Acute coronary syndromes and diabetes: is intensive lipid lowering beneficial? Results of the PROVE IT-TIMI 22 trial

Shaheeda Ahmed, Christopher P. Cannon*, Sabina A. Murphy, and Eugene Braunwald

The TIMI Study Group, Cardiovascular Division, Brigham and Women’s Hospital, Harvard Medical School, 350 Longwood Avenue, First Floor, Boston, MA 02115, USA

Received 12 February 2006; revised 11 August 2006; accepted 17 August 2006; online publish-ahead-of-print 5 September 2006

Aims The impact of intensive lipid lowering therapy with statins in acute coronary syndrome (ACS) patients with diabetes mellitus (DM) is not well characterized.

Methods and results We explored this question in data from the Pravastatin or Atorvastatin Evaluation and Infection Therapy (PROVE IT) TIMI 22 trial, which tested standard (pravastatin 40 mg) vs. intensive (atorvastatin 80 mg) statin therapy among patients treated early in the post-ACS period. We compared outcomes between patients with DM (identified by history, fasting plasma glucose ≥126 mg/dL or haemoglobin A1C ≥7%; n = 978) against those without DM (n = 3184). The rate of acute cardiac events (death, myocardial infarction, and unstable angina requiring rehospitalization) was much higher in patients with DM, but was reduced with intensive vs. standard therapy similarly in diabetic (21.1 vs. 26.6%, HR = 0.75, P = 0.03) and non-diabetic patients (14.0 vs. 18.0%, HR = 0.76, P = 0.002); P-interaction = 0.97. Despite intensive therapy, the majority of diabetics (62%) did not reach the dual goal of LDL-C < 70 mg/dL and high-sensitivity C-reactive protein < 2 mg/L.

Conclusion In ACS patients with DM, intensive statin therapy reduces acute cardiac events as it does in those without DM, with 55 vs. 40 events prevented per 1000 patients treated. However, our data highlight the need for additional strategies in this high-risk group.

KEYWORDS Diabetes mellitus; Acute coronary syndromes; Lipid lowering; Inflammation

Introduction

Diabetes mellitus (DM) is a significant worldwide health burden with a growing prevalence globally, particularly in the US.1 The majority of DM-related death and morbidity are due to cardiovascular events.2 In the US, the absolute risk of cardiovascular complications are two-fold greater in persons with DM compared with those without DM.3

Dyslipidaemia is an important contributing factor to the cardiovascular complications in DM. Lipid disturbances in DM are dominated by hypertriglyceridaemia, and low HDL cholesterol (HDL-C). Although average LDL cholesterol (LDL-C) levels may not be increased, diabetic patients have higher concentrations of small dense LDL-C. These proatherogenic particles are readily oxidized and taken up by monocytes and endothelial smooth muscle cells,4 contributing to atherogenesis and subsequent progression of atherosclerosis.

HMG-CoA reductase inhibitors or statins in ‘standard’ (low to moderate) doses reduce LDL-C and cardiovascular events in patients with average to high LDL-C levels and known coronary artery disease (CAD),5–8 including those with DM.9–12

A growing literature supports additional clinical benefit with high-dose statin therapy administered early in the post-acute coronary syndrome (ACS) period.13–15 However, it is not clear whether diabetic patients, in whom average LDL-C levels are typically not elevated, also benefit from intensive LDL-C lowering.

The Pravastatin or Atorvastatin Evaluation and Infection Therapy (PROVE IT) TIMI (Thrombolysis in Myocardial Infarction) 22 trial demonstrated fewer cardiovascular complications in ACS patients treated with ‘intensive’ (atorvastatin 80 mg) vs. standard (pravastatin 40 mg) statin therapy.14 Since patients with DM have a substantially greater risk of death and ischaemic complications following an ACS than in those without DM,4 the potential for benefit in these patients with intensive statin therapy is large. The purpose of this analysis was to determine the impact of intensive vs. standard statin therapy on outcomes in ACS patients with DM based on data from PROVE IT-TIMI 22.

Methods

This was a prespecified subgroup analysis of data from PROVE IT-TIMI 22, a 2 × 2 factorial design trial, which evaluated the effects of intensive (atorvastatin 80 mg) vs. standard (pravastatin 40 mg) oral daily statin therapy and of gatifloxacin vs. placebo in the...
prevention of recurrent coronary events among patients with ACS. Details of the trial design\textsuperscript{16} and principal findings have been previously reported.\textsuperscript{14,17}

In brief, 4162 ACS patients were enrolled between November 2000 and December 2001 and were followed for clinical events for 18–36 months (mean = 24 months). Patients were randomized in a 1:1 ratio to atorvastatin or pravastatin and to gatifloxacin for ten days or placebo every month during the trial. Follow-up visits were performed at 30 days, four months, and every four months thereafter until the final visit. Plasma samples for lipid profiles and high-sensitivity C-reactive protein were obtained at four time points and, for the purposes of this analysis, are reported at randomization and 30 days.

**Patient population**

Patients with an ACS within the prior ten days were randomized into PROVE IT-TIMI 22, provided they were stable for at least 24 h. Diabetes was identified by any of a known clinical history, a fasting plasma glucose $\geq 126$ mg/dL or a haemoglobin A1C (HbA1C) $>7\%$. All patients were classified at the time of their initial presentation to hospital. Patients with uncontrolled DM (fasting plasma glucose $\geq 230$ mg/dL, an episode of hyperosmolar non-ketotic coma or ketoacidosis) within the prior 6 months were excluded as per protocol.

**Clinical endpoints**

The primary endpoint, a composite of death, myocardial infarction (MI), unstable angina requiring rehospitalization, revascularization with percutaneous coronary intervention (PCI) or coronary artery bypass surgery occurring at least 30 days following randomization or stroke was assessed from randomization through follow-up. In addition, we have assessed a ‘triple’ endpoint of acute cardiac events (death, MI, or unstable angina requiring rehospitalization).\textsuperscript{18}

**Biochemical parameters**

The ‘achieved’ LDL-C and high-sensitivity C-reactive protein with statin therapy were defined as the levels at 30 days, a period of time adequate to observe the effects of statin therapy on these parameters in the absence of any residual ischaemic influences. We assessed the association between baseline and achieved LDL-C and high-sensitivity C-reactive protein with the triple endpoint at 2 years.

**Statistical analysis**

All analyses were performed according to the intent-to-treat principle. Continuous variables are reported as the mean $\pm$ standard deviation (SD) or as the median with their interquartile range, as specified. The $\chi^2$ test and Wilcoxon ranksum test were used when appropriate. All tests were two-sided. A $P$-value $\leq 0.05$ was considered statistically significant. Cox proportional hazard models were used for the analysis of clinical endpoints and statin-randomization treatment stratified by the presence of diabetes and to assess the interaction between DM and therapy. Models for clinical endpoints comparing statin-randomized treatment also included stratification for randomization to gatifloxacin or placebo. All analyses were performed using Stata version 8.2 (College Station, Texas, USA).

**Results**

**Baseline characteristics**

We identified 978 patients with DM (734 by clinical history, 219 without a clinical history but with a fasting plasma glucose $\geq 126$ mg/dL, assessed at a mean of 4.1 days post-ACS, and an additional 25 without the first two criteria but with a HbA1C $>7\%$), and 3184 patients without DM (Table 1). Compared with those without DM, patients with DM were significantly older, more often female, had more cardiovascular morbidity (prior MI), hypertension, peripheral vascular disease, and smoked less often. The index event in diabetic patients was more often high-risk unstable angina and less often non-STEMI or STEMI than in non-diabetics. Diabetic patients had higher TIMI risk scores (TRS) on presentation compared with those without DM. The use of cardiac medications prior to ACS was also higher in diabetic patients. The median baseline LDL-C level was 101 mg/dL (84, 122) in diabetics and 108 mg/dL (89, 129) in non-diabetics ($P = 0.0001$). The median triglyceride levels were higher in patients with vs. without DM; median HDL-C and apolipoprotein B levels were similar. The median high-sensitivity C-reactive protein was also significantly higher in patients with DM at baseline [13.2 mg/L (5.2, 34.1) vs. 11.9 mg/L (4.8, 27.9), $P = 0.006$].

**Achieved LDL-C and high-sensitivity C-reactive protein**

In patients with DM, intensive statin therapy lowered the median LDL-C to 57 mg/dL (43, 72) compared with 81 mg/dL (68, 102) with standard statin therapy by 30 days (Table 2). A significant reduction in median LDL-C was also observed in those without DM [57 mg/dL (45, 72) vs. 91 mg/dL (74, 108)]. In diabetic patients, this represented a fall in LDL-C from baseline by 44% with atorvastatin and by 18% with pravastatin. The proportional LDL-C reductions in non-diabetic patients were 47 and 18\% respectively.

By 30 days, the median high-sensitivity C-reactive protein level fell to 2.0 mg/dL (1.0, 4.7) with intensive therapy, and to 2.6 mg/dL (1.4, 5.3) with standard therapy in patients with DM (Table 2), but each was slightly higher than in those without DM [1.6 mg/dL (0.7, 3.5) vs. 2.2 mg/dL (1.1, 4.5)].

**Clinical endpoints**

Overall, diabetic patients had more clinical events than those without DM by 2 years in terms of the primary (Figure 1) and triple endpoints (Figure 2).

The Kaplan–Meier event rate of the primary endpoint was 28.4\% with the intensive regimen and 31.8\% with the standard statin in diabetic patients. Although underpowered to reach statistical significance, the direction of change favoured atorvastatin [hazards ratio (HR) 0.88, $P = 0.28$]. In the larger non-diabetic subgroup, the primary endpoint was significantly reduced with intensive therapy. The interaction term between DM status and intensive therapy was not significant ($P = 0.62$). This suggests that the benefit of intensive therapy did not differ significantly in diabetic and non-diabetic patients.

The Kaplan–Meier event rate for the triple endpoint on intensive vs. standard statin therapy was 21.1 vs. 26.6\% ($P = 0.03$) in patients with DM and 14 vs. 18\% ($P = 0.002$) in those without DM. With intensive therapy, the number of events prevented per 1000 diabetic patients was 55 compared with 40 events prevented per 1000 patients without DM.

Among the individual components of the primary and triple endpoints, the event rate in diabetic patients on intensive vs. standard statin therapy was 3.7 vs. 3.9\%, $P = 0.75$ for death; 9.2 vs. 12.1\%, $P = 0.11$ for MI; 3.1 vs. 7.4\%, $P = 0.003$ for unstable angina requiring rehospitalization; 19.3 vs. 22.5\%, etc.
\( P = 0.28 \) for revascularization occurring at least 30 days post-randomization; and 2.6 vs. 2.2%, \( P = 0.45 \) for stroke. In non-diabetic patients, the event rates were 1.8 vs. 3.0%, \( P = 0.045 \); 5.8 vs. 6.0%, \( P = 0.77 \); 4.0 vs. 4.4%, \( P = 0.37 \); 15.4 vs. 17.7%, \( P = 0.08 \); and 0.5 vs. 0.7%, \( P = 0.65 \), respectively, for these five endpoints.

### Clinical events and the dual goal

Diabetic and non-diabetic patients achieved the dual goal of LDL-C < 70 mg/dL and high-sensitivity C-reactive protein < 2 mg/L more often with intensive therapy (Figure 3). Compared with those without DM, fewer patients
with DM achieved the dual goal despite treatment with the intensive regimen (37.6 vs. 45.4%, \( P = 0.004 \)).

Patients with DM who achieved the dual goal had significantly lower rates of the triple endpoint at 2 years compared with those who did not (17.7 vs. 24.7%, \( P = 0.021 \)) (Figure 4). This was also observed in patients without DM. Achieving the dual goal was associated with a lower risk of developing the triple endpoint by 34% in patients with DM and by 28% in patients without DM.

**Effect of gatifloxacin by diabetes status**

There were no significant differences in clinical event rates among those treated with gatifloxacin vs. placebo when the analysis was restricted to patients with DM (primary end point 31.6 vs. 28.5%, \( P = 0.45 \); triple endpoint 24.6 vs. 23.0%, \( P = 0.50 \)) or patients without DM (primary endpoint 21.2 vs. 24.1%, \( P = 0.13 \); triple endpoint 14.7 vs. 17.3%, \( P = 0.08 \)).

**Discussion**

Intensive statin therapy with high-dose atorvastatin compared with standard-dose pravastatin in the post-ACS period was associated with lower achieved LDL-C and high-sensitivity C-reactive protein levels in patients with as well as those without DM. Improved clinical outcomes were seen in patients with and without DM, but since diabetic patients were at higher risk, more acute cardiac events (death, MI, or unstable angina) were prevented with intensive therapy in those with DM (55 vs. 40 per 1000 patients treated without DM).

We identified DM in 23% of the ACS population in PROVE IT-TIMI 22. The prevalence of DM in our analysis was higher than in earlier secondary prevention statin trials which ranged from 4.5 to 14%, \( P = 0.021 \) (Figure 4). This was also observed in patients without DM. Achieving the dual goal was associated with a lower risk of developing the triple endpoint by 34% in patients with DM and by 28% in patients without DM.

**Effect of gatifloxacin by diabetes status**

There were no significant differences in clinical event rates among those treated with gatifloxacin vs. placebo when the analysis was restricted to patients with DM (primary end point 31.6 vs. 28.5%, \( P = 0.45 \); triple endpoint 24.6 vs. 23.0%, \( P = 0.50 \)) or patients without DM (primary endpoint 21.2 vs. 24.1%, \( P = 0.13 \); triple endpoint 14.7 vs. 17.3%, \( P = 0.08 \)).

**Discussion**

Intensive statin therapy with high-dose atorvastatin compared with standard-dose pravastatin in the post-ACS period was associated with lower achieved LDL-C and high-sensitivity C-reactive protein levels in patients with as well as those without DM. Improved clinical outcomes were seen in patients with and without DM, but since diabetic patients were at higher risk, more acute cardiac events (death, MI, or unstable angina) were prevented with intensive therapy in those with DM (55 vs. 40 per 1000 patients treated without DM).

We identified DM in 23% of the ACS population in PROVE IT-TIMI 22. The prevalence of DM in our analysis was higher than in earlier secondary prevention statin trials which ranged from 4.5 to 14%, \( P = 0.021 \) (Figure 4). This was also observed in patients without DM. Achieving the dual goal was associated with a lower risk of developing the triple endpoint by 34% in patients with DM and by 28% in patients without DM.

**Effect of gatifloxacin by diabetes status**

There were no significant differences in clinical event rates among those treated with gatifloxacin vs. placebo when the analysis was restricted to patients with DM (primary end point 31.6 vs. 28.5%, \( P = 0.45 \); triple endpoint 24.6 vs. 23.0%, \( P = 0.50 \)) or patients without DM (primary endpoint 21.2 vs. 24.1%, \( P = 0.13 \); triple endpoint 14.7 vs. 17.3%, \( P = 0.08 \)).

**Discussion**

Intensive statin therapy with high-dose atorvastatin compared with standard-dose pravastatin in the post-ACS period was associated with lower achieved LDL-C and high-sensitivity C-reactive protein levels in patients with as well as those without DM. Improved clinical outcomes were seen in patients with and without DM, but since diabetic patients were at higher risk, more acute cardiac events (death, MI, or unstable angina) were prevented with intensive therapy in those with DM (55 vs. 40 per 1000 patients treated without DM).

We identified DM in 23% of the ACS population in PROVE IT-TIMI 22. The prevalence of DM in our analysis was higher than in earlier secondary prevention statin trials which ranged from 4.5 to 14% \( P = 0.021 \) (Figure 4). This was also observed in patients without DM. Achieving the dual goal was associated with a lower risk of developing the triple endpoint by 34% in patients with DM and by 28% in patients without DM.

**Effect of gatifloxacin by diabetes status**

There were no significant differences in clinical event rates among those treated with gatifloxacin vs. placebo when the analysis was restricted to patients with DM (primary end point 31.6 vs. 28.5%, \( P = 0.45 \); triple endpoint 24.6 vs. 23.0%, \( P = 0.50 \)) or patients without DM (primary endpoint 21.2 vs. 24.1%, \( P = 0.13 \); triple endpoint 14.7 vs. 17.3%, \( P = 0.08 \)).

**Discussion**

Intensive statin therapy with high-dose atorvastatin compared with standard-dose pravastatin in the post-ACS period was associated with lower achieved LDL-C and high-sensitivity C-reactive protein levels in patients with as well as those without DM. Improved clinical outcomes were seen in patients with and without DM, but since diabetic patients were at higher risk, more acute cardiac events (death, MI, or unstable angina) were prevented with intensive therapy in those with DM (55 vs. 40 per 1000 patients treated without DM).

We identified DM in 23% of the ACS population in PROVE IT-TIMI 22. The prevalence of DM in our analysis was higher than in earlier secondary prevention statin trials which ranged from 4.5 to 14%, \( P = 0.021 \) (Figure 4). This was also observed in patients without DM. Achieving the dual goal was associated with a lower risk of developing the triple endpoint by 34% in patients with DM and by 28% in patients without DM.
epidemiological trends of this growing population and may also reflect the changing and broader definition of diabetes with time. Thus, unlike some of the earlier analyses, we also identified diabetic patients with HbA1C and fasting plasma glucose in addition to a clinical history of DM.

Intensive statin therapy achieved a large reduction in LDL-C (44%) in diabetic patients. This is a substantial improvement compared with earlier secondary prevention trials that have reported LDL-C reductions in diabetic patients of 25% in LIPID and CARE, 28% in HPS, and 34% in 4S achieved with pravastatin or simvastatin in standard doses.

Similar to patients without DM, the intensive statin regimen was also associated with lower achieved high-sensitivity C-reactive protein levels than with standard-statin therapy in patients with DM. High doses of atorvastatin have previously been demonstrated to attenuate the inflammatory response in Type II diabetic patients with no known CAD and in the general population in the post-ACS setting. Our analysis extends these observations to ACS patients with DM. These clinical data take particular importance in light of the research that has linked inflammation to the development of atheroma formation, plaque instability, and thromboses.

On presentation, diabetic patients more often had a history of stable or unstable angina, prior MI, or a coronary revascularization procedure compared with those with no DM. Despite the differences in the types of pre-existing CAD, the reduction in the relative risk of the triple endpoint of death, MI, or unstable angina by 2 years with the intensive regimen was ‘nearly identical’ in patients with DM (HR = 0.75) as in those without (HR = 0.76). The direction of the primary endpoint also favoured atorvastatin in diabetics, although this was likely underpowered to reach statistical significance. The lack of a significant interaction between DM and statin therapy on outcomes underlines that the response to the intensive regimen is not significantly different between diabetic and non-diabetic patients.

Figure 4 Kaplan–Meier rate of the triple endpoint by 2 years based on achievement of the dual goal. Triple endpoint was a composite of death, MI, and unstable angina requiring hospitalization. $P = 0.68$ for DM and treatment interaction.

Owing to their higher event rates, the absolute risk reduction (ARR) in the triple endpoint (death, MI, or unstable angina) of 5.5% in diabetics was larger in magnitude than the ARR of 4.0% in non-diabetics. Thus, although patients with DM have a dyslipidaemic profile dominated by high triglycerides and low HDL-C, the focus on targeting LDL-C to very low levels remains central for these patients. Diabetic patients with MI or angina treated with standard-statin therapy vs. placebo have been previously shown to have an ARR of 2.7% of cardiovascular events in CARE [for coronary heart disease death, MI, coronary bypass surgery, or percutaneous transluminal coronary angioplasty (PTCA)], 10 of 3.8% in LIPID (for coronary heart disease death/MI), 7 of 3.2% in the Heart Protection Study (for coronary heart disease death/MI), 12 and of 10.4% in 4S (for death). Unlike these reports, clinical benefits with intensive therapy in our analysis were (i) ‘additional’ to standard-statin therapy and (ii) observed in only 2 years, not 5 to 6 years as in the earlier placebo-controlled trials. Since PROVE IT-TIMI 22, the A to Z trial has also reported an additional clinical benefit with high vs. standard doses of simvastatin in ACS patients with DM by 2 years (ARR reduction 2.0% for CV death, MI, readmission for ACS, or stroke).

There was a large magnitude of clinical benefit [25% relative risk reduction (RRR) in the triple endpoint] proportional to the absolute difference in LDL-C lowering between the intensive and standard regimen (24 mg/dL) in our analysis. This is consistent with Treating to New Targets (TNT), where the difference in LDL-C by 22 mg/dL with intensive vs. standard therapy (atorvastatin 80 vs. 10 mg) was associated with a 25% RRR in major cardiovascular events in patients with stable CAD and DM.

In support of the importance of the lipid-independent effects of statins, ACS patients who achieve both an LDL-C <70 mg/dL and a high-sensitivity C-reactive protein <2 mg/L by 30 days, i.e. ‘the dual goal’, have been demonstrated to have fewer long-term ischaemic complications than those who meet only one or neither of these targets. Our analysis extends this to ACS patients with DM and underlines its particular importance in this subgroup since diabetic patients who did not achieve the dual goal had a very high event rate of 24.7%, almost double the rate in non-diabetic patients who did achieve the dual goal (12.8%).

Clinical implications

Current clinical practice guidelines do not agree on the target LDL-C in patients with DM. The American College of Physicians supports statin therapy in Type II DM patients without specifying an LDL-C goal, 28 the American Diabetes Association suggests a target of LDL-C <100 mg/dL, 29 and the National Cholesterol Education Program Adult Treatment Panel III Guidelines advocates an LDL-C <100 mg/dL with the option to treat to <70 mg/dL in patients with DM. 30 In our analysis, the LDL-C in the intensive and standard arms at ‘baseline’ was already in this range and further LDL-C lowering to 57 mg/dL with intensive therapy reduced adverse outcomes. The TNT trial demonstrated fewer cardiovascular events in patients with DM and stable CAD when the LDL-C was 77 mg/dL on intensive (atorvastatin 80 mg) therapy. Taken together, these data suggest that patients with DM benefit from an LDL-C that is considerably less than 100 mg/dL, and in the post-ACS setting, the achieved level should be <70 mg/dL.
In view of the very high event rate in patients with DM who did not achieve the dual goal even on intensive therapy, additional strategies to attain this goal are warranted. Lifestyle modifications such as smoking cessation, exercise, and weight loss, are effective high-sensitivity C-reactive protein reducing measures and should be strongly encouraged in these patients. Pharmacological therapies that lower high-sensitivity C-reactive protein and improve lipid disturbances apart from statins include fibrates, that lower high-sensitivity C-reactive protein and improve, and thiazolidinediones, ezetimibe, and rimonabant. Although interesting, the role of these drugs in the post-ACS setting is not yet defined.

Study limitations
This represents an analysis of a prespecified subgroup of patients. However, it was not possible to classify patients according to the type of DM (I or II), although presumably the majority had Type II DM since only 21% were on insulin and their mean age was 60 years. Patients who may have developed DM during the follow-up period remained classified as non-diabetic and this may have influenced the treatment impact of intensive statin therapy in non-diabetic patients.

Conclusions
In ACS patients with DM, intensive statin therapy reduces acute cardiac events as it does in those without DM, with 55 vs. 40 events prevented per 1000 patients treated. Despite achieving lower LDL-C and high-sensitivity C-reactive protein with intensive therapy, the majority of patients with DM did not reach the dual goal of <70 mg/dL and <2 mg/L, respectively, highlighting the need for additional strategies in this high-risk group.

Conflict of interest: S.A. has no disclosures. C.P.C. receives research grant support from AstraZeneca, Merck, Schering Plough, and serves on scientific advisory boards for these companies and Bristol Myers Squibb, Glaxo SmithKline, Pfizer, Sanofi-Aventis. S.A.M. and E.B. receive research grant support currently from: AstraZeneca, Sanofi-Aventis, CV Therapeutics, Eli Lilly, Millennium, Schering-Plough, Nuvelo, Pfizer, Inotek, and Merck, and in the past from Bristol Myers Squibb. E.B. serves as a consultant or on scientific advisory boards: for Momenta, Sanofi-Aventis, Bristol Myers Squibb, Bayer, AG, and Pfizer.

References


