Intensive Lipid Lowering With Atorvastatin in Patients With Coronary Artery Disease, Diabetes, and Chronic Kidney Disease

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OBJECTIVE: To investigate the effect of intensive lipid lowering with high-dose atorvastatin on the incidence of major cardiovascular events compared with low-dose atorvastatin in patients with coronary artery disease and type 2 diabetes, with and without chronic kidney disease (CKD).

PATIENTS AND METHODS: Following 8 weeks' open-label therapy with atorvastatin (10 mg/d), 10,001 patients with coronary artery disease were randomized to receive double-blind therapy with either 80 mg/d or 10 mg/d of atorvastatin between July 1, 1998, and December 31, 1999. Of 1501 patients with diabetes, renal data were available for 1431. Patients with CKD were defined as having a baseline estimated glomerular filtration rate (eGFR) below 60 mL/min per 1.73 m², using the Modification of Diet in Renal Disease equation.

RESULTS: After a median follow-up of 4.8 years, 95 (17.4%) of 546 patients with diabetes and CKD experienced a major cardiovascular event vs 119 (13.4%) of 885 patients with diabetes and normal eGFRs (hazard ratio [HR], 1.32; 95% confidence interval [CI], 1.00-1.72; P<.05). Compared with 10 mg of atorvastatin, 80 mg of atorvastatin reduced the relative risk of major cardiovascular events by 35% in patients with diabetes and CKD (20.9% [57/273] vs 13.9% [38/273]; HR, 0.65; 95% CI, 0.43-0.98; P=.04) and by 10% in patients with diabetes and normal eGFR (14.1% [62/441] vs 12.8% [57/444]; HR, 0.90; 95% CI, 0.63-1.29; P=.56). The absolute risk reduction in patients with diabetes and CKD was substantial, yielding a number needed to treat of 14 to prevent 1 major cardiovascular event over 4.8 years. Both treatments were well tolerated.

CONCLUSION: Patients with diabetes, stable coronary artery disease, and mild to moderate CKD experience marked reduction in cardiovascular events with intensive lipid lowering, in contrast to previous observations in patients with diabetes and end-stage renal disease.

Trial Registration: clinicaltrials.gov identifier: NCT00327691


AE = adverse event; CAD = coronary artery disease; CI = confidence interval; CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; HDL-C = high-density lipoprotein cholesterol; HR = hazard ratio; LDL-C = low-density lipoprotein cholesterol; MI = myocardial infarction; MDRD = Modification of Diet in Renal Disease; TNT = Treating to New Targets

The prevalence of chronic kidney disease (CKD) in the United States is increasing. Chronic kidney disease currently affects 11% of US men and 15% of US women, and this increasing prevalence raises concern about future increases in kidney failure and associated complications of CKD.1 The observed increase in CKD can partly be explained by the increasing prevalence of diabetes in the United States.2 These 2 clinical conditions often cluster; the prevalence of CKD in patients with diabetes is estimated to be 40%,1 and diabetes is recognized as the primary cause of kidney failure in 45% of patients receiving dialysis.4

Patients with both diabetes and CKD are at much greater risk of major cardiovascular events and death than those with either condition alone,3 and this risk appears to increase with progressive renal insufficiency. Cardiovascular risk also increases in patients with diabetes and renal complications such as albuminuria or low glomerular filtration rate.6,8 Cardiovascular disease is the leading cause of death in patients with end-stage renal disease (stage 5).9 Mild to moderate CKD (stages 3-4) is also associated with an increased incidence of cardiovascular events,10-13 and...
patients with CKD, particularly those who also have diabetes, are substantially more likely to die of cardiovascular disease before they reach the end stage of renal failure.9,14,15 Dyslipidemia is recognized as a modifiable cardiovascular risk factor for both diabetes and CKD. Current guidelines recommend intensive lipid-lowering therapy with statins for high-risk patients, such as those with preexisting coronary artery disease (CAD) and diabetes or CKD.16-20 However, recent evidence indicates that modest lipid-lowering therapy in patients with diabetes and end-stage renal disease is too late to translate into consistent improvements in cardiovascular outcomes,21 and cardiovascular outcomes data for patients with concomitant diabetes and mild to moderate CKD who take statins are limited.5

Data from the Treating to New Targets (TNT) study demonstrated that intensive lipid-lowering therapy with 80 mg/d of atorvastatin significantly reduced the risk of major cardiovascular events by 25% compared with moderate lipid lowering with 10 mg/d of atorvastatin in high-risk patients with CAD and diabetes.22 The current post hoc analysis of the TNT study was undertaken to investigate the effect of intensive lipid lowering with 80 mg/d of atorvastatin on future cardiovascular events in patients with diabetes, with or without mild to moderate CKD.

PATIENTS AND METHODS
The design of the TNT study has been described in detail.23,24 All patients gave written informed consent, and the study was approved by the local research ethics committee or institutional review board at each center. A total of 10,011 patients were randomized to double-blind treatment with either 80 mg/d or 10 mg/d of atorvastatin between July 1, 1998, and December 31, 1999.23 Eligible patients were men and women aged 35 to 75 years with clinically evident CAD, defined as myocardial infarction (MI), previous or current angina with objective evidence of atherosclerotic CAD, or a history of coronary revascularization. Patients were included in the current analysis if they had a history of diabetes (fasting glucose levels at screening were not used). Patients with nephrotic syndrome were excluded from the study; however, no exclusions were made on the basis of serum creatinine concentration at baseline. Detailed exclusion criteria have been described previously.24

STUDY DESIGN
All prescribed lipid-regulating drugs were discontinued at screening, and all patients required a washout period of 1 to 8 weeks. To ensure that all patients had low-density lipoprotein cholesterol (LDL-C) levels at baseline that were consistent with existing guidelines for the treatment of stable CAD, patients with LDL-C levels between 130 and 250 mg/dL (to convert to mmol/L, multiply by 0.0259) and triglyceride levels of 600 mg/dL or less (to convert to mmol/L, multiply by 0.0113) entered an 8-week run-in period of open-label treatment with 10 mg/d of atorvastatin. At the end of the run-in phase (baseline), patients with a mean LDL-C level below 130 mg/dL were randomized to receive double-blind therapy with either 80 mg/d or 10 mg/d of atorvastatin. 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 months thereafter.

EFFICACY AND SAFETY OUTCOMES
The primary efficacy outcome was occurrence of a major cardiovascular event, defined as death from CAD, nonfatal non–procedure-related MI, resuscitation after cardiac arrest, or fatal or nonfatal stroke.

As recommended by the National Kidney Foundation clinical practice guidelines for CKD1 and a recent American Heart Association Science Advisory,25 renal function was assessed using the Modification of Diet in Renal Disease (MDRD) equation,26 an estimated glomerular filtration rate (eGFR) based on serum creatinine, as described previously.27 According to these guidelines, patients with baseline eGFR below 60 mL/min per 1.73 m² (to convert to mLs per m², multiply by 0.0167) were classified as having CKD; patients with baseline eGFR of 60 mL/min per 1.73 m² or more were classified as having normal or near-normal renal function. Urinary protein measurements were unavailable for these patients.

Safety was assessed by monitoring vital signs, clinical end points, adverse events (AEs) (both clinical and laboratory based), and concurrent medication information at each visit. Physical examinations and electrocardiography were performed and laboratory specimens collected at alternate visits. Elevations in liver function enzymes (alanine aminotransferase and aspartate aminotransferase) were reported by the central laboratory as levels 3 times the upper limit of normal or higher, and creatine kinase as a level 2 times the upper limit of normal or higher.

STATISTICAL ANALYSES
Detailed statistical methods have been reported.23 The primary analysis of efficacy in the TNT study was the difference between the 80-mg/d and 10-mg/d treatment groups for the first occurrence of a major cardiovascular event during the 5-year follow-up period, on the basis of log-rank analyses. The primary composite end point was analyzed from the time of the first dose of randomized study drug to the first event according to the Kaplan-Meier method. Hazard ratios (HRs) and their 95% confidence intervals (CIs)
were also calculated using the Cox regression model. Relative risk reductions on the basis of HRs were reported, as well as absolute risk reductions on the basis of event incidence. Two-sided \( P < 0.05 \) was regarded as significant. Tests for heterogeneity were used to determine whether the treatment effects observed in patients with diabetes and CKD differed from those in patients with diabetes and normal eGFR. Mean changes from baseline eGFR during the course of the study and at the end of follow-up (last observation carried forward analysis) were compared using an analysis of covariance model with items for treatment, center, race, age, sex, and baseline eGFR. All analyses were performed on an intention-to-treat basis and included all randomized patients who received at least 1 dose of study drug.

Of the overall TNT population, \(^{21} 1501 (15\%) \) had diabetes, 1431 of whom had complete renal data (baseline and at least 1 postbaseline serum creatinine measurement) and were included in the current analysis (Figure 1). At baseline, 546 patients with diabetes (38.1%) had CKD, of whom 536 had stage 3 (eGFR, 30-59 mL/min per 1.73 m\(^2\)) and 10 had stage 4 (eGFR, 15-29 mL/min per 1.73 m\(^2\)) CKD. Patients with diabetes and CKD were older (mean age 66.6 vs 60.8 years) and comprised more women (42.1% [230/546] vs 17.6% [156/885]) and fewer smokers (7.0% [38/546] vs 12.8% [113/885]) than patients with diabetes and normal eGFR values. Preexisting cardiovas-
cultural morbidity and risk factors at baseline were generally more prevalent among patients with diabetes and CKD than among patients with diabetes and normal eGFRs (Table). Despite characteristic differences at baseline between patients with diabetes, with or without CKD, there was no imbalance by randomized treatment assignment (Table).

### SERUM LIPID LEVELS

Baseline lipid levels (after 8 weeks’ open-label 10-mg doses of atorvastatin) were well matched between patients with diabetes and CKD and those with diabetes and normal eGFRs for levels of LDL-C, total cholesterol, and high-density lipoprotein cholesterol (HDL-C) (Table); patients with diabetes and CKD had a higher triglyceride level at baseline than those with diabetes and normal eGFRs (149.1 mg/dL) and patients with diabetes (168.5 mg/dL) compared with 10 mg of atorvastatin (190.5 and 161.8 mg/dL). However, 80 mg of atorvastatin lowered triglycerides to a similar level in patients with CKD (149.1 mg/dL) and patients with normal eGFRs (142.3 mg/dL) compared with 10 mg of atorvastatin (190.5 and 168.5 mg/dL, respectively). Mean LDL-C levels over the course of the study with 80 mg vs 10 mg of atorvastatin were similar for patients with diabetes and CKD (74.9 vs 72.5 mg/dL) and for patients with diabetes and normal eGFRs (79.9 vs 74.9 mg/dL). Values for HDL-C remained stable in all treatment groups over the 5 years of course of the study with 80 mg vs 10 mg of atorvastatin (190.5 and 161.8 mg/dL); however, 80 mg of atorvastatin lowered triglycerides to a similar level in patients with CKD (149.1 mg/dL) and patients with normal eGFRs (142.3 mg/dL) compared with 10 mg of atorvastatin (190.5 and 168.5 mg/dL, respectively).

![Table: Baseline Demographics and Clinical Characteristics of Patients With Diabetes by Chronic Kidney Disease (CKD) Status and Treatment](https://www.mayoclinicproceedings.com/content/83/8/870)

<table>
<thead>
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<th>Baseline characteristic (at randomization)</th>
<th>Patients with diabetes and CKD</th>
<th>Patients with diabetes and normal eGFR</th>
<th>Atorvastatin 10 mg (n=273)</th>
<th>Atorvastatin 80 mg (n=273)</th>
<th>All (n=546)</th>
<th>Atorvastatin 10 mg (n=441)</th>
<th>Atorvastatin 80 mg (n=444)</th>
<th>All (n=885)</th>
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<tbody>
<tr>
<td>Male</td>
<td>145 (53.1)</td>
<td>171 (62.6)</td>
<td>316 (57.9)</td>
<td>371 (84.1)</td>
<td>358 (80.6)</td>
<td>729 (82.4)</td>
<td>60.7±16.0</td>
<td>61.0±28.0</td>
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<td>Age, y</td>
<td>66.3±3.6</td>
<td>66.8±3.6</td>
<td>66.6±3.6</td>
<td>60.7±16.0</td>
<td>61.0±28.0</td>
<td>60.8±28.1</td>
<td>150 (34.0)</td>
<td>157 (35.4)</td>
</tr>
<tr>
<td>Race</td>
<td>174 (63.7)</td>
<td>180 (65.9)</td>
<td>354 (64.8)</td>
<td>150 (34.0)</td>
<td>157 (35.4)</td>
<td>307 (34.7)</td>
<td>23 (5.2)</td>
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<td>Body mass index</td>
<td>30.3±2.5</td>
<td>29.7±2.4</td>
<td>30.0±2.3</td>
<td>30.9±2.5</td>
<td>30.4±2.5</td>
<td>30.6±2.3</td>
<td>51 (11.6)</td>
<td>62 (14.0)</td>
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<tr>
<td>Current smoker</td>
<td>17 (6.2)</td>
<td>21 (7.7)</td>
<td>38 (7.0)</td>
<td>51 (11.6)</td>
<td>62 (14.0)</td>
<td>113 (12.8)</td>
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<td>Lipids, mg/dL.b</td>
<td>97.0±17.9</td>
<td>95.5±17.9</td>
<td>96.3±17.9</td>
<td>96.8±17.5</td>
<td>95.9±18.7</td>
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<td>150 (34.0)</td>
<td>157 (35.4)</td>
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<td>Total cholesterol</td>
<td>178.0±25.6</td>
<td>176.1±24.0</td>
<td>177.0±25.0</td>
<td>172.9±23.0</td>
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<td>Triglycerides, median (IQR)</td>
<td>180.2±84.9</td>
<td>181.6±84.1</td>
<td>180.9±84.3</td>
<td>167.3±72.5</td>
<td>163.3±77.3</td>
<td>161.8±74.9</td>
<td>140.2 (107.5-197.0)</td>
<td>150.0 (108.5-192.8)</td>
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<td>Serum creatinine, mg/dL.c</td>
<td>149.8±51.4</td>
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<td>150.4±51.1</td>
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<td>eGFR, mL/min per 1.73 m².d</td>
<td>50.7±7.8</td>
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<td>364 (82.5)</td>
<td>352 (79.3)</td>
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<tr>
<td>Cardiovascular history</td>
<td>232 (85.0)</td>
<td>227 (83.2)</td>
<td>459 (84.1)</td>
<td>364 (82.5)</td>
<td>352 (79.3)</td>
<td>716 (80.9)</td>
<td>22 (5.0)</td>
<td>38 (8.6)</td>
</tr>
</tbody>
</table>

aData presented as number (percentage) or mean ± SD unless otherwise indicated. eGFR = estimated glomerular filtration rate; HbA₁c = glycated hemoglobin A₁c; HDL-C = high-density lipoprotein cholesterol; IQR = interquartile range; LDL-C = low-density lipoprotein cholesterol.

bSI conversion factor: To convert HDL-C and LDL-C values to mmol/L, multiply by 0.0259; to convert triglyceride values to mmol/L, multiply by 0.0113.

cSI conversion factor: To convert serum creatinine values to µmol/L, multiply by 88.4.

dSI conversion factor: To convert eGFR to mL/s per m², multiply by 0.0167.

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BLOOD PRESSURE

In patients with diabetes and CKD, baseline systolic blood pressure was higher and diastolic blood pressure lower than in patients with diabetes and normal eGFRs (Table). There was little change in systolic and diastolic blood pressure over the course of the study; no significant differences in blood pressure were observed between randomized treatment groups. There was slightly greater use of inhibitors of the renin-angiotensin system during the trial in patients with diabetes and CKD (81.7% [223/273] of patients receiving 80 mg of atorvastatin and 83.5% [228/273] of patients receiving 10 mg of atorvastatin) than in patients with diabetes and normal eGFR values (76.6% [340/444] and 80.3% [354/441], respectively).

RENAL OUTCOMES

During the course of the study, the anticipated decrease in eGFR was not observed. Mean change from baseline eGFR showed a progressive increase in both atorvastatin treatment groups in patients with diabetes, with or without CKD (Figure 2). At the end of follow-up, mean ± SE change from baseline eGFR showed an increase of 0.5±0.43 mL/min per 1.73 m² in the 10-mg group and 2.6±0.5 mL/min per 1.73 m² in the 80-mg group (P=0.001 between treatment groups). Level of LDL-C during treatment (at 3 months) was not a significant predictor of change in eGFR (P=0.20 for a slope of –0.016).

CARDIOVASCULAR OUTCOMES

After a median follow-up of 4.8 years, irrespective of treatment assignment, 95 patients with diabetes and CKD (17.4%) experienced a first major cardiovascular event compared with 119 with diabetes and normal eGFR values at baseline (13.4%). Thus, patients with diabetes and CKD were at a significantly greater risk of experiencing a major cardiovascular event than patients with normal renal function (HR, 1.32; 95% CI, 1.00-1.72; P<.05; Figure 3). A similar increase in the risk of a first major cardiovascular event with CKD compared with normal eGFR was observed in patients without diabetes (10.0% [256/2561] vs 7.8% [442/5664]; HR, 1.30; 95% CI, 1.12-1.52; P<.001; Figure 3). In patients with diabetes and CKD at baseline, 38 (13.9%) receiving 80 mg of atorvastatin and 57 (20.9%) receiving 10 mg of atorvastatin had a first major cardiovascular event, a 35% relative reduction in risk with intensive lipid lowering (HR, 0.65; 95% CI, 0.43-0.98; P=0.04; Figure 4). The absolute risk reduction in patients with diabetes and CKD was substantial (7.0%), yielding a number needed to treat of 14 to prevent 1 major cardiovascular event over 4.8 years. In patients with diabetes and normal eGFR values, no significant treatment effect was observed with 80 mg of atorvastatin (12.8% [57/444]) vs 10 mg of atorvastatin (14.1% [62/441]) (HR, 0.90; 95% CI, 0.63-1.29; P=.56; number needed to treat = 82; Figure 4).

For all predefined secondary end points, event rates were higher in patients with diabetes and CKD than in...
those with normal eGFR values (Figure 5). In patients with diabetes and CKD, trends were toward reduction in events with 80 mg vs 10 mg of atorvastatin for all end points except peripheral artery disease and all-cause mortality; however, none of these differences were statistically significant. The primary and secondary event rates in patients with diabetes and CKD treated with 80 mg of atorvastatin remained higher than in the normal eGFR group, but were generally similar to or only slightly higher than those seen in patients with diabetes and normal eGFR values treated with the 10-mg dose of atorvastatin (Figure 5). There was no significant heterogeneity of treatment effect between patients with diabetes and CKD and patients with diabetes and normal eGFR values for any primary or secondary outcome.

**SAFETY**

Safety of 80 mg of atorvastatin in patients with diabetes and CKD was similar to that reported for the overall TNT population, with no unexpected safety concerns identified. In patients with diabetes and CKD, AEs related to treatment occurred in 22 (8.1%) receiving 80 mg of atorvastatin and in 11 (4.0%) receiving 10 mg of atorvastatin. The respective rates of discontinuation due to treatment-related AEs were 3.3% (9/273) and 0.4% (1/273). Similar rates of treatment-related AEs occurred in patients with diabetes and normal eGFR (6.3% [28/444] of patients receiving 80 mg of atorvastatin and 5.7% [25/441] of patients receiving 10 mg of atorvastatin); discontinuations because of treatment-related AEs were 3.4% [15/444] and 3.2% [14/441], respectively. Persistent elevations in liver enzymes (2 measurements of alanine aminotransferase or aspartate aminotransferase ≥3 times the upper limit of normal, obtained 4-10 days apart) were more frequent in the 80-mg atorvastatin group but were generally low and similar to those in the overall TNT population for both patients with diabetes and CKD (1.5% [4/273] vs 0.4% [1/273]) and patients with normal eGFR (0.7% [3/444] vs 0.5% [2/441]). No patient had persistent elevations in creatine kinase (2 measurements ≥10 times the upper limit of normal obtained 4-10 days apart).
INTENSIVE ATORVASTATIN TREATMENT OF PATIENTS WITH DIABETES AND CKD

The prevalence of CKD is rising in the United States, and diabetes is a major contributor to the development of CKD and end-stage renal disease. Both these clinical conditions are associated with poor medical outcomes and high health care costs. This post hoc analysis of the TNT study extends the cardiovascular benefit of aggressively lowering LDL-C to a very high-risk population of patients with stable CAD and diabetes, as well as CKD.

We observed a high frequency of CKD (approximately 38%) in this population of patients with stable CAD and diabetes, similar to the 40% estimate in patients with diabetes from the National Health and Nutrition Examination Survey (NHANES) 1999 to 2004. However, given that no urine protein measurements were available, the occurrence of CKD in this study population could have been underestimated. Consistent with recognized demographic characteristics of patients with CKD, there was greater established cardiovascular morbidity, and cardiovascular risk factors were generally more prevalent in patients with diabetes and CKD than in those with diabetes and normal eGFR values.

In accord with earlier studies, data from the TNT study have shown increased cardiovascular risk associated with both diabetes and CKD in patients with stable CAD. The current analysis of the TNT study indicates that renal function is an important independent predictor of future cardiovascular events in both the presence and absence of diabetes among patients with CAD. As other studies have shown, inherent cardiovascular risk is greater with diabetes than with CKD, yet risk of a first major cardiovascular event is approximately 30% higher in patients with CKD (eGFR <60 mL/min per 1.73 m²) than in those with normal or near-normal renal function, whether or not patients have diabetes.

Published data on the overall group of patients with diabetes from the TNT study provided direct evidence of cardiovascular risk reduction with high-dose atorvastatin therapy, irrespective of baseline LDL-C, duration of diabetes, or glycemic control. Among patients with diabetes and CKD in the current analysis, aggressive lipid-lowering therapy with 80 mg of atorvastatin resulted in a significant reduction in major cardiovascular events when compared with 10 mg of atorvastatin. No significant effect of 80 mg

<table>
<thead>
<tr>
<th></th>
<th>Patients with diabetes and CKD</th>
<th>Patients with diabetes and normal eGFR</th>
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<tbody>
<tr>
<td>Atorvastatin 10 mg</td>
<td>273</td>
<td>441</td>
</tr>
<tr>
<td>Atorvastatin 80 mg</td>
<td>273</td>
<td>444</td>
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<tr>
<td>Normal eGFR</td>
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<tr>
<td>Atorvastatin 10 mg</td>
<td>264</td>
<td>424</td>
</tr>
<tr>
<td>Atorvastatin 80 mg</td>
<td>256</td>
<td>409</td>
</tr>
</tbody>
</table>

![FIGURE 4. Time to first major cardiovascular event in patients with diabetes by treatment and baseline chronic kidney disease (CKD) status.](image)

DISCUSSION
The current observations are in part consistent with data from the Pravastatin Pooling Project, which included 19,737 high-risk patients treated with moderate-dose pravastatin or placebo. Of these patients, 4,099 had stage 2 or early stage 3 CKD, 873 had diabetes without CKD, and 517 had both conditions. Despite higher baseline LDL-C levels and higher incidence of primary cardiovascular events, there was a similar pattern of intermediate risk for patients with either CKD or diabetes only, with greatly increased risk of cardiovascular events in patients with both diabetes and CKD. Pravastatin treatment reduced the relative risk of cardiovascular events by a similar magnitude in all patient subgroups; however, the absolute reduction in risk was greatest in patients with both diabetes and CKD (6.9%), yet residual risk remained high (23.9%).

Other statins have shown modest effects on renal function in patients with CKD or diabetes in clinical trials. In the Cholesterol And Recurrent Events trial that compared 40 mg of pravastatin and placebo in patients with previous MI, pravastatin significantly reduced the rate of renal function decline in patients with more severe renal insufficiency (MDRD eGFR <40 mL/min per 1.73 m²).30

![Table showing event rates and P values for heterogeneity](image-url)

**FIGURE 5.** Primary and secondary event rates in patients with diabetes and chronic kidney disease (CKD) and patients with diabetes and normal estimated glomerular filtration rate (eGFR). CI = confidence interval.
The Heart Protection Study, which used 20 to 40 mg of simvastatin in a high-risk population, also showed a significantly smaller yearly decrease in MDRD eGFR in patients with diabetes when compared with placebo. The improvement in renal function seen in the diabetic cohort in the current subanalysis of the TNT study appears to be unique and could be related to more intensive statin therapy.

Patients with diabetes and mild to moderate CKD likely differ from those with more advanced or end-stage renal disease. Data from the German Diabetes and Dialysis (4D) study showed limited benefit with moderate-dose atorvastatin in a group of patients with diabetes and long-standing end-stage renal disease receiving hemodialysis and a complete absence of benefit for stroke as well as a 2-fold increase in the risk of fatal stroke. The 4D investigators suggested that atorvastatin therapy should be initiated early in the course of CKD, because potential benefits would be attenuated if therapy were postponed until the development of end-stage renal disease. The cardiovascular benefits observed in the current analysis of TNT patients, together with other data in patients with diabetes and predominantly early stage CKD, support this conclusion. Further, high-dose atorvastatin showed some benefit for the outcomes of stroke and cerebrovascular events.

Use of statins as lipid-lowering agents in patients with diabetes is well established, and current recommendations suggest lowering LDL-C to a level below 70 mg/dL in patients with CAD and diabetes, and recommendations for patients with diabetes and CKD also suggest an optional LDL-C goal of less than 70 mg/dL. Concerns about potential toxicity in patients with impaired renal clearance could have limited the widespread use of statins in the CKD population. However, recent recommendations from the National Lipid Association Statin Safety Assessment Task Force indicate that CKD should not preclude use of a statin. The significant cardiovascular benefits of 80 mg/d of atorvastatin in patients with stable CAD, diabetes, and mild to moderate CKD were achieved without additional safety concerns or increased risk, consistent with other data that have shown low toxicity and favorable tolerability with high-dose atorvastatin.

The current analysis has several limitations. Categorization of patients by CKD on the basis of eGFR is subject to the limitations of the MDRD formula. However, the difference in baseline serum creatinine between patients with CKD and those with normal or near-normal eGFR provides a useful indication that the MDRD assessment of eGFR differences was accurate. General comparisons of TNT data to other diabetes and CKD populations without CAD were accurate. General comparisons of TNT data to other diabetes and CKD populations without CAD were accurate. Nonetheless, the longer duration of diabetes in patients with CKD suggests that the renal insufficiency was a complication of diabetes. Conclusions regarding patients with diabetes and without CKD are limited given the few patients included in this post hoc analysis, although there was no significant heterogeneity of treatment effect on the basis of CKD status. Conclusions are also limited to patients with diabetes and mild to moderate CKD because no patient with end-stage renal disease was enrolled in TNT.

CONCLUSION

This TNT subanalysis indicates that mild to moderate CKD is an important comorbidity that imparts additional cardiovascular risk to patients with diabetes and CAD. Contrary to observations of patients with diabetes and end-stage renal disease, clear benefits can be attained with lipid-lowering therapy in patients with diabetes and mild to moderate renal insufficiency, and such therapy should be initiated early in the course of kidney disease for optimal patient benefit. These data support the existing guidelines that recommend the use of high-dose statin therapy to achieve lower LDL-C levels for the prevention of cardiovascular events in high-risk patients.

We acknowledge the contribution of David DeMicco, PharmD, an employee of Pfizer, to the development of the submitted manuscript.

A full list of the Treating to New Targets Steering Committee and Investigators has been published.

REFERENCES


25. Brossius FC III, Hostetter TH, Kekuopous E, et al. Detection of chronic kidney disease in patients with or at increased risk of cardiovascular disease: a science advisory from the American Heart Association Kidney And Cardiovascular Disease Council; the Councils on High Blood Pressure Research, Cardiovascular Disease in the Young, and Epidemiology and Prevention; and the Quality of Care and Outcomes Research Interdisciplinary Working Group; developed in collaboration with the National Kidney Foundation. Circulation. 2006 Sep 5;114(10):1083-1087. Epub 2006 Aug 7.


