Title

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Journal

Journal of the American Heart Association, 7(2)

ISSN

2047-9980

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Publication Date

2018-01-23

DOI

10.1161/jaha.117.007387

Peer reviewed

ORIGINAL RESEARCH

Relationship of High-Density Lipoprotein Cholesterol With Renal Function in Patients Treated With Atorvastatin

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***Background*—**It is not known whether the concentration of high-density lipoprotein (HDL) cholesterol is related to renal function in statin-treated patients. We therefore investigated whether HDL cholesterol levels predicted renal function in atorvastatin-treated patients in the TNT (Treating to New Targets) trial.

***Methods and Results*—**A total of 9542 participants were included in this analysis. Renal function was assessed by estimated glomerular filtration rate (eGFR). HDL cholesterol levels at month 3 were used as this is the time point at which on-treatment HDL cholesterol levels became stable. Among 6319 participants with a normal eGFR (≥60 mL/min per 1.73 m^2) at baseline, higher HDL cholesterol levels at month 3 were significantly associated with lower risk of decline in eGFR (ie, having eGFR <60 mL/min per 1.73 m^2) during follow-up (HR of 1.04, 0.88, 0.85, and 0.77 for HDL cholesterol quintiles 2, 3, 4, and 5, respectively, relative to quintile 1, *P* for trend=0.006). Among 3223 participants with an eGFR (<60 mL/min per 1.73 m^2) at baseline, higher HDL cholesterol levels at month 3 had less impact on eGFR during follow-up, with statistical significance observed only when analyzing HDL cholesterol levels as a continuous variable (*P*=0.043), but not as a categorical quintile variable (*P* for trend=0.27).

***Conclusions*—**In patients treated with atorvastatin, higher HDL cholesterol levels were associated with lower risk of eGFR decline in patients with normal eGFR at baseline. However, further study is needed to establish whether there is any causal relationship between HDLs and renal function.

***Clinical Trial Registration*—**URL: https://www.clinicaltrials.gov. Unique identifier: NCT00327691. **(*J Am Heart Assoc*. 2018;7: e007387. DOI: 10.1161/JAHA.117.007387.)**

Key Words: atorvastatin • epidemiology • estimated glomerular filtration rate • high-density lipoprotein cholesterol • kidney • renal function

Epidemiological studies have suggested that people with elevated plasma high-density lipoprotein (HDL) cholesterol levels are at decreased cardiovascular risk.[1] Patients with chronic kidney disease (CKD) often have abnormalities of plasma lipids and lipoproteins, including a reduced level of HDL cholesterol.[2] Previous longitudinal studies investigating the relationship of low levels of HDL cholesterol (or its main apolipoprotein, apoA-I) on kidney function have been inconsistent, with both positive[3–5] and negative findings reported.[6,7] It is not known whether a low HDL cholesterol level can predict either CKD or a decline in renal function in patients who are treated with a statin. Recent findings from the PLANET I (Prospective Evaluation of Proteinuria and Renal Function in Diabetic Patients With Progressive Renal Disease) and PLANET II (Prospective Evaluation of Proteinuria and Renal Function in Non-diabetic Patients With Progressive Renal Disease) studies have demonstrated that atorvastatin rendered better renoprotection as compared with rosuvastatin.[8] Moreover, these studies showed that patients randomized to atorvastatin had stabilization of eGFR during follow-up, while those randomized to rosuvastatin still had progression of eGFR decline. Post hoc analyses of other double-blind placebo-controlled randomized controlled trials indicate that treatment with atorvastatin is associated with eGFR improvement over time.[9–11] The mechanism explaining the discrepant effects within the same class of statins on eGFR trajectories is unclear. In this study, we investigated whether HDL cholesterol levels predict renal function in the Treating to New Targets (TNT)

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Received August 11, 2017; accepted December 11, 2017.

Clinical Perspective

What Is New?

- In patients treated with atorvastatin from the TNT (Treating to New Targets) trial, higher high-density lipoprotein (HDL) cholesterol levels were associated with lower risk of estimated glomerular filtration rate decline in patients with normal estimated glomerular filtration rate at baseline.
- However, higher HDL cholesterol levels were not robustly associated with an improvement in estimated glomerular filtration rate during follow-up.

What Are the Clinical Implications?

- This study provides evidence that higher HDL cholesterol levels may predict a lower risk of renal function decline in patients with normal renal function at baseline, even on treatment with a statin.
- In patients with renal impairment, increasing HDL cholesterol level may not improve renal function.

trial, a double-blind controlled trial in which patients with stable coronary disease were randomized to 2 doses of atorvastatin (either 10 or 80 mg daily).[12]

Methods

Study Population

The study design and results of the TNT trial have been published.[12] Briefly, 10 001 patients with stable coronary disease and a low-density lipoprotein (LDL) cholesterol level off-therapy of 3.4 to 6.5 mmol/L (130–250 mg/dL), decreasing to <3.4 mmol/L (130 mg/dL) after an 8-week run-in period on atorvastatin 10 mg/d, were randomized to 10 mg or 80 mg/d of atorvastatin. Mean LDL cholesterol during follow-up was 2.6 mmol/L (101 mg/dL) in the 10 mg/d group and 2.0 mmol/L (77 mg/dL) in the 80 mg/d group. All patients gave written informed consent. The study was approved by local research ethics committees or institutional review boards at each center, and was performed in accordance with the Helsinki Declaration. Pfizer's policies on the provision of clinical trial data are set out on their website (http://www.pfizer.com/research/clinical_trials/trial_data_and_results). In addition to posting clinical trial results on the clinicaltrials.gov registry, Pfizer will provide access to anonymized patient-level data in response to scientifically valid research protocols.

Renal Function

Renal function was assessed using the estimated glomerular filtration rate (eGFR), calculated using the creatinine-based Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.[13] Serum creatinine measurements using the modified alkaline picrate method of Jaffè[14,15] were taken at baseline and after 12, 24, 36, 48, 60, and 72 months of treatment by individuals. The assays were conducted at a central study laboratory that was blinded to treatment assignment. Details on creatinine measurements and quality control assurance have been described previously.[9] Baseline was defined as the time of randomization, when all patients had been taking atorvastatin 10 mg/d for at least 8 weeks.

Statistical Analysis

For this study, subjects were stratified into quintiles based on their HDL cholesterol levels determined at the 3-month time point of the double-blind treatment phase. HDL cholesterol levels at month 3 were used as this is the time point at which HDL cholesterol levels became stable after statin treatment.[12,16] Data were presented as mean±SD or percentage (n).

As data on serum creatinine were collected at baseline and after 12, 24, 36, 48, 60, and 72 months of treatment by individuals, eGFR was calculated for each individual at all available visits. The association of quintile of HDL cholesterol level at month 3 with time-to-first decline or improvement in eGFR was assessed by the Cox proportional hazard regression analysis, and hazard ratios were estimated with and without adjustment for important covariates. Participants with a normal eGFR (≥60 mL/min per 1.73 m^2) at baseline were defined to have a decline in eGFR if their eGFR levels were <60 mL/min per 1.73 m^2 during follow-up. Participants with an abnormal eGFR (<60 mL/min per 1.73 m^2) at baseline were defined to have improvement in eGFR if their eGFR levels increased to ≥60 mL/min per 1.73 m^2 during follow-up. In this analysis, for each participant who developed events (decline or improvement in eGFR), the time to event (number of days) was considered as the time interval between the date of the visit at which the earliest event was ascertained and the date of randomization. For participants who remained event-free, the follow-up time was censored at last visit or last day known to be alive, whichever was later. For subjects who died, the follow-up time was censored at their death date. The proportional hazards assumption was checked using Schoenfeld residuals and by adding an interaction between HDL cholesterol at month 3 and event time as a time-dependent covariate. No significant violation of proportional hazards assumption was found for both decline and improvement in eGFR. The covariates considered in the Cox regression analyses were prespecified variables that may affect HDL cholesterol, other lipids, and risk factors for CKD and CVD. These included treatment allocation, age, sex, smoking status, body mass index, systolic blood pressure, fasting glucose, LDL cholesterol, triglyceride levels, ratio of apoB to apoA-I,

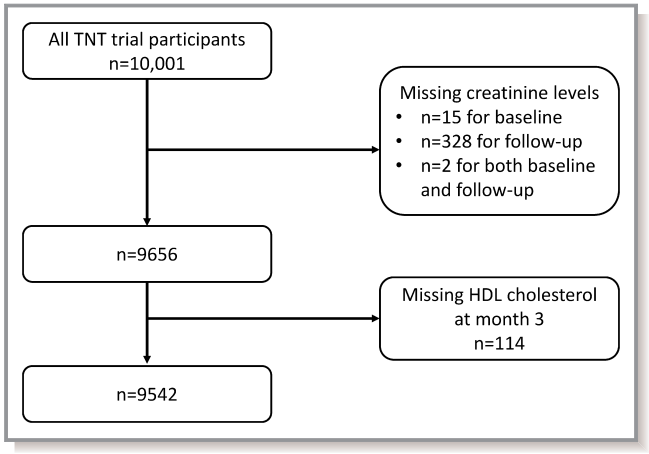

Figure. Flow diagram of study participants. HDL indicates high-density lipoprotein; TNT, Treating to New Targets.

and the presence or absence of a history of diabetes mellitus, myocardial infarction, cerebrovascular accident, and hypertension at baseline, as well as LDL cholesterol and triglycerides at month 3 of the trial.[16] In a separate analysis, HDL cholesterol levels at month 3 were analyzed as a continuous variable, rather than as a categorical quintile variable. A 2-sided $P<0.05$ was considered statistically significant.

Results

Figure shows the flow diagram of the study participants. Of the overall TNT population, 9656 participants (4829 on 10 mg/d atorvastatin and 4827 on 80 mg/d atorvastatin) had complete renal data (both baseline and postbaseline eGFR). After excluding 114 patients with missing data on HDL cholesterol levels at month 3, 9542 participants were included in this analysis. Table 1 shows the baseline characteristics of these 9542 participants included in this analysis and 459 participants excluded from the analysis. There was no significant difference in age, body mass index, blood pressure, atorvastatin treatment allocation and HDL cholesterol at baseline, as well as HDL cholesterol at month 3 between these 2 groups, although participants excluded from this study were less likely to be men with white race, and were more likely to have higher total cholesterol, LDL cholesterol, and triglyceride levels at baseline (Table 1). Table 2 shows the baseline characteristics of the patients according to HDL cholesterol level at month 3. Participants who had higher HDL cholesterol at month 3 were more likely to be female and not a current smoker, with lower body mass index, lower fasting glucose, lower plasma triglyceride levels, but higher age, higher systolic blood pressure, higher total cholesterol levels, and higher HDL cholesterol levels at baseline. They were also less likely to be in the high-dose atorvastatin group, and less likely to have a history of diabetes mellitus, myocardial infarction, coronary artery bypass graft, cerebrovascular accident, peripheral vascular disease, and congestive heart failure. The median follow-up duration was 4.9 (interquartile range: 4.6–5.2) years, which was the same for each quintile.

Table 1. Baseline Characteristics Between Participants Included and Not Included in This Study

Baseline Characteristics	Included in This Study	Excluded in This Study	*P* Value
n	9542	459	
Age, y	61.0±8.8	60.9 (9.3)	0.76
Male sex	7746 (81.2%)	353 (76.9%)	0.023
White race	8990 (94.2%)	420 (91.5%)	0.016
Body mass index, kg/m^2	28.5±4.5	28.5±5.1	0.96
Systolic blood pressure, mm Hg	130.7±16.7	131.1±17.3	0.64
Diastolic blood pressure, mm Hg	77.9±9.5	78.4±9.3	0.32
Treatment with atorvastatin 80 mg	4763 (49.9%)	232 (50.5%)	0.79
Baseline lipids, mg/dL			
Total cholesterol	174.6±23.7	177.7±26.6	0.0066
LDL cholesterol	97.4±17.5	99.4±19.6	0.017
HDL cholesterol	47.3±10.9	46.9±11.5	0.41
Triglycerides	150.2±70.5	158.8±78.2	0.012
HDL cholesterol at mo 3, mg/dL	47.3±11.2	47.0±11.8	0.75

Data are expressed as mean±SD or n (%). Comparison of baseline characteristics at randomization were performed using a χ^2 test for categorical variables, and ANOVA for continuous variables. HDL indicates high-density lipoprotein; LDL, low-density lipoprotein.

As shown in Table 3, the proportion of participants with normal eGFR (≥60 mL/min per 1.73 m^2) at baseline was lower in those with higher HDL cholesterol levels at month 3 (63.3% in those in the highest quintile of HDL cholesterol versus 68.0% in those in the lowest HDL cholesterol quintile, $P=0.002$). However, within each quintile of HDL cholesterol level at month 3, eGFR increased significantly, and to approximately the same extent in all HDL cholesterol quintiles, from baseline to the last visit (all $P<0.001$).

As shown in Table 4, among 6319 participants with a normal eGFR (≥60 mL/min per 1.73 m^2) at baseline, higher HDL cholesterol levels at month 3 were significantly associated with a lower risk of a decline in eGFR (ie, having eGFR <60 mL/min per 1.73 m^2) during follow-up after adjusting for age, sex, and treatment allocation. The association remained significant in the full adjustment model. Among 3223

Table 2. Baseline Characteristics of the Participants According to Quintile of HDL Cholesterol at Month 3

Baseline Characteristics	HDL Cholesterol at 3 Mo					*P* for Trend
	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5	
n	2033	1977	1828	1819	1885	…
HDL cholesterol range, mg/dL	19 to 38	39 to 43	44 to 48	49 to 55	56 to 116	…
Treatment with atorvastatin 80 mg	1043 (51.3%)	1030 (52.1%)	901 (49.3%)	874 (48.0%)	915 (48.5%)	0.008
Age, y	59.1±9.2	60.3±8.8	61.3±8.6	61.8±8.7	62.9±8.3	<0.001
Male sex	1866 (91.8%)	1744 (88.2%)	1504 (82.3%)	1427 (78.4%)	1205 (63.9%)	<0.001
White race	1909 (93.9%)	1857 (93.9%)	1723 (94.3%)	1720 (94.6%)	1781 (94.5%)	0.29
Body mass index, kg/m^2	29.8±4.7	29.0±4.7	28.6±4.3	28.0±4.2	27.2±4.3	<0.001
Smoking status						
Current	402 (19.8%)	293 (14.8%)	188 (10.3%)	200 (11.0%)	171 (9.1%)	<0.001
Former	1249 (61.4%)	1259 (63.7%)	1180 (64.6%)	1154 (63.4%)	1206 (64.0%)	
Never	382 (18.8%)	425 (21.5%)	460 (25.2%)	465 (25.6%)	508 (26.9%)	
Systolic blood pressure, mm Hg	129.5±17.3	129.9±16.0	131.1±16.7	130.7±16.7	132.4±16.8	<0.001
Diastolic blood pressure, mm Hg	77.8±9.6	77.9±9.5	78.2±9.2	77.6±9.4	78.2±9.5	0.51
Fasting glucose, mg/dL	113.4±35.2	109.7±31.8	106.6±28.2	105.2±28.1	102.8±26.8	<0.001
Lipids, mg/dL						
Total cholesterol	169.3±24.0	170.8±23.3	173.5±23.0	176.3±22.4	183.7±23.0	<0.001
LDL cholesterol	96.6±17.5	97.3±17.2	98.0±17.3	98.3±17.6	97.0±17.8	0.14
HDL cholesterol	36.3±4.6	42.0±4.6	46.1±4.9	51.2±5.9	62.3±10.2	<0.001
Triglycerides	184.3±84.7	158.2±67.8	148.1±66.3	134.8±55.6	122.0±54.8	<0.001
Cardiovascular history						
Myocardial infarction	1268 (62.4%)	1211 (61.3%)	1028 (56.2%)	1037 (57.0%)	1014 (53.8%)	<0.001
Coronary artery bypass graft	1018 (50.1%)	943 (47.7%)	865 (47.3%)	800 (44.0%)	811 (43.0%)	<0.001
Coronary angioplasty	1094 (53.8%)	1072 (54.2%)	997 (54.5%)	992 (54.5%)	1019 (54.1%)	0.82
Cerebrovascular accident	121 (6.0%)	105 (5.3%)	82 (4.5%)	96 (5.3%)	83 (4.4%)	0.044
Angina	1665 (81.9%)	1613 (81.6%)	1514 (82.8%)	1455 (80.0%)	1534 (81.4%)	0.36
Peripheral vascular disease	279 (13.7%)	241 (12.2%)	207 (11.3%)	191 (10.5%)	192 (10.2%)	<0.001
Hypertension	1132 (55.7%)	1072 (54.2%)	992 (54.3%)	959 (52.7%)	1005 (53.3%)	0.082
Arrhythmia	409 (20.1%)	336 (17.0%)	335 (18.3%)	317 (17.4%)	345 (18.3%)	0.23
Congestive heart failure	197 (9.7%)	162 (8.2%)	122 (6.7%)	117 (6.4%)	122 (6.5%)	<0.001
Diabetes mellitus	411 (20.2%)	338 (17.1%)	252 (13.8%)	229 (12.6%)	189 (10.0%)	<0.001

Data are expressed as mean±SD or n (%). Comparisons of baseline characteristics were based on linear regression for continuous variables and Cochran-Armitage trend test for categorical variables. HDL indicates high-density lipoprotein; LDL, low-density lipoprotein.

participants with lower eGFR (<60 mL/min per 1.73 m^2) at baseline, higher HDL cholesterol levels at month 3 were not robustly associated with an improvement in eGFR (ie, having eGFR ≥60 mL/min per 1.73 m^2) during follow-up in the full adjustment model, with statistical significance only when analyzing HDL cholesterol levels as a continuous variable, but not as a categorical variable. In a separate analysis, similar results were obtained when sex-specific cutoff points were used to define quintiles, instead of the categorical quintile variable (data not shown).

Discussion

This is the first report of the association of HDL cholesterol levels with change in renal function in patients treated with a statin in a large-scale double-blind clinical trial. In this analysis of atorvastatin-treated patients, we observed a significant association of higher HDL cholesterol levels with a lower risk of eGFR decline in patients in whom eGFR was normal at baseline. However, higher HDL cholesterol levels were not associated with improvement in eGFR in patients with lower baseline levels of eGFR.

Table 3. Baseline and Follow-Up Changes in eGFR by Quintile of HDL Cholesterol Level at Month 3

	HDL Cholesterol at Mo 3					
	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5	
	(19–38 mg/dL)	(39–43 mg/dL)	(44–48 mg/dL)	(49–55 mg/dL)	(56–116 mg/dL)	*P* for Trend
N	2033	1977	1828	1819	1885	
Baseline eGFR						
≥60 mL/min per 1.73 m^2	1383 (68.0%)	1330 (67.3%)	1208 (66.1%)	1205 (66.3%)	1193 (63.3%)	0.002
30 to 59 mL/min per 1.73 m^2	635 (31.2%)	642 (32.5%)	613 (33.5%)	606 (33.3%)	687 (36.4%)	
<30 mL/min per 1.73 m^2	15 (0.7%)	5 (0.3%)	7 (0.4%)	8 (0.4%)	5 (0.3%)	
Mean baseline eGFR, mL/min per 1.73 m^2	65.5±13.1	65.0±11.9	64.8±12.2	65.1±12.3	64.5±12.4	0.034
Mean change from baseline to last visit, mL/min per 1.73 m^2	3.0±10.3	3.8±9.7	3.6±9.8	3.1±9.1	2.9±9.7	0.26
P for change	<0.001	<0.001	<0.001	<0.001	<0.001	

All data are expressed as mean±SD, or n (%). eGFR indicates estimated glomerular filtration rate; HDL, high-density lipoprotein.

In population studies, high HDL cholesterol levels correlate inversely with the risk of having a cardiovascular event.[1] HDLs have several potentially cardioprotective properties, including participation in reverse cholesterol transport,[17] inhibition of vascular inflammation,[18] reduction of oxidative stress in macrophages,[19] prevention of oxidation of LDLs,[20] promotion of endothelial function and repair,[21,22] and promotion of angiogenesis.[23] As a decline in renal function is a recognized cardiovascular risk factor,[24] it is likely that a higher HDL cholesterol level may predict a lower risk of renal function decline in atorvastatin patients with normal eGFR. In fact, lipotoxicity has been suggested as one of the underlying mechanisms for the renal disease development.[25] Dyslipidemia could cause renal lipid accumulation at both the glomerular and tubular level, and hence alternations in glomerular filtration barrier and renal failure.[25]

Besides reduced HDL cholesterol levels, elevated triglycerides are often found in patients with CKD, and are associated with rapid loss of renal function.[25] Although HDL cholesterol levels often correlate inversely with triglycerides, the association of high HDL cholesterol levels with lower risk of eGFR decline in statin-treated patients with normal renal function observed in this study was likely to be independent of triglycerides, as the data were adjusted for triglycerides at baseline and month 3. Interestingly, a recent Mendelian randomization study has suggested a causal relationship of HDL cholesterol levels, but not LDL cholesterol and triglyceride levels, with renal function.[26] Moreover, in patients with CKD, genetic variants of apoL-1, a minor apolipoprotein of HDLs, is associated with CKD progression, which may explain the racial disparities in CKD progression risk.[27,28] Further studies are needed to establish the role of HDLs and their apolipoproteins, including apoL-1 in CKD progression.

Previous longitudinal studies investigating the relationship of HDL cholesterol or apoA-I levels on kidney function have not been well established. In a study of 12 728 participants from the ARIC (Atherosclerosis Risk in Communities) study with a follow-up period of 2.9 years, lower levels of HDL cholesterol and HDL_2 cholesterol predicted a higher risk of renal dysfunction, which was defined as a rise in creatinine levels.[3] In another study of 4483 healthy men from the Physicians' Health Study, lower baseline HDL cholesterol levels also predicted a higher risk of elevated creatinine levels after 14 years.[4] In a community-based cohort of 2585 men and women, long-term, 12-year averaged HDL cholesterol was found to be a predictor of developing kidney disease after 18.5 years of follow-up.[5] However, in a previous study of 73 nondiabetic patients with primary chronic renal disease, HDL cholesterol levels were not related to the rate of renal progression over 3 years.[6] In a more recent prospective study of 3939 patients with CKD from the CRIC (Chronic Renal Insufficiency Cohort) study, all serum lipids, including HDL cholesterol, were not related to the progression of kidney disease over a median follow-up period of 4.1 years.[7] From these studies, lower HDL cholesterol levels were more likely to be predictive of renal function decline in healthy people than in those with existing renal function impairment. This trend was consistent with our study of statin-treated patients. However, improvement in renal function was not assessed in these previous studies. In this study, the association of HDL cholesterol at month 3 with decline or improvement in eGFR was not significant in the unadjusted model, but a significant association was revealed after adjusting the data for age, sex, and treatment allocation. This suggests important confounding effects of age and sex, which may also contribute to the inconsistent findings on the relationship of HDL cholesterol and renal function in the literature.

Table 4. Univariate and Multivariate Analyses of the Association of HDL Cholesterol at Month 3 With Decline and Improvement in eGFR

Outcomes	N	Outcome (%)	Unadjusted model		Model 1		Model 2	
			HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Decline in eGFR among participants with normal baseline eGFR (≥60 mL/min per 1.73 m^2)								
HDL cholesterol								
Per 10-mg/dL increase	6319	23.1	1.05 (1.00–1.09)	0.056	0.89 (0.85–0.93)	<0.001	0.93 (0.87–1.00)	0.047
Quintile								
1	1383	21.5	1.00 (referent)	…	1.00 (referent)	…	1.00 (referent)	…
2	1330	24.0	1.14 (0.98–1.34)	0.094	1.00 (0.85–1.17)	0.95	1.04 (0.88–1.23)	0.67
3	1208	23.0	1.09 (0.92–1.28)	0.33	0.82 (0.69–0.97)	0.018	0.88 (0.73–1.06)	0.19
4	1205	23.4	1.11 (0.94–1.30)	0.23	0.78 (0.66–0.92)	0.004	0.85 (0.69–1.04)	0.12
5	1193	23.9	1.11 (0.95–1.31)	0.19	0.68 (0.57–0.80)	<0.001	0.77 (0.61–0.97)	0.028
P for trend				0.32		<0.001		0.006
Improvement in eGFR among participants with abnormal baseline eGFR (<60 mL/min per 1.73 m^2)								
HDL cholesterol								
Per 10 mg/dL increase	3223	52.9	1.00 (0.96–1.04)	0.94	1.10 (1.05–1.14)	<0.001	1.07 (1.00–1.14)	0.043
Quintile								
1	650	51.5	1.00 (referent)	…	1.00 (referent)	…	1.00 (referent)	…
2	647	56.6	1.14 (0.98–1.32)	0.082	1.18 (1.02–1.37)	0.029	1.10 (0.94–1.29)	0.23
3	620	50.0	0.95 (0.81–1.11)	0.52	1.09 (0.94–1.28)	0.27	1.00 (0.84–1.20)	0.97
4	614	52.8	1.02 (0.88–1.19)	0.76	1.21 (1.04–1.42)	0.014	1.10 (0.91–1.33)	0.32
5	692	53.5	1.03 (0.88–1.19)	0.73	1.37 (1.17–1.59)	<0.001	1.16 (0.93–1.44)	0.18
P for trend				0.73		<0.001		0.27

Model 1: Data were adjusted for age, sex, and treatment allocation at baseline. Model 2: Data were further adjusted for smoking status, body mass index, systolic blood pressure, fasting glucose, low-density lipoprotein cholesterol, triglyceride levels, ratio of apolipoprotein B to apolipoprotein A-I, and the presence or absence of a history of diabetes mellitus, myocardial infarction, cerebrovascular accident, and hypertension at baseline, as well as low-density lipoprotein cholesterol and triglycerides at month 3 of the trial. CI indicates confidence interval; eGFR, glomerular filtration rate; HDL, high-density lipoprotein; HR, hazard ratio.

It is not clear why the inverse relationship between HDL cholesterol levels and renal function was not observed in the atorvastatin-treated patients with reduced baseline levels of eGFR. It is possible that the smaller sample size of patients with reduced eGFR provided insufficient statistical power. However, it is also possible that the cardioprotective functions of HDLs are impaired in patients with reduced eGFR, with HDL cholesterol levels no longer reflecting HDL function. Although the underlying mechanism is unknown, it has been reported that HDL particles from patients with CKD have impaired antioxidative and anti-inflammatory properties, possibly secondary to a reduced activity of HDL-associated enzymes, such as paraoxonase[29,30] and also to glycation of apoA-I.[31] Further studies using HDL functional assays may help to elucidate this hypothesis.

It should be noted that the post hoc analysis reported here has some limitations. The participants included in this analysis showed significant difference in some baseline characteristics, such as sex, white race, total cholesterol, LDL cholesterol, and triglyceride levels compared with participants excluded from the analysis. Therefore, we could not exclude the possibility of selection bias. However, such selection bias should be small as we included 9542 (95.4%) out of the total 10 001 participants from the TNT trial and data were adjusted for these baseline characteristics. Moreover, there was no significant difference in HDL cholesterol levels at baseline and month 3. Another limitation is that we assessed renal function using eGFR only, with no data available on the presence or absence of albuminuria. Furthermore, since the cause of renal function impairment in the TNT population was unknown, any generalizations should be made with caution. Nevertheless, despite a reduced HDL cholesterol level being a frequent finding in patients with CKD, this analysis does not suggest any causal relationship between HDLs and renal function.

In conclusion, higher HDL cholesterol levels were associated with lower risk of eGFR decline in patients with normal eGFR and treated with atorvastatin. However, in patients with lower levels of eGFR, higher levels of HDL cholesterol were not associated with an improvement in eGFR. Further study is needed to confirm these findings.

Sources of Funding

The TNT trial was sponsored by Pfizer. Dr Ong was supported by the Australian National Health and Medical Research Council NHMRC Career Development Fellowship (1122854).

Disclosures

Dr Ong has consulted for Pfizer. Waters has consulted for Pfizer, and has received remuneration for participating in clinical trial committees from Cerenis, CSL, DalCor, the Medicines Company, Merck Schering-Plough, Pfizer, Regeneron, Resverlogix, and Sanofi-Aventis. Dr Vogt has consulted for Pfizer. Barter has been a member of advisory boards for Amgen, Merck, Pfizer, and Sanofi-Aventis; received honoraria from Amgen, Lilly, Merck, Pfizer, and Sanofi-Regeneron; and participated in clinical trials sponsored by AstraZeneca, Lilly, Merck, Pfizer, and Roche. Drs Fayyad, Melamed, and DeMicco are Pfizer employees. The remaining authors have no disclosures to report.

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