d]	3.5 ± 0.5
Calcium, mg/dl ± SD	9.2 ± 0.5	9.2 ± 0.5	9.1 ± 0.5	9.1 ± 0.5
Albumin, g/dl ± SD	4.2 ± 0.3	4.3 ± 0.3	4.2 ± 0.3[d]	4.2 ± 0.3
Uric acid, mg/dl ± SD	8.3 ± 1.9	8.3 ± 1.9	8.1 ± 1.9	8.6 ± 1.8
hs-CRP, mg/L [interquartile range][e]	7.6 [2.0 to 9.2]	3.4 [1.7 to 6.1]	13.6 [5.8 to 20.2][a]	—
NT-proBNP, pg/ml [interquartile range][f]	154 [63 to 447]	150 [61 to 418]	175 [71 to 501]	190 [60 to 453]
Abnormal electrocardiogram, *n* (%)				
yes	794 (80)	549 (80)	245 (81)	86 (83)
no	196 (20)	137 (20)	59 (19)	18 (17)
Annual income, *n* (%)				
<$15,000	474 (48)	311 (45)	163 (54)[d]	47 (45)
≥$15,000	335 (34)	258 (38)	77 (25)[d]	35 (34)
decline to provide information	181 (18)	117 (17)	64 (21)	22 (21)

M-I group is defined as body mass index < 23 kg/m^2 or hs-CRP > 10 mg/L. In the excluded group, 102 and 2 participants were excluded from this study because of missing measurements of high sensitivity C reactive protein (hs-CRP) and total cholesterol, respectively. NT-proBNP, N-terminal prohormone brain natriuretic peptide.

[a]$P < 0.005$ and [d]$P < 0.05$ compared with the group without malnutrition-inflammation.

[b]Eight missing values.

[c]Five missing values.

[e]One hundred twelve missing values.

[f]Ninety-eight missing values.

tively. However, in the M-I group, the corresponding HRs did not vary by cholesterol category: HR = 1, 1.03 [0.49, 2.15] and 0.76 [0.35, 1.68]. In the full cohort, combining participants with and without M-I, total cholesterol level as a categorical variable ≥240 mg/dl had an adjusted HR of 1.60 [1.14, 2.26], predicting the primary composite CVD outcome compared with the reference category of cholesterol level <200 mg/dl.

In unadjusted analyses, participants without M-I with baseline cholesterol levels <200, 200 to 239, and ≥240 mg/dl had a gradual increased incidence rate of the primary CVD outcome from 2.4 to 3.0 to 4.9 events per 100 patient-years of follow-up, respectively. In participants with M-I, the corresponding incidence rates of the primary CVD outcome were 3.5, 3.5, and 2.4 events per 100 patient-years of follow-up, respectively. As shown in Figure 2, the cumula-

Table 2. Participants' characteristics in the African-American study of kidney disease and hypertension according to baseline total cholesterol categories stratifying by the absence or presence of malnutrition-inflammation at entry in the trial

Malnutrition-Inflammation Baseline Variables	Total Cholesterol Categories					
	<200 mg/dl (*n* = 429)		200 to 239 mg/dl (*n* = 297)		≥240 mg/dl (*n* = 264)	
	Absence (*n* = 293)	Presence (*n* = 136)	Absence (*n* = 214)	Presence (*n* = 83)	Absence (*n* = 179)	Presence (*n* = 85)
Age, years ± SD	53 ± 12	54 ± 10	56 ± 10	56 ± 10	56 ± 10	54 ± 10
Women, *n* (%)	84 (29)	60 (44)[a]	65 (30)	41 (49)[a]	86 (48)	51 (60)
History of pre-existing cardiovascular disease	143 (49)	74 (54)	117 (55)	46 (55)	88 (49)	47 (55)
Years with hypertension[b]	13 ± 9	13 ± 9	16 ± 10	15 ± 10	15 ± 11	14 ± 11
Tobacco use, *n* (%)						
current	74 (25)	57 (42)[a]	52 (24)	33 (40)[a]	38 (21)	36 (42)[a]
past	90 (31)	33 (24)	57 (27)	26 (31)	59 (33)	19 (22)
never	129 (44)	46 (34)	105 (49)	24 (29)	82 (46)	30 (35)
Body mass index, kg/m^2 ± SD	31.2 ± 5.7	28.9 ± 8.3[a]	31.4 ± 5.9	28.6 ± 7.7	31.6 ± 5.6	29.7 ± 8.1
Clinic systolic blood pressure, mmHg ± SD	150 ± 25	149 ± 23	150 ± 24	150 ± 22	150 ± 24	155 ± 24
Clinic diastolic blood pressure, mmHg ± SDd	96 ± 15	94 ± 14	96 ± 15	95 ± 14	95 ± 13	98 ± 13
Alcohol use, *n* (%)						
yes	87 (30)	31 (23)	63 (30)	25 (31)	46 (26)	27 (32)
no	205 (70)	104 (77)	150 (70)	56 (69)	133 (74)	58 (68)
Women HDL cholesterol, mg/dl ± SD	51 ± 12	51 ± 14	55 ± 15	51 ± 11	52 ± 18	58 ± 23[c]
Men HDL cholesterol, mg/dl ± SD	42 ± 12	45 ± 12	44 ± 12	52 ± 26	45 ± 14	51 ± 25
Non-HDL cholesterol, mg/dl ± SD	127 ± 23	123 ± 22	170 ± 18	168 ± 23	218 ± 32	215 ± 37
GFR, ml/min per 1.73 m^2 ± SD	47 ± 13	43 ± 14[c]	48 ± 13	45 ± 13	47 ± 14	46 ± 14
Urinary urea nitrogen, g/day ± SD	8.5 ± 4	7.4 ± 3.1[c]	8.5 ± 3.6	7.8 ± 3.3	9.2 ± 4.1	7.5 ± 3.8[a]
Serum creatinine, mg/dl ± SD	2.06 ± 0.67	2.05 ± 0.68	2.05 ± 0.79	2.00 ± 0.68	1.95 ± 0.76	1.89 ± 0.54
Blood urea nitrogen, mg/dl ± SD	24 ± 9	26 ± 10[c]	24 ± 9	25 ± 10	25 ± 10	25 ± 11
UP/Cr, g/g [interquartile range]	0.08 [0.03 to 0.34]	0.08 [0.04 to 0.35]	0.07 [0.03 to 0.28]	0.10 [0.04 to 0.45]	0.08 [0.03 to 0.47]	0.11 [0.04 to 0.66]
Urine sodium to potassium ratio, g/g ± SD	2.2 ± 1.2	2.3 ± 1.1	2.3 ± 1.2	2.3 ± 1.2	2.2 ± 1.3	2.4 ± 1.1
Phosphate, mg/dl ± SD	3.5 ± 0.6	3.6 ± 0.5[c]	3.4 ± 0.5	3.6 ± 0.6	3.6 ± 0.5	3.7 ± 0.6
Calcium, mg/dl ± SD	9.1 ± 0.5	9 ± 0.5	9.2 ± 0.5	9.2 ± 0.5	9.2 ± 0.6	9.3 ± 0.5
Albumin, g/dl ± SD	4.2 ± 0.3	4.0 ± 0.3[a]	4.3 ± 0.3	4.3 ± 0.3	4.3 ± 0.3	4.3 ± 0.4
Uric acid, mg/dl ± SD	8.3 ± 1.9	7.8 ± 1.8[c]	8.4 ± 1.8	8.6 ± 2.0	8.3 ± 1.9	8.2 ± 1.9
hs-CRP, mg/L [interquartile range]	3.2 [1.4 to 5.8]	13.4 [4.1 to 19.1][a]	3.3 [1.8 to 6.1]	13.8 [9.0 to 19.9][a]	4.1 [2.2 to 6.7]	13.8 [10.0 to 21.0][a]
NT-proBNP, pg/ml [interquartile range][d]	195 [77 to 496]	199 [81 to 565]	143 [62 to 371]	157 [73 to 424]	98 [25 - 262]	144 [53–433]
Abnormal electrocardiogram, *n* (%)						
yes	237 (81)	113 (83)	178 (83)	62 (75)	134 (75)	70 (82)
no	56 (19)	23 (17)	36 (17)	21 (25)	45 (25)	15 (18)
Annual income, *n* (%)						
<$15,000	141 (48)	79 (58)	90 (42)	38 (46)	80 (45)	46 (54)[a]
≥$15,000	95 (32)	31 (23)	87 (41)	28 (34)	76 (42)	18 (21)
decline to provide information	57 (20)	26 (19)	37 (17)	17 (20)	23 (13)	21 (25)

M-I group is defined as hs-CRP > 10 mg/L or body mass index < 23 kg/m^2. hs-CRP, high sensitivity C reactive protein; NT-proBNP, N-terminal prohormone brain natriuretic peptide.

[a] $P < 0.005$.

[b] Eight missing values.

[c] $P < 0.05$.

[d] Ninety-eight missing values.

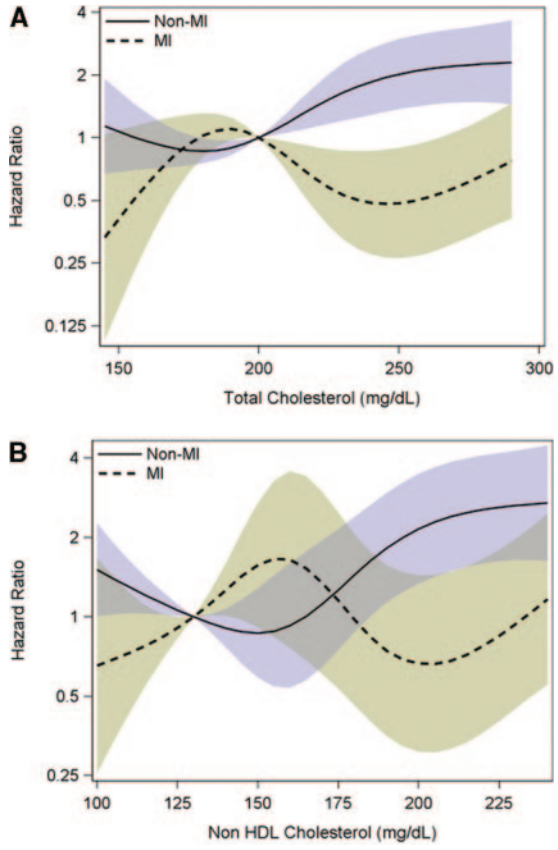

Figure 1. Associations of the adjusted HRs with 95% confidence intervals for the primary composite cardiovascular disease outcome with total cholesterol (A; $P = 0.002$) and with non-HDL cholesterol (B; $P = 0.008$) are significantly different between the M-I and non–M-I groups. (A) The total cholesterol reference value is 200 mg/dl. Total cholesterol level was modeled nonparametrically by using restricted cubic spline with four degrees of freedom, where the knots are 144, 191, 226, and 288 mg/dl. (B) The non-HDL cholesterol reference value is 130 mg/dl. Non-HDL cholesterol level was modeled nonparametrically by using restricted cubic spline with four degrees of freedom, where the knots are 97, 143, 179, and 237 mg/dl. All models were adjusted for age, gender, pre-existing cardiovascular disease, baseline iodine 125-iothalamate GFR, annual income, abnormal electrocardiogram, randomization group, and statin use and were stratified by center.

tive incidence of the primary CVD outcome increased significantly as cholesterol level increased in participants without M-I (Figure 2A; $P < 0.001$), whereas the incidence of the primary CVD outcome according to cholesterol level was not significantly different in participants with M-I (Figure 2B; $P = 0.45$).

Interaction of M-I with Non-HDL Cholesterol

A similar pattern of relationship was observed using non-HDL cholesterol as the exposure variable (Figure 1B; Table 3). The adjusted HR for the primary CVD outcome exhibited a stronger relationship with non-HDL cholesterol

Table 3. Risk association between baseline lipids levels and primary composite cardiovascular disease outcome (cardiovascular death or first hospitalization for coronary artery disease, stroke, or congestive heart failure event) is modified by M-I

	Overall			Non-M-I			M-I			*P* for Interaction[a]
	No. Patient Events	No. per 100 Patient-Years	HR (95% CI)	No. Patient Events	No. per 100 Patient-Years	HR (95% CI)	No. Patient Events	No. per 100 Patient-Years	HR (95% CI)	
Total cholesterol										0.016
<200 mg/dl	76	2.7	1.00	47	2.4	1.00	29	3.5	1.00	
200 to 239 mg/dl	58	3.1	1.10 (0.77, 1.57)	42	3.0	1.19 (0.77, 1.84)	16	3.5	1.03 (0.49, 2.15)	
≥240 mg/dl	68	4.1	1.60 (1.14, 2.26)	55	4.9	2.18 (1.43, 3.33)	13	2.4	0.76 (0.35, 1.68)	
Non-HDL cholesterol										0.11
<130 mg/dl	41	2.6	1.00	27	2.6	1.00	14	2.7	1.00	
130 to 159 mg/dl	45	2.6	0.91 (0.59, 1.41)	29	2.2	0.85 (0.49, 1.48)	16	4.1	1.79 (0.78, 4.10)	
≥160 mg/dl	115	3.7	1.35 (0.93, 1.95)	87	4.0	1.45 (0.92, 2.27)	28	3.1	1.44 (0.67, 3.11)	

All Cox models were adjusted for age, gender, pre-existing cardiovascular disease, baseline iodine 125-iothalamate GFR, annual income, abnormal electrocardiogram, randomization group, and statin use and were stratified by center. The hazard ratios with 95% confidence intervals are expressed for lipids levels as categorical variables using the reference category of total cholesterol <200 mg/dl and for non-HDL cholesterol <130 mg/dl. 95% confidence intervals in parentheses that do not include 1 are significantly different with $P < 0.05$. HR, hazard ratio; CI, confidence interval.

[a]The interaction *P* values assess the modifying effect of M-I on the risk relationship between baseline lipid levels and the primary composite cardiovascular disease outcome. The interaction *P* values are from the Cox models treating the lipids variables as categorical factors; interaction *P* values from the cubic spline models treating the lipids variables as continuous factors are given in Figure 1, A and B.

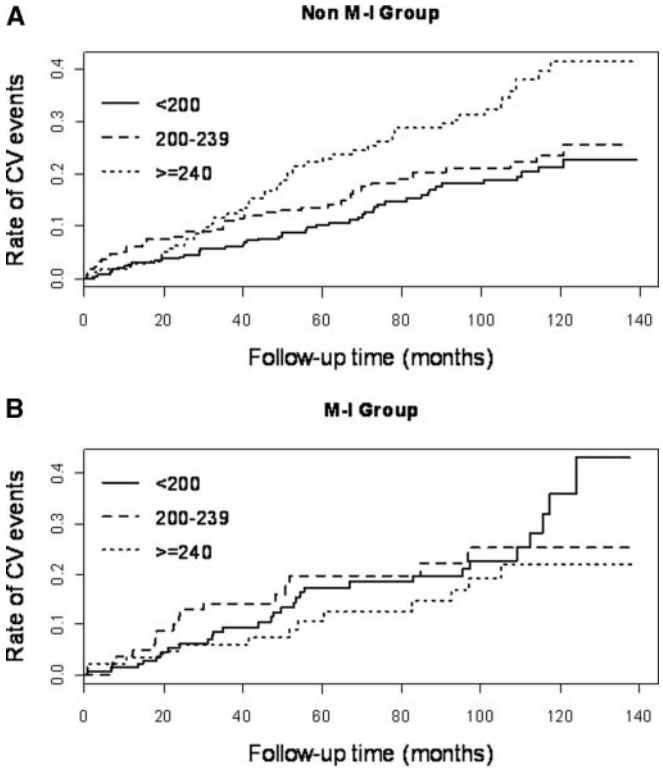

Figure 2. Higher total cholesterol level associates with a gradual and significantly greater cumulative incidence of the primary composite cardiovascular disease outcome only in participants without M-I. The *P* value is <0.001 for the non–M-I group and is 0.45 for the M-I group. Cumulative cardiovascular (CV) event by cholesterol categories: <200, 200 to 239, and ≥240 mg/dl.

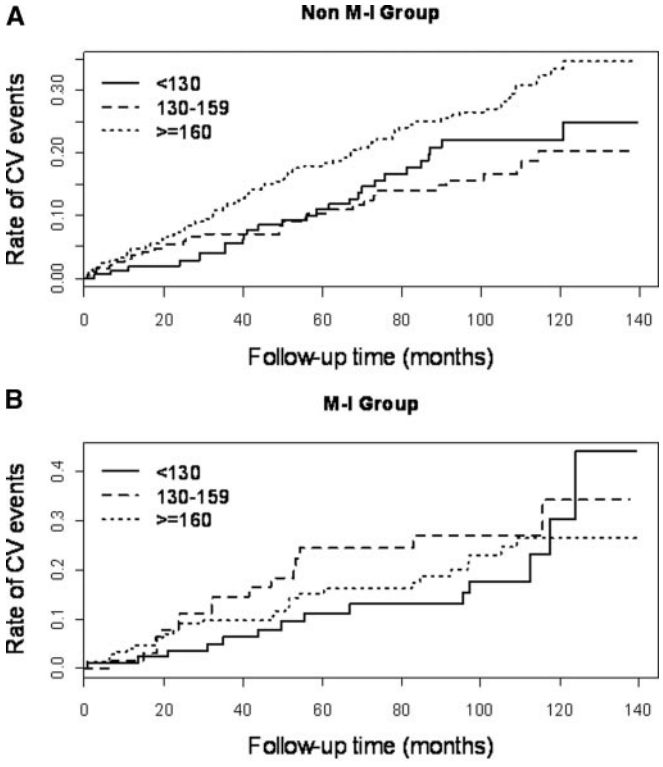

Figure 3. Higher non-HDL cholesterol level associates with a significantly greater cumulative incidence of the primary composite CVD outcome only in participants without M-I. The *P* value is 0.009 for the non–M-I group and is 0.47 for the M-I group. Cumulative cardiovascular (CV) event by non-HDL cholesterol categories: <130, 130 to 159, and ≥160 mg/dl.

among participants in the non M-I group than among participants in the M-I group for the cubic spline model (interaction, $P = 0.008$; *P* for nonlinearity = 0.001) and to a lesser extent for the corresponding Cox regression model treating non-HDL as a categorical variable (interaction, $P = 0.11$). In unadjusted analyses, higher non-HDL cholesterol level was associated with a significantly greater cumulative incidence of the primary CVD outcome only in participants without M-I ($P = 0.009$; Figure 3A).

Sensitivity Analyses Using Alternative M-I Definitions

Under adjusted cubic spline models, the risk relationship between cholesterol level and the primary CVD outcome was also modified to varying extents when participants were restratified using three additional definitions of M-I: (*1*) low serum albumin ≤3.6 mg/dl or low BMI <23 kg/m^2 or high hs-CRP >10 mg/L (interaction, $P = 0.004$; *P* for nonlinearity = 0.02); (*2*) low serum albumin ≤3.6 mg/dl or high hs-CRP >10 mg/L (interaction, $P = 0.002$; *P* for nonlinearity = 0.002); and (*3*) low serum albumin ≤3.6 mg/dl or high hs-CRP >3 mg/L (interaction, $P = 0.07$; *P* for nonlinearity = 0.12). In each of these analyses, the adjusted HR relating the primary CVD outcome to total cholesterol increased with higher cholesterol level for participants without M-I but not for participants with M-I for each alternative M-I definition (data not shown). These interactions were also evident in the corresponding Cox regressions treating total cholesterol as a categorical variable for the first two of these alternative definitions of M-I, although not so when M-I was defined as serum albumin ≤3.6 mg/dl or hs-CRP >3 mg/L (Table 4).

The interaction between total cholesterol and M-I status (defined as BMI < 23 kg/m^2 or hs-CRP > 10 mg/L) did not reach statistical significance when a more homogenous secondary composite CVD outcome of cardiovascular death or first hospitalization for CAD or stroke event was used as the outcome (interaction, $P = 0.12$ for the cubic spline model; *P* for nonlinearity = 0.35; interaction, $P = 0.11$ when total cholesterol was treated as a categorical variable). However, the stratified analyses showed that higher total cholesterol level was associated with a substantially and progressively greater risk for the development of the secondary CVD outcome only in the non–M-I group: HR = 1.0, 1.22 [0.74, 1.99] and 1.97 [1.21, 3.22] in participants with total cholesterol <200, 200 to 239, and ≥240 mg/dl, respectively. In the M-I group, the corresponding HRs progressively decreased but did not vary significantly by cholesterol level: HR = 1.0, 0.86 [0.35, 2.13], and 0.62 [0.24, 1.55].

Table 4. Sensitivity analyses using different definitions of M-I as a modifier of the risk relationship between total baseline cholesterol and the primary composite cardiovascular disease outcome

Categorical	Non M-I		M-I		*P* for Interaction[a]
	HR (95% CI)	*P*	HR (95% CI)	*P*	
Albumin ≤3.6 g/dl or BMI < 23 kg/m^2 or hs-CRP > 10 mg/L					0.019
<200 mg/dl	1.00		1.00		
200 to 239 mg/dl	1.29 (0.82, 2.01)	0.27	0.91 (0.45, 1.85)	0.80	
≥240 mg/dl	2.29 (1.48, 3.55)	<0.001	0.94 (0.46, 1.93)	0.87	
Albumin ≤3.6 g/dl or hs-CRP >10 mg/L					0.044
<200 mg/dl	1.00		1.00		
200 to 239 mg/dl	1.38 (0.93, 2.03)	0.11	0.99 (0.44, 2.21)	0.98	
≥240 mg/dl	2.01 (1.37, 2.95)	<0.001	1.16 (0.51, 2.68)	0.72	
Albumin ≤3.6 g/dl or hs-CRP >3 mg/L					0.64
<200 mg/dl	1.00		1.00		
200 to 239 mg/dl	1.34 (0.76, 2.36)	0.32	1.11 (0.72, 1.71)	0.64	
≥240 mg/dl	1.84 (1.03, 3.28)	0.04	1.39 (0.91, 2.12)	0.13	

All Cox models were adjusted for age, gender, pre-existing cardiovascular disease, baseline iodine 125-iothalamate GFR, annual income, abnormal electrocardiogram, randomization group, and statin use and were stratified by clinical center. The hazard ratios with 95% confidence intervals are expressed for total cholesterol level as a categorical variable using the reference category of total cholesterol <200 mg/dl. BMI, body mass index; hs-CRP, high sensitivity C reactive protein; HR, hazard ratio; CI, confidence interval.

[a]The interaction *P* values reported in the last column assess the modifying effect of M-I on the risk relationship between baseline total cholesterol level and the primary composite cardiovascular disease outcome. These *P* values are from Cox models using total cholesterol as a categorical variable; interaction *P* values from corresponding cubic spline models treating total cholesterol as a continuous variable are given in the text with the corresponding *P* values for nonlinearity test.

DISCUSSION

In studies of the general population, the risk relationship of total cholesterol with CVD mortality is direct, strong, and progressive without evidence of a threshold.[21–23] In moderate CKD and ESRD populations,[1–8] the relationship of serum cholesterol level with CVD events and overall mortality is inconsistent and often paradoxical. Liu *et al.*[8] recently provided evidence that the paradoxical relationship of cholesterol level with overall mortality and its U-shaped relationship with CVD mortality can be explained by the confounding effect of the commonly present M-I in dialysis populations. Our data extend these findings by documenting that M-I is a modifier of the risk relationship of cholesterol levels with CVD in African Americans not yet on maintenance dialysis with moderate CKD attributed to hypertension.

In the study by Liu *et al.*[8] of ESRD participants, lower baseline cholesterol levels were associated with greater total mortality and CVD events in the overall cohort. In the 23% of participants without M-I, however, there was a significant, continuous, and positive relationship of total cholesterol with total mortality. In contrast, the risk relationship of total cholesterol with total mortality was significant, continuous, and inverse in the 77% of participants with M-I. In our study of CKD participants not on maintenance dialysis, the prevalence of M-I was only 31%. The association of high cholesterol level with CVD events was limited to the 69% of participants without M-I. This finding is noteworthy because participants with and without M-I had similar high prevalence of cholesterol level ≥ 200 mg/dl (55 *versus* 57%) and cumulative incidence of the primary CVD outcome (19 *versus*. 21%), respectively.

Our results should be discussed in the context of *post hoc* analyses in the subgroup of participants with mild CKD included in clinical trials of statins and CVD. In the meta-regression study by Tonelli *et al.*,[24] of three clinical trials, statin therapy significantly reduced cholesterol levels by 48 ± 24 mg/dl in participants with mild CKD. Additionally, statin therapy compared with placebo significantly reduced the risk of CVD events by 23% (unadjusted CVD incidence of 27.7% in the statin group *versus* 34.1% in the placebo group; adjusted HR 0.77 [0.68, 0.86]). Trials of statin therapy in mild CKD and our findings indicate that hypercholesterolemia is an important risk factor for CVD in CKD. However, the pathogenesis of CVD in CKD is complex, with multiple risk factors contributing to the disease. Whereas traditional risk factors such as hypercholesterolemia remain important, they seem to compete and interact with nontraditional risk factors such as M-I. Ongoing randomized clinical trials such as the study of heart and renal protection will help to confirm the efficacy of statin therapy for CVD directly in populations with moderate to severe CKD not yet on maintenance dialysis.[25]

Our results and those of Liu *et al.*[8] should be also placed in the context of two recently published studies of statin therapy in ESRD, the Die Deutche Diabetes Dialyze Studie (4D trial)[6] and a trial to evaluate the use of rosuvastatin in subjects on regular hemodialysis: an assessment of survival and CVD events (AURORA),[7] that failed to show a benefit of statin therapy on CVD despite highly significant reductions in cholesterol levels of approximately 42 to 43%. Additionally, a modifying effect of hs-CRP on the relationship between statin therapy and CVD events was not found in the AURORA[7] trial (interaction, $P = 0.32$). We consider three reasons for the lack of overall statin therapy effect and lack of interaction between hs-CRP level and statin therapy on

CVD in the 4D and AURORA trials. First, in the 4D trial,[26] the high hs-CRP level was one of the most important risk factors of CVD events (relative risk, 1.10 [1.01, 1.18] per unit increase in log-transformed hs-CRP) and mortality (relative risk, 1.25 [1.17, 1.33] per unit increase in log-transformed hs-CRP) independent of other risk factors including statin therapy. Hence, prevalent M-I might be competing with hypercholesterolemia and other risk factors for the risk attributed to CVD events and mortality. Second, the benefits of statins are increasingly attributed to pleiotropic effects, *i.e.,* reducing inflammation and improving endothelial function.[27,28] However, in both trials,[6,7,26] hs-CRP levels were only minimally lowered in the participants randomized to statins, at best by 11.5% in the AURORA trial[7] from a baseline median level of 4.8 to 4.1 mg/L and from 4.6 to 4.4 mg/L in the 4D trial,[26] which seem ineffective in ameliorating the inflammatory state of CKD, reflected by the 5- to 10-fold higher hs-CRP levels compared with the general population. Third, the 4D and AURORA trials[6,7,26] only assessed high hs-CRP as a surrogate of chronic inflammation, whereas Liu *et al.*[8] assessed a composite of high hs-CRP or high IL6 or low albumin as surrogates of chronic inflammation and/or malnutrition. Hence, the results of these studies, while informative, do not contradict our results and those of Liu *et al.*[8]

Our study has limitations. First, the modifying effect of M-I on the risk relationship between cholesterol and CVD events may still be subject to residual confounding. Second, the cause of increased inflammation is uncertain, but it was probably not related to underlying infection. The enrolled participants in the AASK trial did not have any clinical symptoms or signs of infection at baseline that would have excluded them from participating in the study. Third, total cholesterol levels were drawn from nonfasting baseline specimens; however, serum total cholesterol and non-HDL cholesterol are not considered to be sensitive to food intake. Fourth, in our population, we were unable to confirm the diagnosis of protein energy wasting caused by lacking the measurement of prealbumin (a more reliable marker of protein nutritional status) with the simultaneous assessment of markers of reduced muscle mass as recommended by the International Society of Renal Nutrition and Metabolism.[29] However, as in the study of Kovesdy *et al.*,[15] we added to the definitions of the modifier a low serum albumin as a marker of protein malnutrition, excluding participants with the urine protein to creatinine ratio >2.5 g/g and results remained similar (Table 4). Fifth, in our analyses, the risk relationship between cholesterol and CVD in participants with M-I is uncertain. Based on crude incidence rates (Table 3), the relationship is inversed with a trend toward decreasing event rates by increasing serum cholesterol. However, in adjusted analyses, the relationship between cholesterol and CVD in the M-I group appears ι-shaped, albeit nonsignificant. Sixth, our study did not have sufficient statistical power to explore analyses of the individual CVD components of the composite primary outcome.

Strengths of our study include the study population (*i.e.,* African Americans with hypertensive CKD), the long duration of follow-up (up to 12 years), and the unbiased event ascertainment procedures. Second, in most but not all sensitivity analyses, our results were robust to alternative definitions of the modifier (Table 4). Third, our results and those by Liu *et al.*[8] have biologic plausibility.[30–44] In CKD patients, progressive reduction in GFR,[31,32] superimposed inflammatory illnesses or comorbidities,[33–36] and the use of vascular access material, the use of bioincompatible membranes,[37] nonsterile dialysate,[38] and the presence of backfiltration[39] during dialysis contribute to the generation of interleukins and/or enhancement of their inflammatory effects. The inflammatory milieu of progressive uremia increases catabolism and predispose to wasting, contributing to the low BMI and the high hs-CRP, which are markers of M-I in CKD.[29,30,41–44] Hence, in populations with moderate to severe CKD, where the prevalence of M-I is common, ranging from 23 to 77%,[8,30,40,41] with the highest prevalence observed in ESRD populations,[8] one can expect M-I acting as a modifier of the risk relationship of cholesterol with CVD, which would not always be consistently continuous and positive.

Our study has important clinical implications. Traditional CVD risk prediction equations, such as the Framingham equation, do not stratify on M-I status. To date, the equations developed in general populations perform poorly in CKD patients.[45] Given the substantial burden of CVD in patients with CKD, efforts to predict which CKD patients will develop CVD are critically important for patient management. As large cohort studies, such as the Chronic Renal Insufficient Cohort Study,[46] develop risk prediction equations, our study provides strong evidence that the equation development process should consider the role of M-I and potentially test separate equations based on the presence or absence of M-I.

In summary, our data suggest that M-I is a modifier of the risk relationship of cholesterol levels with CVD events in African Americans with hypertensive CKD. Whereas higher cholesterol levels were gradually and significantly associated with greater risk for the development of CVD events in the group of participants without M-I, higher cholesterol levels were not associated with CVD events in the M-I group.

CONCISE METHODS

Study Design and Population

The AASK was a multicenter, randomized trial that examined the effect on CKD progression of two BP goals, a low goal (mean arterial pressure $\leq$ 92 mmHg) or a usual goal (mean arterial pressure = 102 to 107 mmHg), and three different classes of antihypertensive drugs, ramipril, amlodipine, or metoprolol, double blinded in a 2×3 factorial design. The clinical trial enrolled 1094 participants between February 1995 and September 1998. The trial ended in September 30 2001.[16,17] On completion of the trial in September 2001, participants were provided open label treatment

for hypertension including an angiotensin converting enzyme inhibitor or an angiotensin II receptor blocker. From the 787 participants alive and not on dialysis at the end of the trial phase, 691 were enrolled in the AASK cohort phase[18] for an additional 5 years. The protocol and procedures were approved by the institutional review board at each center, and all participants gave written informed consent.

Definitions of Variables and Measurements

Participants were categorized for their risk of CVD events using total cholesterol and non-HDL cholesterol, drawn from nonfasting baseline specimens. According to the National Cholesterol Education Program guidelines for lipids,[47] participants were categorized in three groups: <200, 200 to 239, and ≥240 mg/dl using total cholesterol levels. Participants were categorized in three groups: <130, 130 to 159, and ≥160 mg/dl using non-HDL cholesterol levels. Presence of malnutrition was defined as a baseline BMI <23 kg/m^2, a marker of malnutrition accepted by the International Society of Renal Nutrition and Metabolism.[29] Presence of inflammation was defined as a baseline hs-CRP of >10 mg/L, consistent with the definition used by Liu *et al.*[8] A composite definition of M-I was used to stratify the study participants in two groups: absence or presence of M-I. In sensitivity analyses, participants were restratified using three additional definitions of M-I: (*1*) low serum albumin ≤3.6 mg/dl or low BMI <23 kg/m^2 or high hs-CRP >10 mg/L; (*2*) low serum albumin ≤3.6 mg/dl or high hs-CRP >10 mg/L; and (3) low serum albumin ≤3.6 mg/dl or high hs-CRP >3 mg/L. All laboratory assays were measured at the Cleveland Clinic Foundation central laboratory according to standardized methods. The hs-CRP level was measured by the nephelometry method with interassay coefficient of variation percentage (CV) of 3.79%. The cholesterol level was measured by the Roche enzymatic system with interassay CV of 1.16%. The serum albumin level was measured by the bromocresol green method with interassay CV of <1%.

Outcomes Ascertainment

The primary CVD outcome was a composite of cardiovascular death or first hospitalization for a CAD, stroke, or CHF event. Cardiovascular death was defined as the one occurring as a consequence of cardiac arrhythmias, CAD, CHF, and stroke events (no autopsy was required). Hospitalization for a CAD event was defined as the need for cardiac revascularization procedure, confirmed nonfatal myocardial infarction (supported by the presence of elevated creatine kinase level >2 times the upper limit of normal for the given hospital with elevation of cardiac specific enzyme above the normal range or elevation of cardiac troponin I, or in the absence of cardiac specific enzymes, a typical evolutionary pattern defined as elevated creatine kinase >2 times the upper limit of normal followed by a fall of at least 50% or the appearance of new pathologic Q-waves in two or more contiguous leads, or the appearance of an R-wave with R/S ratio in lead V1>1.0 in the absence of another explanation for these changes or a loss of progression of R-waves V2 through V5) or a report of nonfatal myocardium infarction without supporting documentation. Hospitalization for stroke event was defined as permanent neurologic deficit of at least 24-hour duration attributed to a stroke with or without confirmation by radiographic imaging. Hospitalization for CHF event was defined as requiring therapy with an inotropic agent, vasodilator, angiotensin converting enzyme inhibitor, angiotensin II receptor blocker, an increase dose of a diuretic, or ultrafiltration. A secondary composite CVD outcome of cardiovascular death or first hospitalization for CAD or stroke event was used in sensitivity analyses. The Cardiovascular Outcome Committee reviewed and classified all cardiovascular hospitalizations and deaths occurring in both the trial and cohort phases of the study according to a common prespecified protocol.[16–20]

Statistical Analysis

Participants' baseline characteristics are presented according to the cholesterol categories and the absence or presence of M-I at entry. Baseline characteristics were summarized as frequencies and proportions for categorical variables and as means and SD or medians and interquartile ranges for continuous variables. χ^2 tests, *t* tests, and Wilcoxon rank sum tests were used to compare these variables between the groups with and without M-I. Kaplan-Meier cumulative incidence curves of the CVD outcome were estimated for categories of total cholesterol and non-HDL cholesterol levels stratifying by the absence or presence of M-I. The log-rank test was used to compare the curves among groups.

Two sets of multivariable Cox proportional hazards regression models were used to investigate the role of M-I as a potential effect modifier for relationships between total cholesterol and non-HDL cholesterol levels with risk of CVD events. In the first set of Cox models, the cholesterol measures were incorporated as continuous variables using restricted cubic spline functions with four degrees of freedom, with knot points located at the tertiles of the cholesterol variables. In the second set of Cox models, the cholesterol variables were modeled as categorical variables based on the pre-existing cut-offs defined above. Both set of Cox models allow for nonlinear relationships of the cholesterol variables with risk of CVD, as has been previously reported.[8] The cubic spline models have the advantage of providing results that are relatively insensitive to arbitrary cut-off values between cholesterol categories.[8] Both sets of Cox regression models included interaction terms between the M-I classification and the factors representing the cholesterol levels. The Cox regression also included age, gender, pre-existing CVD, baseline levels of iodine 125-iothalamate GFR, annual income, abnormal electrocardiogram, randomization group, and statin use as covariates and were stratified by clinical center. Adjusted HRs with 95% confidence intervals were reported. *P* values for interactions between the M-I indicators and the cholesterol levels were computed using likelihood ratio tests. Crude incidence rates (event rate per 100 patient-years) were also estimated without covariate adjustment.

In sensitivity analyses, the Cox regression analyses described above were repeated after reclassifying participants using three alternative definitions of M-I mentioned above. All survival analyses censored follow-up at the time of non-CVD death, ESRD, the administrative end of the study, or loss to follow-up. All hypothesis tests are reported on a comparison-wise basis, without adjustment for multiple com-

parisons. Proportional hazards were assessed by checking the Schoenfeld residual plots for all Cox models. All analyses were performed using the Splus 8 (Palo Alto, CA) statistical package.

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DISCLOSURES

None.

REFERENCES

1. Degoulet P, Legrain M, Réach I, Aime F, Devries C, Rojas P, Jacobs C: Mortality risk factors in patients treated by chronic hemodialysis: Report of the Diaphane collaborative study. *Nephron* 31: 103–110, 1982
2. Lowrie EG, Lew NL: Death risk in hemodialysis patients: The predictive value of commonly measured variables and an evaluation of death rate differences between facilities. *Am J Kidney Dis* 15: 458–482, 1990
3. Nishizawa Y, Shoji T, Kakiya R, Tsujimoto Y, Tabata T, Ishimura E, Nakatani T, Miki T, Inaba M: Non-high-density lipoprotein cholesterol (non-HDL-C) as a predictor of cardiovascular mortality in patients with end-stage renal disease. *Kidney Int* 63: S117–S120, 2003
4. Kilpatrick RD, McAllister CJ, Kovesdy CP, Derose SF, Kopple JD, Kalantar-Zadek K: Association between serum lipids and survival in hemodialysis patients and impact of race. *J Am Soc Nephrol* 18: 293–303, 2007
5. Kovesdy CP, Anderson JE, Kalantar-Zadek K: Inverse association be-

tween lipid levels and mortality in men with chronic kidney disease who are not yet on dialysis: Effect of case mix and the malnutrition-inflammation-cachexia syndrome. *J Am Soc Nephrol* 18: 304–311, 2007
6. Wanner C, Krane V, März W, Olschewski M, Mann JF, Ruf G, Ritz E, German Diabetes and Dialysis Study Investigators: Atorvastatin in patients with type 2 diabetes mellitus undergoing hemodialysis. *N Engl J Med* 353: 238–248, 2005
7. Fellström BC, Jardine AG, Schmieder RE, Holdaas H, Bannister K, Beutler J, Chae DW, Chevaile A, Cobbe SM, Gronhagen-Riska C, De Lima JJ, Lins R, Mayer G, McMahon AW, Parving HH, Remuzzi G, Samuelsson O, Sonkodi S: Sci D, Suleymanlar G, Tsakiris D, Tesar V, Todorov V, Wiecek A, Wuthrich RP, Gottlow M, Johnsson E, Zannad F, AURORA Study Group: Rosuvastatin and cardiovascular events in patients undergoing hemodialysis *N Engl J Med* 360: 1395–1407, 2009
8. Liu Y, Coresh J, Eustace JA, Longenecker JC, Jaar B, Fink NE, Tracy RP, Powe NR, Klag MJ: Association between cholesterol level and mortality in dialysis patients: Role of inflammation and malnutrition. *JAMA* 291: 451–459, 2004
9. London GM, Marchais SJ, Guerin AP, Metivier F, Adda H, Pannier B: Inflammation, arteriosclerosis, and cerebrovascular therapy in hemodialysis patients. *Kidney Int* 63): S88–S93, 2003
10. Foley RN, Parfrey PS, Morgan J, Barre PE, Campbell P, Cartier P, Coyle D, Fine A, Handa P, Kingma I, Lau CY, Levin A, Mendelssohn D, Muirhead N, Murphy B, Plante RK, Posen G, Wells GA: Effect of hemoglobulin level in hemodialysis patients with asymptomatic cardiomyopathy. *Kidney Int* 58: 1325–1335, 2000
11. deFilippi C, Wasserman S, Rosario S, Tiblier E, Sperger H, Tocchi M, Christenson R, Uretsky B, Smiley M, Gold J, Muniz H, Badalamenti J, Herzog C, Henrich W: Cardiac troponin T and C-reactive protein for predicting prognosis, coronary atherosclerosis, and cardiomyopathy in patients undergoing long-term hemodialysis. *JAMA* 290: 353–359, 2003
12. Foley RN, Parfrey PS, Harnett JD, Kent GM, Murray DC, Barre PE: Hypoalbuminemia, cardiac morbidity, and mortality in end-stage renal disease. *J Am Soc Nephrol* 7: 728–736, 1996
13. Shlipak MG, Fried MG, Crump C, Bleyer AJ, Manolio TA, Tracy RP, Furberg CD, Psaty BM: Elevation of inflammatory and procoagulant biomarkers in elderly persons with renal insufficiency. *Circulation* 107: 87–92, 2003
14. Menon V, Greene T, Wang X, Pereira AA, Marcovina SM, Beck GJ, Kusek JW, Collins AJ, Levey AS, Sarnak MJ: C-reactive protein and albumin as predictors of all-cause and cardiovascular mortality in chronic kidney disease. *Kidney Int* 68: 766–772, 2005
15. Kovesdy CP, George SM, Anderson JE, Kalantar-Zadeh K: Outcome predictability of biomarkers of protein-energy wasting and inflammation in moderate and advanced chronic kidney disease. *Am J Clin Nutr* 90: 407–414, 2007
16. Agodoa LY, Appel L, Bakris GL, Beck G, Bourgoignie J, Briggs JP, Charleston J, Cheek D, Cleveland W, Douglas JG, Douglas M, Dowie D, Faulkner M, Gabriel A, Gassman J, Greene T, Hall Y, Hebert L, Hiremath L, Jamerson K, Johnson CJ, Kopple J, Kusek J, Lash J, Lea J, Lewis JB, Lipkowitz M, Massry S, Middleton J, Miller ER 3rd, Norris K, O'Connor D, Ojo A, Phillips RA, Pogue V, Rahman M, Randall OS, Rostand S, Schulman G, Smith W, Thornley-Brown D, Tisher CC, Toto RD, Wright JT Jr, Xu S, African American Study of Kidney Disease and Hypertension (AASK) Study Group: Effect of ramipril vs amlodipine on renal outcomes in hypertensive nephrosclerosis: a randomized controlled trial. *JAMA* 285: 2719–2728, 2001
17. Wright JT Jr, Bakris G, Greene T, Agodoa LY, Appel LJ, Charleston J, Cheek D, Douglas-Baltimore JG, Gassman J, Glassock R, Hebert L, Jamerson K, Lewis J, Phillips RA, Toto RD, Middleton JP, Rostand SG, African American Study of Kidney Disease and Hypertension Study Group: Effect of blood pressure lowering and antihypertensive drug class on progression of hypertensive kidney disease: Results from the AASK trial. *JAMA* 288: 2421–2431, 2002
18. Appel LJ, Wright JT, Greene T, Kusek JW, Lewis JB, Wang X, Lipkowitz MS, Norris KC, Bakris GL, Rahman M, Contreras G, Rostand SG, Kopple JD, Gabbai FB, Schulman GI, Gassman JJ, Charleston J, Agodoa LY, for the African American Study of Kidney Disease and Hypertension Collaborative Research Group: Long-term effects of renin-angiotensin system–blocking therapy and a low blood pressure goal on progression of hypertensive chronic kidney disease in African Americans. *Arch Intern Med* 168: 832–839, 2008
19. Norris K, Bourgoigne J, Gassman J, Hebert L, Middleton J, Phillips RA, Randall O, Rostand S, Sherer S, Toto RD, Wright JT Jr, Wang X, Greene T, Appel LJ, Lewis J, for AASK Study Group: Cardiovascular outcomes in the African American Study of Kidney Disease and Hypertension (AASK) Trial. *Am J Kidney Dis* 48: 739–751, 2006
20. Astor BC, Yi S, Hiremath L, Corbin T, Pogue V, Wilkening B, Peterson G, Lewis J, Lash JP, Van Lente F, Gassman J, Wang X, Bakris G, Appel LJ, Contreras G: N-terminal prohormone brain natriuretic peptide as a predictor of cardiovascular disease and mortality in blacks with hypertensive kidney disease: The African American Study of Kidney Disease and Hypertension (AASK). *Circulation* 117: 1685–1692, 2008
21. Wilson PWF, 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
22. Stamler J Wentworth D. Neaton JD: Is relationship between serum cholesterol and risk of premature death from coronary heart disease continuous and graded? Findings in 356,222 primary screenees of the Multiple Risk Factor Intervention Trial (MRFIT). *JAMA* 256: 2823–2828, 1986
23. Pekkanen J, Linn S, Heiss G, Suchindran CM, Leon A, Rifkind BM, Tyroler HA: Ten-year mortality from cardiovascular disease in relation to cholesterol level among men with and without preexisting cardiovascular disease. *N Engl J Med* 322: 1700–1707, 1990
24. Tonelli M, Isles C, Curhan GC, Tonkin A, Pfeffer MA, Shepherd J, Sacks FM, Furgerg C, Cobbe SM, Simes J, Craven T, West M: Effect of pravastatin on cardiovascular events in people with chronic kidney disease. *Circulation* 110: 1557–1563, 2004
25. Baigent C, Landry M: Study of heart and renal protection (SHARP). *Kidney Int* 63: S207–S210, 2003
26. Krane V, Winkler K, Drechsler C, Lilienthal J, März W, Wanner C for the German Diabetes and Dialysis Study Investigators: Effect of atorvastatin on inflammation and outcome in patients with type 2 diabetes mellitus on hemodialysis. *Kidney Int* 74: 1461–1467, 2008
27. Forrester JS, Libby P: The inflammatory hypothesis and its potential relevance to statin therapy. *Am J Cardiol* 99: 732–738, 2007
28. Diomede L, Albani D, Sottocorno M, Donatti MB, Bianchi M, Fruscella P, Salmona M: In vivo anti-inflammatory effect of statins is mediated by nonsterol mevalonate products. *Arterioscler Thromb Vasc Biol* 21: 1327–1332, 2001
29. Fouque D, Kalantar-Zadeh K, Kopple J, Cano N, Chauveau P, Cuppan L, Franch H, Guarnieri G, Ikizler TA, Kaysen G, Lindholm B, Massy Z, Mitch W, Pineda E, Stenvinkel P, Trevinho-Becerra A, Wanner C: A proposed nomenclature and diagnostic criteria for protein-energy wasting in acute and chronic kidney disease. *Kidney Int* 73: 391–398, 2008
30. Kaysen GA, Stevenson FT, Depner TA: Determinants of albumin concentration in hemodialysis patients. *Am J Kidney Dis* 29(5): 658–668, 1997
31. Bolton CH, Downs LG, Victory JG, Dwight JF, Tomson CR, Mackness MI, Pinkney JH: Endothelial dysfunction in chronic renal failure. Roles of lipoprotein oxidation and pro-inflammatory cytokines. *Nephrol Dial Transplant* 16: 1189–1197, 2001
32. Panichi V, Migliori M, De Pietro S, Taccola D, Bianchi AM, Norpoth M, Metelli MR, Giovannini L, Tetta C, Palla R: C-reactive protein in patients with chronic renal diseases. *Renal Fail* 23: 551–562, 2001
33. Sato Y, Takatsu Y, Kataoka K, Yamada T, Taniguchi R, Sasayama S,

Matsumori A: Serial circulating concentrations of C-reactive protein, interleukin (IL)-4, and IL-6 in patients with acute left heart decompensation. *Clin Cardiol* 22: 811–813, 1999
34. Aronson D, Avizohar O, Levy Y, Bartha P, Jacob G, Markiewicz W: Factor analysis of risk variables associated with low-grade inflammation. *Atherosclerosis* 200: 206–212, 2008
35. Fernandez-Real JM, Vayreda M, Richart C, Gutierrez C, Broch M, Vendrell J, Ricart W: Circulating interleukin 6 levels, blood pressure, and insulin sensitivity in apparently healthy men and women. *J Clin Endocrinol Metab* 86: 1154–1159, 2001
36. Mohamed-Ali V, Goodrick S, Rawesh A, Katz DR, Miles JM, Yudkin JS, Klein S, Coppack SW: Subcutaneous adipose tissue releases interleukin-6, but not tumour necrosis factor-α, in vivo. *J Clin Endocrin Metab* 82: 4196–4200, 1997
37. Memoli B, Postglione L, Cianciaruso B, Bisesti V, Cimmaruta C, Marzano L, Minutolo R, Cuomo V, Guida B, Andreucci M, Rossi G: Role of different dialysis membranes in the release of interleukin-6 soluble receptor in uremic patients. *Kidney Int* 58: 417–424, 2000
38. Schiffl H, Lang SM, Stratakis D, Fisher R: Effects of ultrapure dialysis fluid on nutritional status and inflammatory parameters. *Nephrol Dial Transplant* 16: 1863–1869, 2001
39. Panichi V, Tetta C, Rindi P, Palla R, Lonemann G: Plasma C-reactive protein is linked to backfiltration associated interleukin-6 production. *ASAIO J* 44: M415–M417, 1998
40. Zimmermann J, Herrlinger S, Pruy A, Metzger T, Wanner C: Inflammation enhances cardiovascular risk and mortality in hemodialysis patients. *Kidney Int* 55: 648–658, 1999
41. Stenvinkel P, Heimburger O, Paultre F, Diczfalusy U, Wang T, Berglund L, Jogestrand T: Strong association between malnutrition, inflammation, and atherosclerosis in chronic renal failure. *Kidney Int* 55: 1899–1911, 1999
42. Bologa RM, Levine DM, Parker TS, Cheigh JS, Serur D, Stenzel KH, Rubin AL: Interleukin-6 predicts hypoalbuminemia, hypocholesterolemia, and mortality in hemodialysis patients. *Am J Kidney Dis* 32: 107–114, 1998
43. Stenvinkel P, Barany P, Heimburger O, Pecoits-Filho R, Lindholm B: Mortality, malnutrition, and atherosclerosis in ESRD: What is the role of interleukin-6? *Kidney Int* 61: 103–108, 2002
44. Kaysen GA, Dubin JA, Muller HG, Rosales LM, Levin NW: The acute-phase response varies with time and predicts serum albumin levels in hemodialysis patients: The HEMO Study Group. *Kidney Int* 58: 346–352, 2000
45. Weiner DE, Tighiouart H, Elsayed EF, Griffith JL, Salem DN, Levey AS, Sarnak MJ: The Framingham predictive instrument in chronic kidney disease. *J Am Coll Cardiol* 50: 217–224, 2007
46. Feldman HI, Appel LJ, Chertow GM, Cifelli D, Cizman B, Daugirdas J, Fink JC, Franklin-Becker ED, Go AS, Hamm LL, He J, Hostetter T, Hsu CY, Jamerson K, Joffe M, Kusek JW, Landis JR, Lash JP, Miller ER, Mohler ER III, Muntner P, Ojo AO, Rahman M, Townsend RR, Wright JT, and the Chronic Renal Insufficiency Cohort (CRIC) Study Investigators: The Chronic Renal Insufficiency Cohort (CRIC) Study: Design and methods. *J Am Soc Nephrol* 14: S148–S153, 2003
47. National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III): Third report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. *Circulation* 106: 3143–3421, 2002