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Intensive Lipid Lowering With Atorvastatin in Patients With Coronary Heart Disease and Chronic Kidney Disease

The TNT (Treating to New Targets) Study

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Objectives This subanalysis of the TNT (Treating to New Targets) study investigates the effects of intensive lipid lowering with atorvastatin in patients with coronary heart disease (CHD) with and without pre-existing chronic kidney disease (CKD).

Background Cardiovascular disease is a major cause of morbidity and mortality in patients with CKD.

Methods A total of 10,001 patients with CHD were randomized to double-blind therapy with atorvastatin 80 mg/day or 10 mg/day. Patients with CKD were identified at baseline on the basis of an estimated glomerular filtration rate (eGFR) <60 ml/min/1.73 m^2 using the Modification of Diet in Renal Disease equation. The primary efficacy outcome was time to first major cardiovascular event.

Results Of 9,656 patients with complete renal data, 3,107 had CKD at baseline and demonstrated greater cardiovascular comorbidity than those with normal eGFR (n = 6,549). After a median follow-up of 5.0 years, 351 patients with CKD (11.3%) experienced a major cardiovascular event, compared with 561 patients with normal eGFR (8.6%) (hazard ratio [HR] = 1.35; 95% confidence interval [CI] 1.18 to 1.54; p < 0.0001). Compared with atorvastatin 10 mg, atorvastatin 80 mg reduced the relative risk of major cardiovascular events by 32% in patients with CKD (HR = 0.68; 95% CI 0.55 to 0.84; p = 0.0003) and 15% in patients with normal eGFR (HR = 0.85; 95% CI 0.72 to 1.00; p = 0.049). Both doses of atorvastatin were well tolerated in patients with CKD.

Conclusions Aggressive lipid lowering with atorvastatin 80 mg was both safe and effective in reducing the excess of cardiovascular events in a high-risk population with CKD and CHD. (Treating to New Targets Study; NCT00327691) (J Am Coll Cardiol 2008;51:1448–54) © 2008 by the American College of Cardiology Foundation

Increased cardiovascular mortality and morbidity risk in patients with advanced chronic kidney disease (CKD) is well established (1,2), and even mild to moderate CKD is associated with an increased incidence of cardiovascular events (3,4).

Results of cardiovascular outcomes trials in patients with advanced or end-stage kidney disease and safety concerns related to potential toxic effects of high-dose statins in patients with reduced renal clearance may have

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limited the use of statins in the CKD population (5). Despite under-representation of patients with mild to moderate CKD in major statin trials (6), data suggest (7,8) that lower doses of statins in CKD patients are effective in preventing cardiovascular events. However, it remains unclear whether CKD patients benefit from aggressive lipid lowering with statins in the same manner as patients with normal renal function.

Unlike some previous long-term statin trials, the TNT (Treating to New Targets) study (9) did not exclude patients on the basis of serum creatinine levels. The current post-hoc analysis of the TNT study was undertaken to identify and clinically characterize a patient cohort presenting with coronary heart disease (CHD) and mild to moderate CKD and to investigate the effect of intensive lipid lowering with atorvastatin 80 mg on the risk of future cardiovascular events.

Abbreviations and Acronyms

CHD = coronary heart disease
CI = confidence interval
CKD = chronic kidney disease
eGFR = estimated glomerular filtration rate
HR = hazard ratio
LDL-C = low-density lipoprotein cholesterol
MDRD = Modification of Diet in Renal Disease

Methods

The design of the TNT study has been described in detail previously (9).

Patient population. Eligible patients were men and women ages 35 to 75 years with clinically evident CHD, defined as previous myocardial infarction, previous or current angina with objective evidence of atherosclerotic CHD, or a history of coronary revascularization. Exclusion criteria have been described previously (9).

Study design. Any previously prescribed lipid-regulating drugs were discontinued at screening, and all patients required a washout period of 1 to 8 weeks. Patients with low-density lipoprotein cholesterol (LDL-C) levels between 130 and 250 mg/dl and triglyceride levels ≤600 mg/dl entered an 8-week run-in period of open-label treatment with atorvastatin 10 mg/day. At the end of the run-in phase (baseline), patients with a mean LDL-C <130 mg/dl (determined 4 weeks and 2 weeks before randomization) were randomized to double-blind therapy with either 80 mg/day or 10 mg/day of atorvastatin for up to 6 years (Fig. 1).

Efficacy and safety outcomes. The primary efficacy outcome was the occurrence of a major cardiovascular event, defined as death from CHD, nonfatal nonprocedure-related myocardial infarction, resuscitation after cardiac arrest, or fatal or nonfatal stroke.

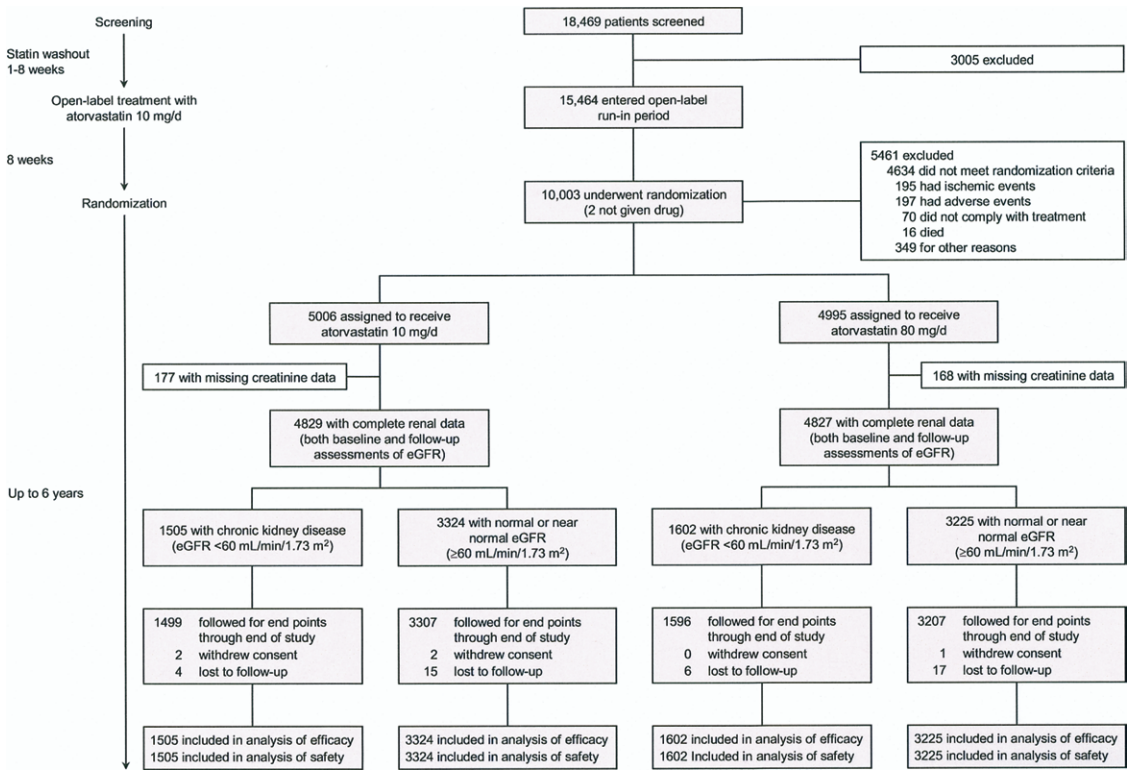

Figure 1 Screening, Enrollment, and Outcomes in Patients With Chronic Kidney Disease and Patients With Normal eGFR

eGFR = estimated glomerular filtration rate.

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As recommended by the American Heart Association and National Kidney Foundation (10,11), renal function was assessed using the Modification of Diet in Renal Disease (MDRD) equation (12), a serum creatinine-based estimate of glomerular filtration rate (eGFR), as described previously (13). Patients with eGFR <60 ml/min/1.73 m^2 at baseline were classified as having CKD; patients with eGFR ≥60 ml/min/1.73 m^2 were classified as having normal or near-normal renal function.

Statistical analyses. The primary analysis of efficacy in the TNT study was the difference between the atorvastatin 80 and 10 mg treatment groups for time to first occurrence of a major cardiovascular event during the 5-year follow-up period, based on log-rank analyses. Hazard ratios (HRs) and their 95% confidence intervals (CIs) were also calculated using the Cox regression model. Relative risk reductions based on the HRs were reported, as well as absolute risk reductions based on event incidence. Two-sided p values <0.05 were regarded as significant. All analyses were performed on an intention-to-treat basis.

Results

Of a total of 10,001 patients randomized, 9,656 (4,827 receiving atorvastatin 80 mg and 4,829 receiving atorvastatin 10 mg) had complete renal data and were included in the current analysis (Fig. 1). At baseline, 3,107 patients had CKD, of whom 3,078 had stage 3 CKD (eGFR 30 to 59 ml/min/1.73 m^2) and 29 had stage 4 CKD (eGFR 15 to 29 ml/min/1.73 m^2). Patients with CKD were older, and there were more women and fewer smokers than among patients with normal eGFR (Table 1). Pre-existing cardiovascular morbidity at baseline was generally greater in patients with CKD than in patients with normal eGFR (Table 1). Despite characteristic differences at baseline between patients with CKD and patients with normal eGFR, there was no imbalance by randomized treatment assignment (Table 1). Median follow-up was 5.0 years after randomization in both eGFR groups.

Serum lipid levels. Baseline lipid levels (following 8 weeks' open-label atorvastatin 10 mg) were generally well matched between patients with CKD and patients with normal

Table 1 Baseline Demographics and Clinical Characteristics of Patients With CKD and Patients With Normal eGFR by Treatment

Baseline Characteristic (at Randomization)	Patients With CKD			Patients With Normal eGFR		
	Atorvastatin 10 mg (n = 1,505)	Atorvastatin 80 mg (n = 1,602)	All (n = 3,107)	Atorvastatin 10 mg (n = 3,324)	Atorvastatin 80 mg (n = 3,225)	All (n = 6,549)
Men	992 (65.9)	1,110 (69.3)	2,102 (67.7)	2,917 (87.8)	2,816 (87.3)	5,733 (87.5)
Age, yrs	65.6 ± 6.9	65.5 ± 7.1	65.5 ± 7.0	58.7 ± 8.8	59.1 ± 8.7	58.9 ± 8.8
≥65	880 (58.5)	956 (59.7)	1,836 (59.1)	923 (27.8)	926 (28.7)	1,849 (28.2)
Race						
White	1,439 (95.6)	1,519 (94.8)	2,958 (95.2)	3,108 (93.5)	3,028 (93.9)	6,136 (93.7)
Black	26 (1.7)	25 (1.6)	51 (1.6)	118 (3.5)	101 (3.1)	219 (3.3)
Other	40 (2.7)	58 (3.6)	98 (3.2)	98 (2.9)	96 (3.0)	194 (3.0)
Body mass index, kg/m^2	28.7 ± 4.7	28.3 ± 4.4	28.5 ± 4.5	28.6 ± 4.6	28.4 ± 4.5	28.5 ± 4.5
Current smoker	130 (8.6)	150 (9.4)	280 (9.0)	510 (15.3)	478 (14.8)	988 (15.1)
eGFR, ml/min/1.73 m^2	52.8 ± 6.6	53.0 ± 6.4	52.9 ± 6.5	71.4 ± 7.9	71.0 ± 7.8	71.2 ± 7.8
Lipids, mg/dl						
LDL cholesterol	96.5 ± 17.5	96.3 ± 17.5	96.4 ± 17.5	98.1 ± 17.5	97.7 ± 17.4	97.9 ± 17.5
Total cholesterol	175.9 ± 24.4	175.9 ± 24.4	175.9 ± 24.4	174.0 ± 23.5	174.0 ± 23.3	174.0 ± 23.4
Triglycerides	159.8 ± 71.9	159.2 ± 72.4	159.5 ± 72.2	145.5 ± 70.3	145.8 ± 67.7	145.7 ± 69.0
HDL cholesterol	47.6 ± 11.2	48.0 ± 11.5	47.8 ± 11.4	47.0 ± 10.6	47.3 ± 10.9	47.1 ± 10.7
Blood pressure, mm Hg						
Systolic	133.3 ± 17.7	132.8 ± 17.8	133.0 ± 17.7	129.7 ± 16.3	129.5 ± 15.9	129.6 ± 16.1
Diastolic	77.5 ± 9.8	77.4 ± 9.8	77.5 ± 9.8	78.4 ± 9.3	78.0 ± 9.2	78.2 ± 9.3
Cardiovascular history						
Angina	1,234 (82.0)	1,305 (81.5)	2,539 (81.7)	2,684 (80.7)	2,655 (82.3)	5,339 (81.5)
Myocardial infarction	836 (55.5)	949 (59.2)	1,785 (57.5)	1,954 (58.8)	1,882 (58.4)	3,836 (58.6)
Hypertension	944 (62.7)	1,005 (62.7)	1,949 (62.7)	1,678 (50.5)	1,594 (49.4)	3,272 (50.0)
Metabolic syndrome	925 (61.5)	973 (60.7)	1,898 (61.1)	1,788 (53.8)	1,697 (52.6)	3,485 (53.2)
Coronary artery bypass graft	824 (54.8)	844 (52.7)	1,668 (53.7)	1,428 (43.0)	1,388 (43.0)	2,816 (43.0)
Coronary angioplasty	759 (50.4)	807 (50.4)	1,566 (50.4)	1,875 (56.4)	1,791 (55.5)	3,666 (56.0)
Arrhythmia	306 (20.3)	350 (21.8)	656 (21.1)	587 (17.7)	525 (16.3)	1,112 (17.0)
Diabetes	273 (18.1)	273 (17.0)	546 (17.6)	441 (13.3)	444 (13.8)	885 (13.5)
Peripheral artery disease	239 (15.9)	268 (16.7)	507 (16.3)	303 (9.1)	316 (9.8)	619 (9.5)
Congestive heart failure	198 (13.2)	180 (11.2)	378 (12.2)	183 (5.5)	174 (5.4)	357 (5.5)
Cerebrovascular accident	123 (8.2)	103 (6.4)	226 (7.3)	128 (3.9)	138 (4.3)	266 (4.1)

Values are number of patients (%) or mean ± SD.
CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; HDL = high-density lipoprotein; LDL = low-density lipoprotein.

eGFR (Table 1). Patients with CKD had a higher triglyceride level at baseline than patients with normal eGFR (159.5 mg/dl vs. 145.7 mg/dl); however, atorvastatin 80 mg lowered triglycerides to a similar level in patients with CKD (139.0 mg/dl) and patients with normal eGFR (134.2 mg/dl) compared with atorvastatin 10 mg (167.6 and 154.9 mg/dl, respectively). Mean LDL-C levels attained at the final visit with atorvastatin 80 mg versus atorvastatin 10 mg were similar for patients with CKD (79.0 mg/dl vs. 99.0 mg/dl) and with normal eGFR (80.0 mg/dl vs. 102 mg/dl). High-density lipoprotein cholesterol levels remained stable during the study, with no differences between treatment groups.

Blood pressure. Systolic blood pressure at baseline was slightly higher in patients with CKD than in patients with normal eGFR (Table 1). There was little change in systolic and diastolic blood pressure over the course of the study, with no significant differences observed between randomized treatment groups. There was a greater use of inhibitors of the renin-angiotensin system during the trial in patients with CKD (64.8% of patients receiving atorvastatin 80 mg and 66.0% of patients receiving atorvastatin 10 mg) than in patients with normal eGFR (56.5% and 59.4%, respectively).

Cardiovascular outcomes. After a median follow-up of 5.0 years, irrespective of treatment assignment, 351 patients with CKD (11.3%) experienced a first major cardiovascular event compared to 561 patients with normal eGFR at baseline (8.6%). Thus, patients with CKD were at a significantly greater risk than patients with normal renal function (HR 1.35; 95% CI 1.18 to 1.54; $p < 0.0001$). In patients with CKD at baseline, a first major cardiovascular event was experienced by 149 patients (9.3%) receiving atorvastatin 80 mg and 202 patients (13.4%) receiving atorvastatin 10 mg, a 32% relative reduction in risk with intensive lipid lowering (HR 0.68; 95% CI 0.55 to 0.84; $p = 0.0003$) (Fig. 2). The absolute risk reduction in patients with CKD was substantial (4.1%), yielding a number needed to treat of 24 to prevent 1 major cardiovascular event over 5 years. In patients with normal eGFR at baseline, a smaller but significant 15% relative reduction in risk of major cardiovascular events was observed with atorvastatin 80 mg (7.9%) versus atorvastatin 10 mg (9.2%) (HR 0.85; 95% CI 0.72 to 1.00; $p = 0.049$; number needed to treat = 74) (Fig. 2).

For all predefined secondary end points, event rates were higher in CKD patients than in patients with normal eGFR. In patients with CKD, treatment with atorvastatin 80 mg resulted in significant reductions in the risk of the secondary outcomes any cardiovascular event (HR 0.76; 95% CI 0.67 to 0.86), major coronary event (HR 0.65; 95% CI 0.51 to 0.83), any coronary event (HR 0.75; 95% CI 0.65 to 0.86), cerebrovascular event (HR 0.66; 95% CI 0.49 to 0.89), and congestive heart failure with hospitalization (HR 0.54; 95% CI 0.38 to 0.77) compared with atorvastatin 10 mg (Fig. 3). We observed a significantly greater treatment effect in patients with CKD than in patients with normal eGFR for major coronary events and hospitalization for congestive heart failure. Otherwise, there was no significant heterogeneity of treatment effect between patients with CKD and patients with normal eGFR for primary or secondary outcomes.

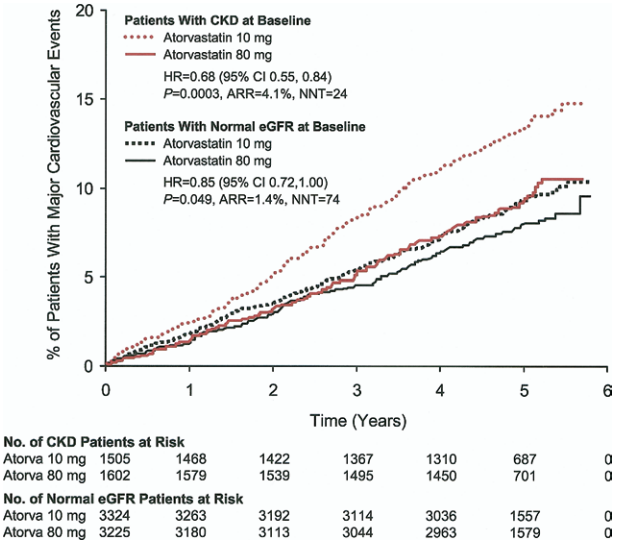

Figure 2 Time to First Major CV Event by Treatment in Patients With CKD and With Normal eGFR at Baseline

In patients with chronic kidney disease (CKD) at baseline, intensive lipid lowering with atorvastatin 80 mg resulted in a 32% relative reduction in risk of major cardiovascular (CV) events compared with atorvastatin 10 mg ($p = 0.0003$). In patients with normal or near-normal estimated glomerular filtration rate (eGFR) at baseline, a smaller but significant 15% relative reduction in risk of major CV events was observed with atorvastatin 80 mg ($p = 0.049$). ARR = absolute risk reduction; CI = confidence interval; HR = hazard ratio; NNT = number needed to treat.

Safety. Safety of atorvastatin 80 mg in patients with CKD was similar to that reported for the overall TNT population (9), with no unexpected safety concerns identified. Rates of treatment-related adverse events and discontinuations due to treatment-related adverse events were similar between patients with CKD and patients with normal eGFR for each treatment group (Table 2). Incidences of hematuria and albuminuria were similar between patients with CKD and patients with normal eGFR for each treatment group (Table 2). There were no reports of serious adverse events associated with these urinary abnormalities in either treatment group.

Discussion

This post-hoc analysis of the TNT study extends the cardiovascular benefit of aggressively lowering LDL-C to a high-risk patient population with mild to moderate CKD and stable CHD. The absolute and relative reductions in cardiovascular events with an aggressive atorvastatin treatment strategy appear to be greater in CHD patients with mild to moderate CKD than in those with normal or near-normal renal function.

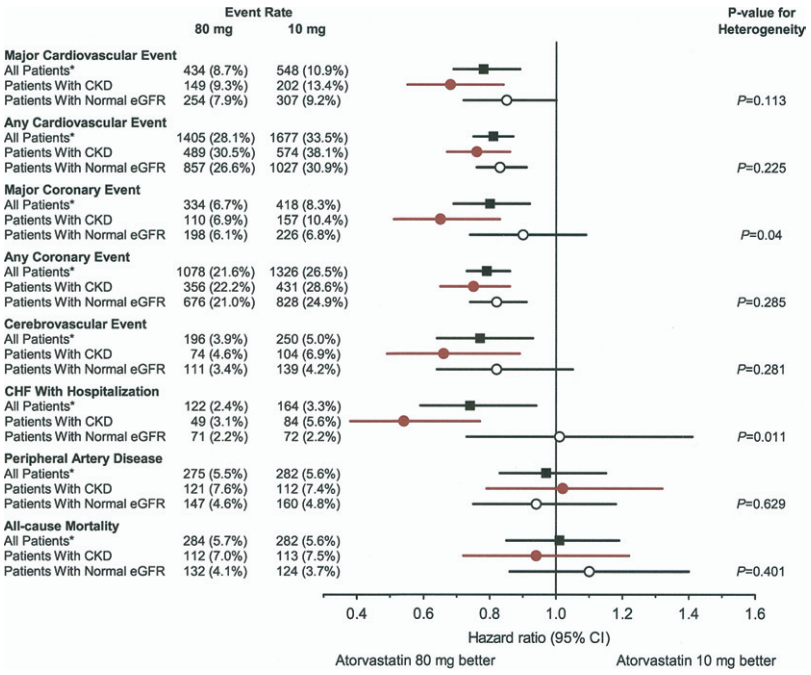

Figure 3 **Primary and Secondary Event Rates in Patients With CKD and Patients With Normal eGFR**

For all predefined secondary end points, event rates were higher in CKD patients than in patients with normal eGFR. In patients with CKD, treatment with atorvastatin 80 mg resulted in significant reductions, compared with atorvastatin 10 mg, in the risk of the following secondary outcomes: any cardiovascular event, major coronary event, any coronary event, cerebrovascular event, and congestive heart failure with hospitalization. *All patients randomized in the TNT study (includes 345 patients without complete renal data). TNT = Treating to New Targets study; other abbreviations as in Figure 2.

Renal insufficiency and cardiovascular disease. The results of the TNT study are consistent with other observations that renal function is an important independent predictor of cardiovascular disease (1–4). At entry to the double-blind phase of the study, CKD patients had a greater prevalence of cardiovascular risk factors, existing cardiovascular disease, and target organ damage. In addition, over the 5 years of follow-up, patients with CKD had a significantly greater risk of a major cardiovascular event than patients with normal or near-normal renal function.

Atorvastatin 80 mg significantly reduced the incidence of major cardiovascular events compared to atorvastatin 10 mg in patients with CKD and patients with normal or near-normal renal function at baseline. The 32% relative risk reduction in patients with CKD was quantitatively larger than the 15% relative risk reduction in patients with normal eGFR and may be related to the higher cardiovascular risk and disease burden in patients with CKD. A significant dose-dependent improvement in renal function for atorvastatin 80 mg versus atorvastatin 10 mg has been reported in this patient cohort (13) and may have contributed to the relatively high beneficial effect on cardiovascular outcomes in the patients with CKD. The increased risk associated with CKD was greatly reduced but not completely eliminated in CKD patients treated with 80 mg of atorvastatin, whose cardiovascular risk fell to a level near that in patients with normal eGFR who received lower-dose atorvastatin. This relative risk reduction with aggressive statin therapy in TNT was substantially greater than that observed previously with a less intensive statin regimen (8).

Almost one-third of TNT participants had stage 3 CKD (based on eGFR 30 to 59 ml/min/1.73 m^2), similar to the CKD rate estimate in patients with cardiovascular disease from NHANES 1999 to 2004 (14). The underuse of statins in patients with CKD may, in part, be attributable to the failure to recognize the heightened cardiovascular risk associated with the early stages of CKD. Thus, the routine use of the MDRD equation appears to be a useful screening tool for patients with CHD to identify a very high-risk subset with CKD who can benefit from intensive lipid lowering.

Patients with mild to moderate CKD and CHD may differ from those with more advanced renal failure or end-stage renal disease. Data from the German Diabetes and Dialysis Study showed limited benefit with moderate-dose atorvastatin in a group of diabetic patients with long-standing end-stage renal disease (15). Our observations in this study of diabetic and nondiabetic patients with CHD provide support for the current suggested evaluation and screening strategies, as well as treatment guidelines recommended by the American Heart Association and the National Kidney Foundation (11).

Table 2 Selected Safety Outcomes in Patients With CKD and Patients With Normal eGFR by Treatment

	Patients With CKD		Patients With Normal eGFR	
	Atorvastatin 10 mg (n = 1,505)	Atorvastatin 80 mg (n = 1,602)	Atorvastatin 10 mg (n = 3,324)	Atorvastatin 80 mg (n = 3,225)
Treatment-related adverse events	78 (5.2)	140 (8.7)	191 (5.7)	241 (7.5)
Discontinuations attributable to treatment-related adverse events	29 (1.9)	68 (4.2)	82 (2.5)	121 (3.8)
Hematuria	51 (3.4)	58 (3.6)	124 (3.7)	121 (3.8)
Albuminuria	25 (1.7)	28 (1.7)	47 (1.4)	53 (1.6)
Persistent elevations in alanine aminotransferase and/or aspartate aminotransferase*	1 (0.1)	22 (1.4)	8 (0.2)	38 (1.2)
Persistent elevations in creatine phosphokinase†	0	0	0	0

*Two measurements ≥3 times the upper limit of normal, obtained 4 to 10 days apart; †2 measurements ≥10 times the upper limit of normal, obtained 4 to 10 days apart. Abbreviations as in Table 1.

Lipid-lowering recommendations. Recent recommendations of the National Lipid Association Statin Safety Assessment Task Force (16) indicate that CKD should not preclude use of a statin. Underuse of statins in patients with CKD may relate to concerns over potential toxicity in patients with reduced renal clearance. Atorvastatin, in contrast to many other statins, does not require dosage modification at any level of renal function (17). The significant cardiovascular benefits of atorvastatin 80 mg/day in patients with CHD and CKD were achieved without additional safety concerns or increased risk, consistent with other data that have shown high-dose atorvastatin to be safe and well tolerated (18). Specifically, there was no increase in serious renal adverse events or events with potential for renal complications.

Study limitations. Our study has several limitations, including the absence of an untreated control group. All patients received either 80 mg or 10 mg of atorvastatin during the double-blind phase of the study to comply with existing CHD guidelines. In addition, despite being evaluated for accuracy in clinical studies, the MDRD estimate of glomerular filtration rate used in the current analysis remains an estimate, and categorization of patients as having CKD or a normal glomerular filtration rate is subject to the limitations of the formula. Classification of CKD based on a single creatinine measurement is not ideal, but in this large study was unlikely to lead to any systematic bias. Generalizations of TNT data to other CKD populations without CHD should be made with caution because the cause(s) of CKD in the TNT population are unknown. Conclusions regarding patients with more advanced renal dysfunction are limited, given the small proportion of advanced CKD patients in this analysis.

Conclusions

Data from this TNT subanalysis demonstrate that mild to moderate CKD is an important comorbidity that increases cardiovascular risk in patients with CHD. Our observations support the current guidelines (19) that advocate the use of high-dose statin therapy to achieve lower target LDL-C levels for optimal prevention of cardiovascular events in high-risk patient groups.

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