Intensive Statin Therapy and the Risk of Hospitalization for Heart Failure After an Acute Coronary Syndrome in the PROVE IT–TIMI 22 Study

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OBJECTIVES

We aimed to determine whether intensive statin therapy reduces hospitalization for heart failure (HF) in high-risk patients.

BACKGROUND

While the relationship between intensive statin therapy and ischemic events is well established, its relationship to the risk of HF after an acute coronary syndrome (ACS) is not well defined.

METHODS

The Pravastatin or Atorvastatin Evaluation and Infection Trial–Thrombolysis In Myocardial Infarction 22 (PROVE IT–TIMI 22) study randomized 4,162 patients, stabilized after ACS, to either intensive statin therapy (atorvastatin 80 mg) or moderate statin therapy (pravastatin 40 mg). Hospitalization for HF occurring more than 30 days after randomization was determined during a mean follow-up of 24 months. B-type natriuretic peptide (BNP) levels were measured at baseline (median seven days after randomization).

RESULTS

Treatment with atorvastatin 80 mg significantly reduced the rate of hospitalization for HF (1.6% vs. 3.1%, hazard ratio [HR] 0.55, 95% confidence interval [CI] 0.35 to 0.85, p = 0.008) independently of a recurrent myocardial infarction or prior history of HF. The risk of HF increased steadily with increasing quartiles of BNP (HR 2.6, 95% CI 1.2 to 5.5, p = 0.016 for the highest quartile compared with the lowest). Among patients with elevated levels of BNP (>80 pg/ml), treatment with atorvastatin significantly reduced the risk of HF compared with pravastatin (HR 0.32, 95% CI 0.13 to 0.8, p = 0.014). A meta-analysis of four trials that included 27,546 patients demonstrates a 27% reduction in the odds of hospitalization for HF with intensive statin therapy.

CONCLUSIONS

Intensive statin therapy reduces the risk of hospitalization for HF after ACS with the most gain in patients with elevated levels of BNP. (J Am Coll Cardiol 2006;47:2326–31) © 2006 by the American College of Cardiology Foundation

Lipid-lowering therapy, and in particular intensive statin therapy, reduces the risk of death and recurrent ischemia in patients hospitalized for an acute coronary syndrome (ACS) (1) and in patients with chronic coronary artery disease (2,3). The relationship between statin therapy and congestive heart failure (HF) is less well described with some investigators raising theoretical concerns that statins could worsen HF. For example, in one study, low cholesterol levels were associated with worse outcomes among patients with HF (4) while another study suggested that statins, via inhibition of the mitochondrial enzyme ubiquinone, may decrease myocardial contraction (5). Trials that compared moderate dose statin therapy versus placebo in stable patients have reported conflicting results with some showing a benefit of statin therapy (6) while others have not (7–10). The primary reports from trials of intensive statin therapy suggest that higher doses of statin may reduce rates of rehospitalization for HF when compared with moderate statin therapy, but there are few details (2,3,11).

Heart failure is an important cause of morbidity and mortality in patients with ACS and is gaining in relative importance as effective therapies reduce the risk of recurrent ischemia (12,13). Identifying those patients at high risk for developing HF after ACS is clearly of clinical importance. The use of biomarkers, in particular B-type natriuretic peptide (BNP) (14,15), has improved the clinician’s ability to identify patients who are at high risk of death or HF after an ACS. However, the influence of intensive statin therapy on this risk is unknown.

METHODS

The Pravastatin or Atorvastatin Evaluation and Infection Trial–Thrombolysis In Myocardial Infarction 22 (PROVE IT–TIMI 22) study has been reported in detail previously (1,16). This trial enrolled 4,162 patients hospitalized for ACS—either acute myocardial infarction (with or without ST-segment elevation) or high-risk unstable angina—in the preceding 10 days. Eligible patients were in stable condition and had a total cholesterol level within the first 24 h after the onset of the index event that was <240 mg/dl (6.21 mmol/l), or <200 mg/dl (5.18 mmol/l) if they were on prior
lipid-lowering therapy. Patients were ineligible for the study if they had a co-existing condition that shortened expected survival to <2 years, had undergone percutaneous coronary intervention within the previous six months (other than for the qualifying event), or coronary artery bypass surgery within the previous two months, or were scheduled to undergo bypass surgery in response to the index event.

**Study protocol.** The protocol specified that patients were to receive standard medical and interventional treatment for ACS. Eligible patients were randomly assigned in a 1:1 ratio to receive 40 mg of pravastatin or 80 mg of atorvastatin daily in a double-blind, double-dummy fashion. Patients were seen for follow-up visits at 30 days, 4 months, and every 4 months thereafter until their final visit. Plasma samples included in this analysis were obtained at baseline in 3,752 patients, and measurements were made in a core facility (Brigham and Women’s Hospital, Boston, Massachusetts). A validated assay for BNP (ADVIA Centaur BNP, Bayer Healthcare Diagnostics, Tarrytown, New York) was used, and concentrations were evaluated as quartiles: BNP ≤15 pg/ml (n = 1,032) for quartile 1, BNP 16 to 32 pg/ml (n = 867) for quartile 2, BNP 33 to 65 pg/ml (n = 928) for quartile 3, and BNP >65 pg/ml (n = 925) for quartile 4 and with the cut-point of 80 pg/ml (17).

**End points.** Heart failure was defined by the need for hospitalization for the condition. The primary efficacy outcome for this analysis was the time from randomization to the first occurrence of hospitalization for congestive HF that occurred 30 days or longer after randomization. Myocardial infarction was defined by the presence of symptoms suggestive of ischemia or infarction, with either electrocardiographic evidence (new Q waves in two or more leads) or cardiac-marker evidence of infarction (1,16).

**Statistical analysis.** All analyses are based on the intention-to-treat principle. Cumulative event curves of hospitalization for HF derived from Kaplan-Meier estimates are presented. Estimates of the hazard ratios (HRs) and associated 95% confidence intervals (CIs) comparing pravastatin with atorvastatin were obtained with a Cox proportional hazards model with randomized treatment as the covariate. For analyses including BNP, cumulative event curves of hospitalization for HF derived from Kaplan-Meier estimates are presented along with the HR from a Cox proportional hazards model that included age, gender, diabetes, hypertension, body mass index, creatinine, index diagnosis, and percutaneous coronary intervention during the index event.

We performed a meta-analysis of four large randomized trials that compared an intensive versus moderate statin therapy in high-risk cardiac patients: the PROVE IT–TIMI 22 trial that compared 40 mg of pravastatin versus 80 mg of atorvastatin in patients stabilized after ACS (1); the Treating to New Targets (TNT) trial that compared 10 versus 80 mg of atorvastatin in patients with stable coronary disease (2); the A to Z trial that compared 20 versus 80 mg of simvastatin in ACS patients (11); and the Incremental Decrease in Clinical End Points Through Aggressive Lipid Lowering (IDEAL) trial that compared 20 mg of simvastatin versus 80 mg of atorvastatin in patients with a history of myocardial infarction (3). Summary data on the rates of congestive HF were abstracted from the publications of the other trials. Odds ratios (ORs) and 95% CIs for the effect of intensive statin therapy versus moderate statin therapy on the incidence of HF were calculated for each trial. The results from trials were combined using a random-effects model that used weighting based on inverse variance. Between-trial heterogeneity was assessed. All statistical analyses were performed using Stata/SE, version 9.1 (Stata-Corp. LP, College Station, Texas).

**RESULTS**

**Benefit of intensive statin therapy of HF.** This analysis included all 4,162 patients enrolled in the PROVE IT–TIMI 22 study. As previously described, patients were enrolled a median of seven days after onset of their index event, and there were no differences between treatment groups in terms of age, gender, index diagnosis, or rates of prior myocardial infarction, revascularization, diabetes, or hypertension (1). There were also no differences in the rate of prior HF between treatment arms (3.2% for atorvastatin vs. 3.5% for pravastatin, p = NS), the rate of ST-segment elevation myocardial infarction (33.4% vs. 35.6%, p = NS), or the rate of revascularization for the index event (69.1% vs. 68.7%, p = NS).

Treatment with atorvastatin 80 mg was associated with a significant 45% reduction in the rate of hospitalization for HF (1.6% vs. 3.1% [HR 0.55, 95% CI 0.35 to 0.85, p = 0.008]) (Fig. 1). This reduction in the risk of HF was not attenuated when controlling for recurrent myocardial infarction (HR 0.58, 95% CI 0.37 to 0.90, p = 0.016) or a history of prior HF (HR 0.55, 95% CI 0.35 to 0.86, p = 0.008). The benefit of atorvastatin 80 mg was similar after excluding all patients (n = 36) who developed HF after having suffered a recurrent myocardial infarction or recurrent ischemia requiring hospitalization or revascularization (HR 0.47, 95% CI 0.26 to 0.86, p = 0.015). The benefit of intensive statin therapy was also similar when the first 30 days after randomization were included in the analysis (HR 0.53, 95% CI 0.35 to 0.80, p = 0.002).

**BNP and the risk of HF.** Compared with those without subsequent hospitalization for HF, patients who developed HF had higher baseline levels of BNP (median 58 vs. 31 pg/ml, p < 0.001) and were more likely to have a concentration of BNP >80 pg/ml (41.2% vs. 23.2%, p < 0.001).
The concentration of BNP showed a significant graded relationship with the risk of HF, with a significantly higher risk of HF among patients in the highest (BNP >65 pg/ml) compared with the lowest quartile (BNP <15 pg/ml, adjusted HR 2.6, 95% CI 1.2 to 5.5, p = 0.016).

**Intensive statin therapy and BNP.** There was no difference in baseline levels of BNP between treatment arms (31 vs. 32 ng/l, p = NS). When examined by elevated (≥80 pg/ml) or normal (<80 pg/ml) baseline levels of BNP and treatment arm, patients with elevated baseline levels (≥80 pg/ml) of BNP randomized to pravastatin had the highest rate of hospitalization for HF (6.9%) followed by those patients with normal BNP randomized to pravastatin (2.3%), patients with an elevated BNP randomized to atorvastatin (2.2%), and then patients normal baseline levels of BNP randomized to atorvastatin were at 1.2% (Fig. 2). Assignment to atorvastatin significantly reduced the risk of the development of HF among patients with elevated levels of BNP (HR 0.32, 95% CI 0.13 to 0.8, p = 0.014). Although patients with such elevated levels of BNP had a greater absolute reduction in the risk of HF (4.7%, HR 0.29, 95% CI 0.11 to 0.73, p = 0.009) with intensive statin therapy than patients with low BNP (1.1%, HR 0.56, 95% CI 0.29 to 1.1, p = 0.09), formal statistical testing for an interaction of BNP with the effect of treatment was not significant (p interaction = 0.32).

**Meta-analysis of intensive statin therapy trials.** A meta-analysis of the four published large, randomized trials
that compared intensive statin therapy with moderate statin therapy and that reported the rates of congestive HF demonstrates a highly significant 27% reduction in the odds of hospitalization for HF in \((n = 27,546, \text{OR} 0.73, 95\% \text{ CI} 0.63 \text{ to } 0.84, p < 0.001)\) (chi-square for heterogeneity = 2.25 [degrees of freedom = 3], \(p = 0.523\)) (Fig. 3).

**DISCUSSION**

Among patients hospitalized for an ACS, treatment with intensive statin therapy significantly reduced the subsequent development of HF requiring hospitalization. This benefit was independent of recurrent infarction suggesting that intensive statin therapy lowers the risk of HF independently of its ability to reduce recurrent ischemic injury. As anticipated, baseline levels of BNP in patients with ACS were strongly associated with the risk of future HF. However, among patients with elevated levels of BNP (>80 pg/ml), treatment with intensive statin therapy (atorvastatin 80 mg) significantly reduced the risk of HF compared with moderate statin therapy (pravastatin 40 mg); the absolute risk of development of HF in patients with such elevated levels of BNP was reduced by 4.7% by intensive statin therapy (47 hospitalizations for HF prevented per 1,000 patients treated).

Our findings, both from the PROVE IT–TIMI 22 study and from the other large randomized trials, reveal a consistent benefit of intensive statin therapy in reducing episodes of HF by 27% among more than 27,000 patients who had a low baseline incidence of prior HF. The benefit observed in the PROVE IT–TIMI 22 study was directionally, though not statistically, greater than the benefit seen in the other trials (2,3,11). This trend may be because this trial was comprised of a post-ACS population that received immediate intensive statin therapy, as opposed to the A to Z trial, another post-ACS trial, in which intensive statin therapy with simvastatin 80 mg was not started until one month after randomization. In comparison with the Scandinavian Simvastatin Survival Study (4S) trial in which a benefit of moderate dose simvastatin on HF was not observed until three years of therapy (6), the benefit of intensive statin therapy in the PROVE IT–TIMI 22 study was demonstrated at two years, with an early separation of the event curves for hospitalization for HF.

To determine whether the benefit of intensive statin therapy in reducing the occurrence of HF was due to a mechanism other than the reduction of recurrent infarction, we controlled both for the rate of recurrent infarction as well as excluded all patients who suffered a recurrent infarction. The benefit of intensive statin therapy was consistent in both of these analyses, suggesting that statins act to reduce new onset HF via pathways other than by reducing new myocardial necrosis.

There are several proposed mechanisms by which statin therapy, and in particular intensive statin therapy, may reduce the rate of HF. These proposed pathways include potential “pleiotropic” actions of statins, such as decreases in both Ras and Rho protein production via blockade of the mevalonate pathway, which, in turn, prevents cell proliferation and hypertrophy (Ras) (18) and increases nitric oxide production (Rho) (18,19). These effects may, in turn, improve vascular function and potentially enhance ventricular function. A small randomized trial, for example, demonstrated improved ventricular function with one-year of therapy with 20 mg of atorvastatin compared with placebo in patients with non-ischemic cardiomyopathy (20). This finding may provide a mechanistic explanation to the improved outcomes associated with statin therapy observed in several retrospective studies of patients with chronic HF (21–23).

**Figure 3.** Benefit of intensive statin therapy versus moderate statin therapy in reducing the risk of hospitalization for heart failure in 27,546 patients. This analysis includes the Pravastatin or Atorvastatin Evaluation and Infection Trial–Thrombolysis In Myocardial Infarction 22 (PROVE IT–TIMI 22) (1), Treating to New Targets (TNT) (2), A to Z (11), and Incremental Decrease in End Points Through Aggressive Lipid Lowering (IDEAL) (3) studies.
The effect of statins on circulating markers of inflammation in patients with HF has resulted in conflicting results. Several studies in patients with HF have shown that statins reduce biomarkers such as C-reactive protein, endothelin-1 (24), and tumor necrosis factor-alpha (22). On the other hand, another study that compared atorvastatin 80 mg to placebo did not demonstrate any change in levels of inflammatory, hemostatic, or neurohormonal markers after 12 weeks of intense statin therapy (25). The apparent discrepancy in findings may be due to the relative severity of HF in the different studies (the majority of the patients in the negative trial were in class II failure [25] while in the other studies they were class III or IV) and in the duration of therapy (24,26). Studies with longer follow-up are needed to resolve the important questions concerning potential mechanisms of beneficial action seen with statin therapy.

Identifying patients at high risk for developing HF after ACS is clearly of clinical importance. Several reports have now shown that elevated baseline concentrations of BNP are associated with the development of HF after an ACS (14,15). As confirmed in this analysis, measurement of BNP in the different studies (the majority of the patients in the negative trial were in class II failure [25] while in the other studies they were class III or IV) and in the duration of therapy (24,26). Studies with longer follow-up are needed to resolve the important questions concerning potential mechanisms of beneficial action seen with statin therapy.

Conclusions. In addition to the proven benefit of intensive statin therapy in reducing recurrent ischemic events, this analysis demonstrates the ability of intensive statin therapy to lower the risk of the development of HF independently of the reduction in ischemic events. Trials of intensive statins in patients with known HF areongoing. Results from these studies, in particular among patients with non-ischemic cardiomyopathy, will provide further insight into whether statins improve outcome independently of reducing ischemia and potentially identify a new therapy for these patients. In the meantime, the reduction in HF associated with intensive statin therapy observed in the PROVE IT–TIMI 22 study and the other trials of intensive statin therapy further emphasize the clinical importance of aggressive statin therapy in patients at high risk for cardiovascular complications of ACS and chronic coronary artery disease.

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REFERENCES


