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Relation of Improvement in Estimated Glomerular Filtration Rate With *Atorvastatin* to Reductions in Hospitalizations for Heart Failure (from the Treating to New Targets [TNT] Study)

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Impaired kidney function often accompanies heart failure (HF) and is associated with a worse prognosis. This post hoc analysis of the Treating to New Targets (TNT) trial examined whether the observed decrease in HF hospitalizations with high- compared to low-dose atorvastatin could be related to improvements in kidney function. Of 10,001 TNT participants, 9,376 had estimated glomerular filtration rate (eGFR) measurements at baseline and 1 year and were included in this analysis. The association of change in year-1 eGFR and subsequent HF hospitalization was examined using Cox regression models. In total 218 participants developed subsequent HF hospitalization. Little change in eGFR occurred over 1 year in the atorvastatin 10-mg group, whereas eGFR improved in the 80-mg group by 1.48 ml/min/1.73 m^2 (95% confidence interval 1.29 to 1.67, $p < 0.0001$). Subsequent HF was preceded by a decrease in eGFR over 1 year compared to modest improvement in those without subsequent HF (-0.09 ± 7.89 vs 0.81 ± 6.90 ml/min/1.73 m^2, $p = 0.0015$). After adjusting for baseline eGFR, each 5-ml/min/1.73 m^2 increase in eGFR at 1 year was associated with a lower risk of subsequent HF hospitalization (hazard ratio 0.85, 95% confidence interval 0.77 to 0.94, $p = 0.002$). This relation was independent of treatment effect or change in low-density lipoprotein cholesterol level at 1 year. In conclusion, treatment with high- compared to low-dose atorvastatin was associated with improvement in eGFR at 1 year, which was related to a decrease in subsequent HF hospitalization. This suggests that improvement in kidney function may be related to the beneficial effect of high-dose atorvastatin on HF hospitalization. **© 2012 Elsevier Inc. All rights reserved.** **(Am J Cardiol 2012;109:1761–1766)**

In clinical trials, treatment with atorvastatin has been associated with improved estimated glomerular filtration rate (eGFR) in patients with diabetes mellitus, chronic coronary disease, and cerebrovascular disease.[1–5] In the Treating to New Targets (TNT) trial, the mean increase in eGFR was significantly greater in the atorvastatin 80-mg group compared to the 10-mg group, suggesting that this improvement is dose dependent.[2] Treatment with high-dose atorvastatin was also associated with a significant decrease in rate of heart failure (HF) hospitalizations compared to low-dose treatment.[6] We sought to investigate whether the observed decrease in HF hospitalizations with high-dose atorvastatin was related to improvements in kidney function. The purpose of this post hoc analysis of TNT was threefold: (1) to examine the effect of change in eGFR from baseline to 1 year on subsequent rate of HF hospitalizations, (2) to investigate whether treatment effect (high- vs low-dose atorvastatin) modified the relation between eGFR and HF hospitalizations, and (3) to examine changes in eGFR and the potential relation of these changes to risk of HF hospitalization.

Methods

The design of the TNT study has been described in detail previously.[7,8] TNT was a randomized, double-blind parallel-group trial in men and women aged 35 to 75 years with clinically evident coronary heart disease (CHD), defined as previous myocardial infarction, previous or present angina

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Table 1
Baseline characteristics of patients with and without heart failure after one year

Characteristic	HF (n = 218)		No HF (n = 9,158)	
	Atorvastatin 10 mg (n = 118)	Atorvastatin 80 mg (n = 100)	Atorvastatin 10 mg (n = 4,578)	Atorvastatin 80 mg (n = 4,580)
Age (years)	65.9 ± 6.9	65.3 ± 7.3	60.7 ± 8.9	61.1 ± 8.7
Men	91 (77%)	74 (74%)	3,713 (81%)	3,743 (82%)
Caucasian race	115 (98%)	88 (88%)	4,314 (94%)	4,327 (95%)
Systolic blood pressure (mm Hg)	136 ± 19	136 ± 18	131 ± 17	131 ± 17
Diastolic blood pressure (mm Hg)	77 ± 9	76 ± 11	78 ± 10	78 ± 9
Body mass index (kg/m^2)	30.1 ± 5.4	29.7 ± 5.5	28.6 ± 4.6	28.4 ± 4.4
Current smoker	18 (15%)	17 (17%)	605 (13%)	582 (13%)
Heart failure	46 (39%)	29 (29%)	304 (7%)	306 (7%)
Hypertension	94 (80%)	77 (77%)	2,428 (53%)	2,441 (53%)
Diabetes mellitus	45 (38%)	45 (45%)	642 (14%)	649 (14%)
Myocardial infarction	71 (60%)	66 (66%)	2,631 (58%)	2,685 (59%)
Cerebrovascular accident	18 (15%)	11 (11%)	224 (5%)	221 (5%)
Peripheral arterial disease	31 (26%)	37 (37%)	493 (11%)	528 (12%)
Coronary revascularization				
Angioplasty	62 (53%)	54 (54%)	2,499 (55%)	2,460 (54%)
Bypass surgery	76 (64%)	66 (66%)	2,103 (46%)	2,112 (46%)
β Blocker	53 (45%)	48 (48%)	2,471 (54%)	2,491 (54%)
Angiotensin-converting enzyme inhibitor	55 (45%)	53 (53%)	1,201 (26%)	1,225 (27%)
Angiotensin receptor blocker	16 (14%)	9 (9%)	238 (5%)	224 (5%)
Aldosterone antagonist	23 (20%)	24 (24%)	77 (2%)	75 (2%)
Aspirin	87 (74%)	73 (73%)	3,982 (87%)	3,991 (87%)
Diuretic	53 (45%)	51 (51%)	608 (13%)	589 (13%)
Calcium channel blockers	35 (30%)	47 (47%)	1,175 (26%)	1,251 (27%)
Antiplatelet therapy	3 (3%)	3 (3%)	137 (3%)	141 (3%)
Lipids (mg/dl)				
Low-density lipoprotein cholesterol	98 ± 19	100 ± 16	98 ± 18	97 ± 17
Total cholesterol	178 ± 22	176 ± 23	174 ± 24	175 ± 24
Triglycerides	180 ± 76	155 ± 76	149 ± 71	150 ± 69
High-density lipoprotein cholesterol	44 ± 9	45 ± 11	47 ± 11	48 ± 11
Baseline estimated glomerular filtration rate (ml/min/1.73 m^2)	55.8 ± 13.6	63.1 ± 12.6	65.7 ± 11.5	65.1 ± 11.2

with atherosclerotic CHD, or a previous coronary revascularization procedure. To ensure that all patients achieved low-density lipoprotein (LDL) cholesterol levels consistent with then-current guidelines, patients with LDL cholesterol from 130 to 250 mg/dl (3.4 to 6.5 mmol/L) after a wash-out period took open-label treatment with atorvastatin 10 mg/day for 8 weeks. After this run-in period, 10,001 patients with LDL cholesterol <130 mg/dl (<3.4 mmol/L) were randomized to atorvastatin 10 or 80 mg/day and were followed for a median of 4.9 years.

Patients with a known left ventricular ejection fraction <30% or symptoms of advanced HF (New York Heart Association class IIIb or IV) were excluded from the study, as were those with nephrotic syndrome. Of 10,001 subjects enrolled in TNT, 625 were excluded according to the following criteria (310 in atorvastatin 10-mg group, 315 in 80-mg group): missing baseline eGFR data (n = 345), missing year-1 eGFR (n = 229), and death or HF hospitalization before 1 year (n = 51), leaving 9,376 subjects for this analysis.

The main end point of this analysis was hospitalization with a primary diagnosis of HF, which was a prespecified secondary efficacy outcome of TNT. Hospitalization for HF was defined according to the following criteria: (1) the patient was hospitalized with a primary admission diagnosis of HF and demonstrated symptoms and signs consistent with this clinical diagnosis, (2) cause of HF was related to impaired left ventricular emptying or filling characteristics, and (3) cause of HF was not temporally related to an acute myocardial infarction.[6] An independent end-point committee blinded to treatment assignment adjudicated all potential end-point events.

Serum creatinine was measured and eGFR was estimated using the Modification of Diet in Renal Disease equation (eGFR in milliliters per minute per 1.73 m^2 = 175 × serum creatinine × age × 0.742 if a woman, × 1.212 if African-American)[9] as recommended by the National Kidney Foundation Kidney Disease Outcomes Quality Initiative.[10]

Baseline characteristics were depicted by treatment group (high- vs low-dose atorvastatin) and by subsequent HF hospitalization status. Renal function between treatment groups and subsequent HF hospitalization status were compared using 2-sample *t* tests for baseline and year-1 eGFR measurements. Change in year-1 eGFR was compared

Table 2
Changes in estimated glomerular filtration rate from baseline to one year in treatment groups

Variable	Atorvastatin 10 mg (n = 4,696)	Atorvastatin 80 mg (n = 4,680)	Total (n = 9,376)	p Value*
Estimated glomerular filtration rate (ml/min/1.73 m^2)				
Baseline	65.6 ± 11.4	65.0 ± 11.3	65.3 ± 11.3	0.018
1 year	65.7 ± 11.8	66.6 ± 11.9	66.1 ± 11.9	0.0002
Change from baseline to 1 year	0.1 ± 6.8	1.5 ± 7.0	0.8 ± 6.9	<0.0001
Comparison of 1 year to baseline within treatment group†	0.10 (−0.09 to 0.30)	1.48 (1.29–1.67)	0.79 (0.65–0.93)	
p Value	0.29	<0.0001	<0.0001	

* Values for between-treatment estimated glomerular filtration rate were based on 2-sample *t* tests.
† Values are presented as least square means or means difference (95% confidence interval); values for within- and between-treatment comparisons were based on an analysis of covariance model comparing patients with to those without heart failure hospitalization that was adjusted for baseline estimated glomerular filtration rate.

Table 3
Changes in estimated glomerular filtration rate from baseline to one year in patients with and without subsequent heart failure hospitalization

Variable	HF Hospitalization		p Value*
	No (n = 9,158)	Yes (n = 218)	
Modification of Diet in Renal Disease estimated glomerular filtration rate (ml/min/1.73 m^2)			
Baseline	65.4 ± 11.2	61.3 ± 13.9	<0.0001
1 year	66.2 ± 11.8	61.2 ± 14.5	<0.0001
Change from baseline to 1 year	0.8 ± 6.9	−0.1 ± 7.9	0.0015
Comparison of 1 year to baseline within treatment group†	0.82 (0.69–0.96)	−0.65 (−1.54 to 0.25)	
p Value	<0.0001	0.16	

* Values for between-treatment estimated glomerular filtration rate were based on 2-sample *t* tests.
† Least square means or means difference (95% confidence interval) for within- and between-treatment comparisons were based on an analysis of covariance model comparing patients with to those without heart failure hospitalization that was adjusted for baseline estimated glomerular filtration rate.

within and between groups using least squares means and analysis of covariance models with treatment group as the major predictor and baseline eGFR as the covariate. Cox proportional hazards regression was used to assess the effect of change in year-1 eGFR on subsequent HF hospitalization. Nested models were created, adjusting for baseline eGFR, treatment, and change in LDL cholesterol from baseline to year 1. Based on previous data showing a significant treatment effect on subsequent HF hospitalization, analyses were repeatedly stratified by treatment. The potential interaction of treatment group and year-1 eGFR was tested.

Results

Of the 9,376 patients included in this analysis, 218 underwent HF hospitalization after 1 year, 100 of 4,680 in the atorvastatin 80-mg group and 118 of 4,696 in the 10-mg group (2.1% vs 2.5%, hazard ratio [HR] 0.85, 95% confidence interval [CI] 0.65 to 1.11, p = 0.23). Clinical characteristics of patients with and without HF hospitalization after 1 year are listed in Table 1. Clinical features of patients in the 10- and 80-mg groups were similar. There was no significant difference in proportion of patients with previous HF between treatment groups (7.5% in atorvastatin 10-mg group vs 7.2% in 80-mg group, p = 0.61). About 1/3 of participants who developed subsequent HF had a history of HF. Participants who had subsequent HF hospitalizations were older and had a higher prevalence of cardiovascular risk factors including previous HF, diabetes mellitus, hypertension, and peripheral arterial disease. In addition, those with subsequent HF were less frequently treated with β blockade and more frequently treated with angiotensin-converting enzyme inhibitors, aldosterone blockade, and diuretics.

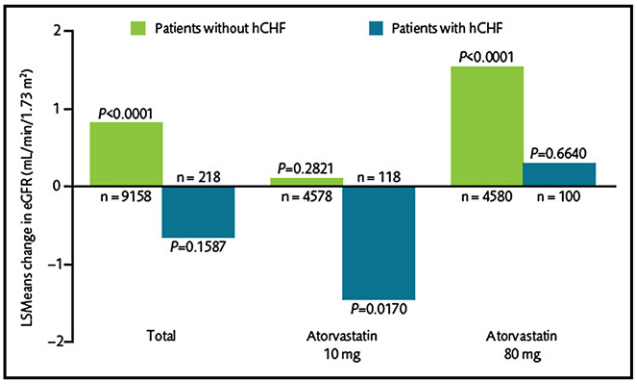

Figure 1. Change in estimated glomerular filtration rate from baseline to year 1 in participants with and without subsequent heart failure hospitalization by treatment subgroup (high- vs low-dose atorvastatin). hCHF = hospitalization for congestive heart failure; LSMeans = least square means.

Despite being significantly lower at baseline, eGFR values were higher at 1 year in the atorvastatin 80-mg compared to the 10-mg group (p = 0.0002), as shown in Table 2. Little change occurred in eGFR from baseline to 1 year with atorvastatin 10 mg (p = 0.29), whereas significant

Table 4
Change in eGFR from baseline to Year 1 predicts subsequent risk of heart failure hospitalization

Model	HR	95% CI	p-value
Unadjusted model			
Change in eGFR at 1 year	0.91	0.83–1.01	0.07
Multivariable model			
Change in eGFR at 1 year	0.85	0.77–0.94	0.002
Baseline eGFR, per 5 ml/min/1.73m^2	0.83	0.79–0.88	<0.0001
Treatment effect (atorvastatin 80 versus 10 mg)	0.81	0.58–1.12	0.20
Change in LDL-C at 1 year, per 10 mg/dL	0.97	0.90–1.05	0.43

HR = hazard ratio; CI = confidence interval; eGFR = estimated glomerular filtration rate; LDL-C = low density lipoprotein cholesterol.

improvement in 1-year eGFR was observed with atorvastatin 80 mg (least squares means 1.48 ml/min/1.73 m^2, 95% CI 1.29 to 1.67; p <0.0001). Improvement in eGFR from baseline to 1 year was greater with atorvastatin 80 mg compared to 10 mg (1.52 ± 7.02 vs 0.07 ± 6.77, p <0.0001). The 5-year change in eGFR in the 2 groups was incrementally higher, suggesting time- and dose-dependent increases, which met statistical significance (data not shown).[2]

As presented in Table 3, baseline and year-1 eGFR were significantly lower in patients with subsequent HF hospitalization compared to those without HF. Subsequent HF hospitalization was preceded by a decrease in eGFR over 1 year compared to modest improvement in those without subsequent HF. Mean difference between the 2 groups for change in eGFR at 1 year was 1.47 ml/min/1.73 m^2 (p = 0.0015). Changes in patients with and without subsequent HF per atorvastatin treatment group are depicted in Figure 1. In the 10-mg group, eGFR did not change over 1 year in patients without HF but decreased in patients with subsequent HF hospitalization (p = 0.017); in the 80-mg group, eGFR increased in patients without HF (p <0.0001) but did not change significantly in patients with subsequent HF.

After adjusting for baseline eGFR, each 5-ml/min/1.73 m^2 increase in eGFR from baseline to year 1 was associated with a lower risk of subsequent HF hospitalization (HR 0.85, 95% CI 0.77 to 0.94, p = 0.002), as presented in Table 4. This effect remained significant after adjustments were made for randomized treatment assignment and/or change in LDL cholesterol levels at 1 year. Conversely, after adjusting for baseline and 1-year change in eGFR, treatment effect and 1-year change in LDL cholesterol levels were no longer predictive of subsequent HF hospitalization. There was no significant interaction between treatment and 1-year change in eGFR (p = 0.89).

In a Cox proportional hazard model adjusting for baseline eGFR and treatment as the stratification variable, change in eGFR was a predictor of hospitalization for HF (HR 0.85, 95% CI 0.77 to 0.95, p = 0.002). In a Cox proportional hazard model by treatment group adjusting for baseline eGFR, change in eGFR remained a predictor of hospitalization for HF in the atorvastatin 10-mg group (HR 0.84, 95% CI 0.72 to 0.96, p = 0.013) and was of borderline statistical significance in the 80-mg group (HR 0.87, 95% CI 0.78 to 1.01, p = 0.067).

Discussion

In this retrospective analysis from the TNT trial, we sought to explore the relation among high- and low-dose atorvastatin treatment, changes in eGFR, and subsequent HF hospitalizations. Our main findings were threefold. First, treatment with high-dose atorvastatin was associated with a significant improvement in eGFR at year 1 compared to low-dose treatment. Second, improvement in eGFR at 1 year was associated with a significant decrease in subsequent HF hospitalization. Third, the previously established association between high-dose atorvastatin treatment and decrease in HF hospitalizations in TNT[6,8] was related to improvements in kidney function.

Mean changes in eGFR over the first year of treatment with atorvastatin reported in our analysis were quite small; however, over the full follow-up period of 4.9 years, eGFR increased by a mean of 3.5 ± 0.14 and a mean of 5.2 ± 0.14 ml/min/1.73 m^2 in the low- and high-dose atorvastatin groups, respectively.[2] This improvement in eGFR with atorvastatin has also been demonstrated in other trials including the Collaborative Atorvastatin Diabetes Study (CARDS),[1] the Greek Atorvastatin and Coronary Heart Disease Evaluation (GREACE),[3] the Incremental Decrease in End Points through Aggressive Lipid-lowering (IDEAL) trial,[11] and the Aggressive Lipid-Lowering Initiation Abates New Cardiac Events (ALLIANCE) trial.[4] These increases contrast with the expected age-related decrease that occurs in eGFR over time. In previous trials of patients with CHD, eGFR decreased up to 6.7 ml/min in control groups during 5 years of follow-up.[12] Although 1- and 5-year increases in eGFR may be small, any modification in the expected eGFR may be clinically relevant and mitigate associated cardiovascular morbidity and mortality.

Long-term effects of other statins on eGFR appear to be variable, with a slower decrease in eGFR over time with simvastatin[13] and pravastatin[14] compared to placebo but no clear protective effect with fluvastatin[15] or rosuvastatin[16,17] in other trials. Effects of different statins on kidney function have rarely been compared in the same randomized long-term study. In the IDEAL study, changes in eGFR over 5 years of follow-up were improved in the atorvastatin 80-mg compared to the simvastatin 20- to 40-mg groups.[11] Of note, high-dose atorvastatin in IDEAL was also associated with a decreased risk of HF hospitalization compared to simvastatin,[18] supporting the findings of our analysis. In the Prospective Evaluation of Proteinuria and Renal Function in

Diabetic (and Nondiabetic) Patients with Progressive Renal Disease (PLANET I and II), atorvastatin 80 mg was compared to rosuvastatin 10 or 40 mg/day in 325 patients with diabetes (PLANET I) and 220 patients without diabetes (PLANET II) over 52 weeks (de Zeeuw D. 2010 European Renal Association–European Dialysis and Transplant Association Congress. Munich (Germany), June 17, 2010). In PLANET I, atorvastatin had no significant effect on eGFR but eGFR decreased by approximately 4 ml/min/1.73 m^2 on rosuvastatin 10 mg and by approximately 8 ml/min/1.73 m^2 on 40 mg. Atorvastatin, but not rosuvastatin, treatment was associated with a 20% decrease in proteinuria. Acute renal failure or doubling or serum creatinine levels occurred significantly more often in the rosuvastatin 40-mg group. In PLANET II, eGFR decreased significantly in the rosuvastatin 40-mg group but did not change in the atorvastatin 80-mg or rosuvastatin 10-mg group.

Our group has previously shown a decreased incidence of HF hospitalization with high- versus low-dose atorvastatin in TNT (HR 0.74, 95% CI 0.59 to 0.94, $p = 0.012$).[6] In patients with chronic HF enrolled in the Controlled Rosuvastatin Multinational Trial in Heart Failure (CORONA), treatment with rosuvastatin decreased the number of HF hospitalizations compared to placebo in patients with systolic HF, although the primary composite cardiovascular end point was not different between groups.[19] The Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardio - Heart Failure (GSSI-HF) trial, however, showed that patients with ischemic and nonischemic cardiomyopathies treated with rosuvastatin versus placebo had similar rates for all outcomes including HF hospitalization.[20]

Other statins have not been tested in large, long-term, randomized trials in patients with HF. However, in a retrospective analysis, simvastatin was reported to decrease the incidence of HF in the Scandinavian Simvastatin Survival Study (4S).[21] In the Pravastatin or Atorvastatin Evaluation and Infection Trial (PROVE IT) involving 4,162 patients with recent acute coronary syndrome, those assigned to atorvastatin 80 mg had a lower incidence of HF compared to those assigned to pravastatin 40 mg (1.6% vs 3.1%, HR 0.55, 95% CI 0.35 to 0.85, $p = 0.008$).[22] A meta-analysis of 4 large trials comparing aggressive to moderate statin therapy and including 27,546 subjects demonstrated a 27% decrease in HF hospitalization in the more aggressively treated groups (odds ratio 0.73, 95% CI 0.63 to 0.84, $p < 0.001$).[22]

Although the progression of HF is closely linked to recurrent ischemic events,[23] most HF hospitalizations in TNT were not precipitated by acute ischemic events,[6] which raises the question of potential pleiotropic effects independent of anti-atherothrombotic mechanisms. Our findings suggest that the link between high-dose atorvastatin treatment and decreased HF hospitalizations may be improvements in eGFR and that this effect is independent of LDL cholesterol lowering.

HF and chronic kidney disease share multiple pathophysiologic mechanisms including neurohormonal activation, inflammation, endothelial dysfunction, and increased oxidative stress. Statins may counteract sympathetic upregulation in HF by decreasing norepinephrine levels and decreasing renal sympathetic nerve activity.[24] Anti-inflammatory effects may be mediated by decreased activation of transcription factor nuclear factor κB, which in turn regulates proinflammatory cytokines.[25] Statins also inhibit reduced nicotinamide adenine dinucleotide phosphate oxidase and free radical production.[26] This limits LDL oxidation, which has beneficial cardiac effects and inhibits the proliferative effects of oxidized LDL on renal mesangial cells.[27] Statins also improve endothelial dysfunction by blocking the mevalonate pathway and decreasing Ras and Rho production, which in turn prevent cell proliferation and hypertrophy and increase nitric oxide production.[28] Increased nitric oxide availability has been shown to prevent end-organ damage including decreased proteinuria in a rat hypertension model.[29] It may be that these pleiotropic actions indirectly influence HF outcomes by improving kidney function or directly affect progression of HF.

Our study has limitations. This analysis is post hoc in nature and the observed association between improvements in eGFR and decreases in HF hospitalization is exploratory; therefore, inferences about causality cannot be drawn. Patients with symptoms of advanced HF or a known ejection fraction <30% were excluded from TNT; however, 7% of the study population had pre-existing HF ascertained by questionnaire at time of enrollment. Given the limited information on type of HF and left ventricular function, generalizations should be made with caution. Furthermore, adjudicated HF outcomes in TNT did not examine left ventricular function and therefore include preserved and decreased ejection fraction HF. Modification of Diet in Renal Disease–derived eGFR is the gold standard of estimating GFR in practice and has been extensively validated in HF populations. However, proteinuria and other renal biomarkers that were not measured in TNT may have provided a better representation of GFR or tubulointerstitial damage than serum creatinine and derived eGFR.

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