Effect of Intensive Lipid Lowering with Atorvastatin on Renal Function in Patients with Coronary Heart Disease: The Treating to New Targets (TNT) Study


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Background and objectives: Data suggest that atorvastatin may be nephroprotective. This subanalysis of the Treating to New Targets study investigated how intensive lipid lowering with 80 mg of atorvastatin affects renal function when compared with 10 mg in patients with coronary heart disease.

Design, setting, participants, & measurements: A total of 10,001 patients with coronary heart disease and LDL cholesterol levels of <130 mg/dl were randomly assigned to double-blind therapy with 10 or 80 mg/d atorvastatin. Estimated GFR using the Modification of Diet in Renal Disease equation was compared at baseline and at the end of follow-up in 9656 participants with complete renal data.

Results: Mean estimated GFR at baseline was 65.6 ± 11.4 ml/min per 1.73 m² in the 10-mg group and 65.0 ± 11.2 ml/min per 1.73 m² in the 80-mg group. At the end of follow-up (median time to final creatinine measurement 59.5 months), mean change in estimated GFR showed an increase of 3.5 ± 0.14 ml/min per 1.73 m² with 10 mg and 5.2 ± 0.14 ml/min per 1.73 m² with 80 mg (P < 0.0001 for treatment difference). In the 80-mg arm, estimated GFR improved to ≥60 ml/min per 1.73 m² in significantly more patients and declined to <60 ml/min per 1.73 m² in significantly fewer patients than in the 10-mg arm.

Conclusions: The expected 5-yr decline in renal function was not observed. Estimated GFR improved in both treatment groups but was significantly greater with 80 mg than with 10 mg, suggesting this benefit may be dosage related.


A pproximately 20 million people in the United States have kidney disease, 8 million of whom have chronic kidney disease (CKD) of at least stage 3 (defined as a GFR of <60 ml/min per 1.73 m²) (1–3). Furthermore, almost half a million have ESRD, accounting for annual direct medical costs of almost $20 billion (1). The increased risk for cardiovascular mortality and morbidity in patients with advanced CKD is well established (3–6), and data have shown (6–8) that renal function is an important independent predictor of cardiovascular disease even in patients with mild renal insufficiency.

Post hoc analyses of randomized, controlled trials have suggested that statins may have a protective effect on renal function (9). In 15,696 patients with coronary disease, other occlusive arterial disease, or diabetes in the Heart Protection Study, allocation to 40 mg/d simvastatin was associated with a smaller fall in the estimated GFR (eGFR) compared with placebo after an average follow-up of 4.6 yr. This difference was small (0.8 ml/min) but significant (10). In patients with hyperlipidemia and previous myocardial infarction in the Cholesterol And Recurrent Events trial, 40 mg of pravastatin significantly reduced the rate of eGFR decline in individuals with more severe chronic renal insufficiency (eGFR of <40 or <50 ml/min per 1.73 m²) compared with placebo; however, these findings did not extend overall to patients with eGFR of <60 or ≥60 ml/min per 1.73 m² (11). Data suggest that atorvastatin may also have nephroprotective effects (12–14). In the Aggressive Lipid-Lowering Initiation Abates New Cardiac Events (ALLIANCE) study, aggressive atorvastatin therapy prevented the anticipated decline in renal function during the 4 yr of the trial and modified the progression of CKD when compared with usual care (14).

Atorvastatin in both primary and secondary cardiovascular prevention studies has been shown to reduce the risk for cardiovascular events in a broad range of patients, without any safety concerns (15–20). The Treating to New Targets (TNT) study prospectively investigated the effects of lowering LDL cholesterol to a target of 75...
mg/dl with 80 mg/d atorvastatin compared with an LDL cholesterol target of 100 mg/dl with 10 mg/d atorvastatin in approximately 10,000 patients with stable coronary heart disease (CHD) (19). After 5 yr of follow-up, treatment with 80 mg of atorvastatin resulted in a significant reduction in major cardiovascular events compared with 10 mg/d atorvastatin. We conducted the current post hoc analysis of the TNT study to investigate further the initial indication from the ALLIANCE study of a renoprotective effect with more intensive atorvastatin treatment. In addition, this is the first study to evaluate whether such an effect could be dosage dependent.

Concise Methods
The design of the TNT study has been described in detail previously (19,21). The study was conducted in compliance with the Declaration of Helsinki and was approved by the local research ethics committee or institutional review board at each center. All participants gave written informed consent and could withdraw from the study at any time.

Patient Population
Patients who were eligible for inclusion were men and women who were aged 35 to 75 yr and had clinically evident CHD, defined as previous myocardial infarction, previous or present angina with objective evidence of atherosclerotic CHD, or previous coronary revascularization procedure. Major exclusion criteria were statin hypersensitivity, current liver disease, nephrotic syndrome, pregnancy or uncontrolled CHD risk factors, CHD event or revascularization within the previous month, congestive heart failure, creatine phosphokinase levels more than six times the upper limit of normal (ULN), life-threatening malignancy, or immunosuppressive or lipid-lowering drug treatment. There were no exclusions based on serum creatinine concentration at baseline.

Study Design
All previously prescribed lipid-regulating drugs were discontinued at screening, and all participants required a washout period of 1 to 8 wk (8 wk for those who had previously received lipid-regulating drugs and 1 wk for those who had not). To ensure that all participants at baseline achieved LDL cholesterol levels consistent with current guidelines for the treatment of stable CHD, those with LDL cholesterol levels between 130 and 250 mg/dl (3.4 to 6.5 mmol/L) and triglyceride levels ≤600 mg/dl (6.8 mmol/L) entered an 8-wk open-label treatment period with 10 mg/d atorvastatin. At the end of the run-in phase (baseline), participants with a mean LDL cholesterol <130 mg/dl (3.4 mmol/L) were randomly assigned to double-blind therapy with either 10 or 80 mg/d atorvastatin. Cholesterol inclusion/exclusion criteria were selected to achieve an average LDL cholesterol level of 100 mg/dl (2.6 mmol/L) in the 10-mg/d treatment arm. For reaching an average LDL cholesterol level in the comparator group of approximately 75 mg/dl (1.9 mmol/L), 80 mg/d atorvastatin was chosen. During the double-blind period, follow-up visits occurred at week 12 and at months 6, 9, and 12 in the first year and every 6 mo thereafter.

Efficacy and Safety Outcomes
In line with a recent American Heart Association Science Advisory (22), renal function was assessed using the Modification of Diet in Renal Disease (MDRD) equation (23), a serum creatinine–based estimate of GFR. The Cockcroft-Gault equation (24), another creatinine-based estimate of GFR, incorporating patient weight, was also used. Serum creatinine measurements using a modified alkaline picrate method of Jaffé (25,26) were taken at baseline and after 12, 24, 36, 48, 60, and 72 mo of treatment by individuals at a central study laboratory who were blinded to treatment assignment. Creatinine measurements were made using the Hitachi 747 analyzer (Roche Diagnostics, Indianapolis). Quality control samples were analyzed every 40 samples. The coefficients of variation for a monthly average creatinine concentration of 0.6 mg/dl were 4.5 to 9.0% and for a monthly average creatinine concentration of 4.7 mg/dl were 1.3 to 1.7%. Internal quality assurance and College of American Pathologists external quality assurance showed the measurement of creatinine to be stable and acceptably calibrated throughout the study. Final availability for each participant was used for the analysis of eGFR changes. For the baseline Cockcroft-Gault GFR estimate, weight at baseline or the visit 2 wk earlier (if baseline weight was not available) was used.

Safety was assessed by monitoring vital signs, clinical end points, adverse events (both clinical and laboratory based), and concurrent medication information at each visit. Physical examinations and electrocardiograms were performed and laboratory specimens were collected at alternate visits. Elevations in liver function enzymes (alanine aminotransferase and aspartate aminotransferase) were reported by the central laboratory as levels more than three times the ULN and creatine phosphokinase as a level >10 times the ULN.

Statistical Analyses
eGFR values at baseline were compared between the two atorvastatin treatment groups using an ANOVA model with items for treatment, center, race, age, and gender. eGFR at the end of follow-up was assessed using a last observation carried forward analysis. Fisher exact test was used for treatment arm comparisons of the proportions of participants who experienced decline or improvement of renal function. Mean changes from baseline eGFR during the course of the study and at the end of the study in the two treatment groups were compared using an analysis of covariance model with items for treatment, center, race, age, gender, and baseline eGFR.

Results
A total of 10,001 patients were randomly assigned between July 1998 and December 1999 to double-blind treatment with either 10 or 80 mg of atorvastatin. Of the overall TNT population, 9656 participants (4829 on 10 mg and 4827 on 80 mg) had complete renal data using the MDRD (both baseline and postbaseline eGFR) and are included in this analysis of renal function (Figure 1). Of the 345 TNT participants who were excluded from the analysis, 15 had no baseline creatinine measurement, 328 had no follow-up creatinine measurements, and two had neither baseline nor follow-up creatinine measurements. Overall patient demographics and disposition were reported previously (19). Baseline characteristics in participants with complete renal data were similar between treatment groups. Most patients were male (81%) and white (94%). Mean age was approximately 61 yr, with 62% of patients younger than 65 yr (Table 1).

Participants with complete renal data were followed for a median of 5.0 yr after randomization. There was no difference between treatment groups with regard to the timing of follow-up creatinine assessments. Median time from baseline to final serum creatinine measurement was 59.5 mo in both the 10- and 80-mg groups (interquartile range 4.3 and 4.2, respectively); 90% of participants had their final creatinine measurement at 46.6 mo or later in the 10-mg group and at 47.1 mo or later in the 80-mg group. In the 10-mg group, 1241 (25.7%) patients discontinued treatment, compared with 995 (20.6%) patients in the 80-mg group. The most common reasons were for adverse events (8.0 versus 9.6%), admin-
istrative issues (9.3 versus 6.6%), and fatal clinical end points (3.3 versus 3.5%).

**Serum Lipid Levels**
Baseline lipid levels (after 8 wk of open-label 10 mg of atorvastatin) in participants with complete renal data were well matched between treatment groups for LDL cholesterol, HDL cholesterol, total cholesterol, and triglycerides (Table 2). The difference between the 10- and 80-mg groups at the end of the study was statistically significant for LDL cholesterol, total cholesterol, and triglycerides, in favor of 80 mg of atorvastatin (Table 2). There was no difference between the treatment groups in HDL cholesterol.

**BP**
Systolic (SBP) and diastolic BP (DBP) levels at baseline were similar in the two treatment groups (Table 1). SBP and DBP did not change during the course of the study and did not differ between treatment groups at the last postbaseline visit (SBP mean ± SD 132.0 ± 17.1 and 131.8 ± 17.0 mmHg; DBP mean ± SD 78.8 ± 9.7 and 78.6 ± 9.6 mmHg in the 10- and 80-mg groups, respectively). Use of angiotensin-converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARB) during the study was slightly higher in participants who received 10 mg of atorvastatin (61.5%) than in those who received 80 mg of atorvastatin (59.3%); 53.9 and 51.4%, respectively, took ACEI, and 16.5 and 15.6%, respectively, took ARB. There was no difference in diuretic use during the study between the 10-mg group (7.2%) and the 80-mg group (7.4%).

**Renal Function**
Mean (±SD) eGFR at baseline as assessed by the MDRD was 65.6 ± 11.4 ml/min per 1.73 m² in the 10-mg group and 65.0 ± 11.2 ml/min per 1.73 m² in the 80-mg group (Table 1). Mean change from baseline eGFR showed a progressive increase during the course of the study in both treatment groups. At the end of follow-up, mean change from baseline eGFR (±SE) showed an increase of 3.5 ± 0.14 ml/min per 1.73 m² in the 10-mg group and 5.2 ± 0.14 ml/min per 1.73 m² in the 80-mg group, which represented increases of 5.6 and 8.3%, respectively (Figure 2). The difference between treatment groups in mean change from baseline eGFR was highly significant (1.68 ± 0.20 ml/min per 1.73 m²; P < 0.0001). In 9644 participants with data available for assessment using the Cockcroft-Gault equation, renal outcomes were consistent with those observed with the MDRD equation (mean...
changes from baseline 1.1 ± 0.17 ml/min for 10 mg of atorvastatin and 2.6 ± 0.17 ml/min for 80 mg of atorvastatin; \( P < 0.0001 \).

On-treatment LDL cholesterol was a significant predictor of change in eGFR (\( P < 0.0001 \) for a slope of −0.022), showing a greater improvement in eGFR for a lower on-treatment LDL cholesterol. When diabetes, any use of ACEI or ARB, baseline lipids (LDL cholesterol, HDL cholesterol, total cholesterol, and triglycerides), and SBP and DBP were included in the analysis of covariance model, mean change in eGFR was 3.3 ± 0.13 ml/min per 1.73 m\(^2\) for 10 mg of atorvastatin and 4.9 ± 0.14 ml/min per 1.73 m\(^2\) for 80 mg of atorvastatin (\( P < 0.0001 \) between treatments), which represented increases of 5.3 and 7.9%, respectively.

The progressive increase in eGFR for both dosages of atorvastatin was consistent in participants with CKD at baseline and in participants with normal eGFR at baseline, with a mean change from baseline of 3.5 ml/min per 1.73 m\(^2\) with 10 mg of atorvastatin and 5.2 ml/min per 1.73 m\(^2\) with 80 mg of atorvastatin in both eGFR categories (Figure 3); however, this represented a greater mean percentage increase from baseline for participants with CKD (9.9% with 80 mg of atorvastatin and 6.6% with 10 mg of atorvastatin) than those with normal eGFR (7.6% with 80 mg of atorvastatin and 5.2% with 10 mg of atorvastatin; Figure 3).

Among participants with a baseline eGFR ≥60 ml/min per 1.73 m\(^2\), significantly fewer in the 80-mg group declined to <60 ml/min per 1.73 m\(^2\) at the end of the study than in the 10-mg group (6.6 versus 9.2%; \( P < 0.0001 \); Figure 4). Among participants with a baseline eGFR <60 ml/min per 1.73 m\(^2\), significantly more in the 80-mg group improved to ≥60 ml/min per 1.73 m\(^2\) at the end of the study than in the 10-mg group (45.6 versus 37.8%; \( P = 0.0001 \); Figure 4). Among participants with CKD at baseline (eGFR <60 ml/min per 1.73 m\(^2\)), 80 (5.3%) who were assigned to 10 mg of atorvastatin and 54 (3.4%) who were assigned to 80 mg of atorvastatin experienced a decline in eGFR of ≥25% (\( P = 0.0077 \)).

### Table 1. Baseline demographics and clinical characteristics of TNT participants included in the renal analysis

<table>
<thead>
<tr>
<th>Baseline Characteristic (at Randomization)</th>
<th>Atorvastatin 10 mg</th>
<th>Atorvastatin 80 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>( n = 4829 )</td>
<td>( n = 4827 )</td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>3909 (80.9)</td>
<td>3926 (81.3)</td>
</tr>
<tr>
<td>Mean age (yr)</td>
<td>60.9 ± 8.9</td>
<td>61.2 ± 8.8</td>
</tr>
<tr>
<td>≥65 yr</td>
<td>1803 (37.3)</td>
<td>1882 (39.0)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
</tr>
<tr>
<td>white</td>
<td>4547 (94.2)</td>
<td>4547 (94.2)</td>
</tr>
<tr>
<td>black</td>
<td>144 (3.0)</td>
<td>126 (2.6)</td>
</tr>
<tr>
<td>other</td>
<td>138 (2.9)</td>
<td>154 (3.2)</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>130.8 ± 16.8</td>
<td>130.6 ± 16.7</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>78.1 ± 9.5</td>
<td>77.8 ± 9.4</td>
</tr>
<tr>
<td>BMI (kg/m(^2))</td>
<td>28.7 ± 4.6</td>
<td>28.4 ± 4.4</td>
</tr>
<tr>
<td>Plasma creatinine (mg/dl)</td>
<td>1.2 ± 0.2</td>
<td>1.2 ± 0.2</td>
</tr>
<tr>
<td>MDRD eGFR (ml/min per 1.73 m(^2))</td>
<td>65.6 ± 11.4</td>
<td>65.0 ± 11.2</td>
</tr>
<tr>
<td>≥60</td>
<td>3324 (68.8)</td>
<td>3225 (66.8)</td>
</tr>
<tr>
<td>30 to 59</td>
<td>1492 (30.9)</td>
<td>1586 (32.9)</td>
</tr>
<tr>
<td>15 to 29</td>
<td>13 (0.3)</td>
<td>16 (0.3)</td>
</tr>
<tr>
<td>&lt;15</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Cockcroft-Gault eGFR (ml/min)</td>
<td>79.2 ± 22.2</td>
<td>77.7 ± 21.7</td>
</tr>
<tr>
<td>Smoking status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>current</td>
<td>640 (13.3)</td>
<td>628 (13.0)</td>
</tr>
<tr>
<td>former</td>
<td>3054 (63.2)</td>
<td>3068 (63.6)</td>
</tr>
<tr>
<td>Cardiovascular history</td>
<td></td>
<td></td>
</tr>
<tr>
<td>angina</td>
<td>3918 (81.1)</td>
<td>3960 (82.0)</td>
</tr>
<tr>
<td>myocardial infarction</td>
<td>2790 (57.8)</td>
<td>2831 (58.6)</td>
</tr>
<tr>
<td>coronary angioplasty</td>
<td>2634 (54.5)</td>
<td>2598 (53.8)</td>
</tr>
<tr>
<td>hypertension</td>
<td>2622 (54.3)</td>
<td>2599 (53.8)</td>
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<tr>
<td>coronary artery bypass graft</td>
<td>2252 (46.6)</td>
<td>2232 (46.2)</td>
</tr>
<tr>
<td>arrhythmia</td>
<td>893 (18.5)</td>
<td>875 (18.1)</td>
</tr>
<tr>
<td>diabetes</td>
<td>714 (14.8)</td>
<td>717 (14.9)</td>
</tr>
<tr>
<td>peripheral vascular disease</td>
<td>542 (11.2)</td>
<td>584 (12.1)</td>
</tr>
<tr>
<td>congestive heart failure</td>
<td>381 (7.9)</td>
<td>354 (7.3)</td>
</tr>
<tr>
<td>cerebrovascular accident</td>
<td>251 (5.2)</td>
<td>241 (5.0)</td>
</tr>
</tbody>
</table>

\(^{a}\) Data are \( n \) (%) or mean ± SD. BMI, body mass index; DBP, diastolic BP; eGFR, estimated GFR; SBP, systolic BP; TNT, Treating to New Targets.
Safety

No unexpected safety concerns were identified and similar incidences of adverse events were experienced in each of the treatment groups. No occurrences of hematuria or proteinuria were reported as a serious adverse event in either treatment group. The percentage of participants who had persistent elevations in liver function enzymes (two measurements of alanine aminotransferase and/or aspartate aminotransferase more than three times ULN obtained 4 to 10 d apart) reported by the central laboratory was numerically larger in the 80-mg group than in the 10-mg group but was generally low and similar to that observed in the overall TNT population for both participants with CKD (1.4 versus 0.1%) and those with normal eGFR (1.2 versus 0.2%). No patient had clinically persistent elevated creatine phosphokinase values (two measurements of creatine phosphokinase >10 times ULN obtained 4 to 10 d apart).

Discussion

The TNT study showed significant cardiovascular benefits of aggressively lowering LDL cholesterol to levels below current clinical treatment guidelines (27) with 80 mg/d atorvastatin in patients with stable CHD, compared with more moderate lipid lowering with 10 mg/d atorvastatin (19). This analysis demonstrates that in addition to improved lipid control and further reductions in major cardiovascular events, the benefits of an aggressive atorvastatin treatment strategy extend to significant improvement in renal function over that achieved with lower dosage atorvastatin therapy.

The expected decline in renal function that was seen in other cardiovascular treatment trials (10,11,28) was not observed during the 5 yr of the TNT study in either the 10- or 80-mg treatment group; however, the absence of an untreated control arm is a recognized limitation of this study, because the actual age-related decline in renal function was not measured in the TNT population and can only be estimated from similar clinical trials. The age-related decline in renal function has been well documented in studies (10) of patients with CHD, with reported eGFR declines in control groups of up to 6.7 ml/min per 1.73 m² during 5 yr of follow-up. Thus, although the 5-yr improvements in eGFR were numerically small, drug-related improvements in renal function or significant modification of the anticipated renal decline should be considered clinically relevant. Such renoprotective effects would be of particular importance in patients who have GFR = 60 ml/min per 1.73 m², who, with additional loss of

<table>
<thead>
<tr>
<th>Lipid Parameter</th>
<th>Atorvastatin 10 mg (n = 4829)</th>
<th>Atorvastatin 80 mg (n = 4827)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL cholesterol (mg/dl [mmol/L])</td>
<td></td>
<td></td>
</tr>
<tr>
<td>baseline (mean ± SD)</td>
<td>97.6 ± 17.5 (2.5 ± 0.5)</td>
<td>97.2 ± 17.5 (2.5 ± 0.4)</td>
</tr>
<tr>
<td>mean at last visit</td>
<td>101.0 (2.6)</td>
<td>79.7 (2.1)</td>
</tr>
<tr>
<td>mean change at last visit</td>
<td>3.4 (0.1)</td>
<td>−17.5 (−0.5)b</td>
</tr>
<tr>
<td>HDL cholesterol (mg/dl [mmol/L])</td>
<td></td>
<td></td>
</tr>
<tr>
<td>baseline (mean ± SD)</td>
<td>47.2 ± 10.8 (1.2 ± 0.3)</td>
<td>47.5 ± 11.1 (1.2 ± 0.3)</td>
</tr>
<tr>
<td>mean at last visit</td>
<td>47.0 (1.2)</td>
<td>47.3 (1.2)</td>
</tr>
<tr>
<td>mean change at last visit</td>
<td>−0.2 (&lt;0.1)</td>
<td>−0.3 (&lt;0.1)</td>
</tr>
<tr>
<td>Total cholesterol (mg/dl [mmol/L])</td>
<td></td>
<td></td>
</tr>
<tr>
<td>baseline (mean ± SD)</td>
<td>174.6 ± 23.8 (4.5 ± 0.6)</td>
<td>174.6 ± 23.7 (4.5 ± 0.6)</td>
</tr>
<tr>
<td>mean at last visit</td>
<td>179.3 (4.6)</td>
<td>153.8 (4.0)</td>
</tr>
<tr>
<td>mean change at last visit</td>
<td>4.7 (0.1)</td>
<td>−20.9 (−0.5)b</td>
</tr>
<tr>
<td>Triglycerides (mg/dl [mmol/L])</td>
<td></td>
<td></td>
</tr>
<tr>
<td>baseline (mean ± SD)</td>
<td>150.0 ± 71.1 (1.7 ± 0.8)</td>
<td>150.3 ± 69.6 (1.7 ± 0.8)</td>
</tr>
<tr>
<td>mean at last visit</td>
<td>158.9 (1.8)</td>
<td>135.8 (1.5)</td>
</tr>
<tr>
<td>mean change at last visit</td>
<td>8.9 (0.1)</td>
<td>−14.5 (−0.2)b</td>
</tr>
</tbody>
</table>

*a*Mean change from the end of the 8-wk, open-label run-in period with 10 mg of atorvastatin.

*b*P < 0.0001 for between-treatment comparisons (80 versus 10 mg).

![Graph: Least squares (LS) mean change from baseline in estimated GFR (eGFR) during the course of the study and at final visit, after treatment with 10 or 80 mg of atorvastatin. “Final” represents the final eGFR availability for each participant (last observation carried forward analysis).](image)
renal function, are at significantly greater risk for future cardiovascular events (7,8). The observation that eGFR showed an improvement in the TNT study may have been related to the intensity of statin therapy. Previous studies with moderate dosages of pravastatin (11,29) and simvastatin (10) demonstrated a slowing in the decline of eGFR (≥60 ml/min per 1.73 m²) whereas improvements have been repeatedly observed with atorvastatin (13,14) and more recently in short-term studies of rosuvastatin (30). Although improvement in eGFR occurred with 10 mg of atorvastatin, by the end of the trial, 80 mg of atorvastatin had demonstrated significantly greater improvement in eGFR than that achieved by low-dosage atorvastatin. This not only suggests that atorvastatin improves renal function but also indicates that there may be a dosage-dependent renoprotective effect.

These data are consistent with two previous studies that demonstrated significant renal benefit of a titrate-to-goal regimen of atorvastatin (10 to 80 mg) over a regimen of “usual care” in patients with established CHD (13,14); however, when compared with the TNT study, patients in both of these trials had substantially higher LDL cholesterol at baseline, and follow-up LDL cholesterol levels in the titrate-to-goal treatment groups were similar to that achieved by the 10-mg atorvastatin arm of TNT. Furthermore, fewer than half of the patients in the ALLIANCE study (18) and only 3% in the Greek Atorvastatin and Coronary Heart Disease Prevention (GREACE) study (13) received 80 mg/d atorvastatin. These factors could possibly reduce the potential for improvement. Observations from ALLIANCE and GREACE tend to reinforce the importance of the TNT findings of the potential dosage-related effect of atorvastatin on eGFR in patients with CHD and the greater renal benefit that is associated with intensive therapy with 80 mg of atorvastatin.

The mechanisms that are involved in this observed nephroprotective effect of atorvastatin have yet to be determined. Such an effect could be linked to the cardiovascular benefits of LDL cholesterol reduction, because on-treatment LDL cholesterol proved to be a significant predictor of change in eGFR. Other cholesterol-independent statin pleiotropic effects could also account for or contribute to the observed clinical findings. In vivo studies (31–35) suggested a variety of mechanisms whereby statins may have an impact on renal endothelial function. In one such study, upregulation of vascular
endothelial nitric oxide synthase and inhibition of oxidative stress
were observed with atorvastatin treatment and were thought to
protect against the development of end-organ injury (31). The gra-
dudal improvement of eGFR over time and differential response be-
tween patients with CKD and patients with normal eGFR observed
in the TNT study may indicate such an effect on the vasculature that
increases over time, rather than a direct effect on increased creatinine
excretion or reduction in muscle mass.

A number of different methods are used to estimate GFR, based on
serum creatinine. Because creatinine generation may be influenced by
dietary protein intake, muscle mass, and activity, GFR estimates
attempt to allow for this by using other variables, such as age, gender,
race, and body size. The MDRD estimate of GFR used in this analysis
has been evaluated for accuracy in clinical studies and is recom-
mended by the National Kidney Foundation Clinical Practice Guide-
lines (3) and a recent American Heart Association Science Advisory
(22) to detect, evaluate, and manage CKD. The MDRD equation
corrects for body surface area and is less accurate in populations
without CKD. The Cockcroft-Gault equation calculates creatinine
clearance rather than GFR. Because creatinine clearance is higher than
GFR (as a result of tubular secretion of creatinine), the Cockcroft-
Gault equation often underestimates changes in GFR. Despite imper-
fec tions with each of these approaches, the results from this analysis
were consistent across both measures.

The prevalence of CKD in the TNT study was approximately
32% (based on eGFR <60 ml/min per 1.73 m²), consistent with
previous studies of CHD populations (11,29,34,36), illustrating
that this is an important and potentially underrecognized condi-
tion in patients with CHD. By the end of the study, renal function
in participants who had CKD and were treated with 80 mg of
atorvastatin had improved by almost 10%, compared with 6.6% in
participants who had CKD and were treated with 10 mg of
atorvastatin. Furthermore, 46% of participants who had CKD and
were treated with 80 mg of atorvastatin and 38% participants who
had CKD and were treated with 10 mg of atorvastatin improved
from an eGFR <60 to an eGFR ≥60 ml/min per 1.73 m². Taking
into account the accelerated increase in risk for cardiovascular
events in patients with GFR <60 ml/min per 1.73 m² (3,4,7,8) and
the increased mortality after a coronary event in patients with
mild to moderate renal impairment (37–40), these patients there-
fore represent those for whom delay in progression of renal dis-
ease has the greatest clinical relevance. It is also of note that the
MDRD estimates of GFR are likely to be more accurate represen-
tations of actual GFR in these patients. The renoprotective effects
that were demonstrated in this and other studies highlight a
clinically relevant slowing of progression to CKD. These data also
reinforce the current trend in guidelines advocating the use of
high-dosage statin therapy to achieve lower target LDL choles-
terol levels for optimal prevention of cardiovascular events (41).

The heightened renal benefit of 80 mg/d atorvastatin was achieved
without additional safety concerns or increased risk to the patients
and was consistent with other data that have shown high-dosage
atorvastatin to be safe and well tolerated (17,18,20,42,43). Specific-
ally, there was no increase in serious renal adverse events or those
with potential for renal complications, and there was no increased
risk with high-dosage atorvastatin to participants with CKD at baseline,
compared with those with normal eGFR. Excretion of atorvastatin is
mainly hepatic, and previous data (44–46) showed that renal disease
has no influence on the achieved plasma concentrations of LDL
cholesterol produced by atorvastatin.

As a post hoc analysis, using estimates of renal function, there are
some limitations to the interpretation of these data. Generalizations
should be made with caution, because the cause of renal disease in
the TNT population is unknown. In addition, conclusions that can be
made regarding patients with severe renal deficiency are limited
given the small proportion of patients who had advanced CKD and
were included in this analysis. The influence of nephrotoxic drugs
such as nonsteroidal anti-inflammatory drugs could not be assessed
because the study was not designed to monitor actively the use of
these drugs; however, we expect that the percentage of participants
who were prescribed such drugs would have been similar between
the treatment groups in this randomized trial.

These data demonstrating renal benefits with 80 mg/d atorvasta-
tin over those achieved with 10 mg/d atorvastatin add to the grow-
ing evidence base for noncardiac benefits of statins. Although the
absolute changes in eGFR with atorvastatin may seem small, the
observation that there was an apparent improvement in GFR during
the 5 yr of the TNT study rather than a steady decline demonstrates
the clinical importance by preventing progression to CKD and ESRD.
Although the mechanisms that are responsible for renoprotection
with statins have yet to be determined, lowering LDL cholesterol
levels to well below 100 mg/dl with high-dosage atorvastatin seems
to maximize renal benefits in high-risk patients with CHD and
should not be contraindicated in moderate CKD. The findings from
this TNT study subanalysis are intriguing and, when taken in concert
with previous statin clinical trials (10,11,13,14), may have significant
clinical and therapeutic implications for the clinical treatment of pa-
tients who have CHD with CKD.

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