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Atorvastatin Efficacy in the Prevention of Cardiovascular Events in Patients with Diabetes Mellitus and/or Metabolic Syndrome

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Abstract

Several large-scale clinical trials have assessed the efficacy of atorvastatin in the primary and secondary prevention of cardiovascular events in patients with diabetes mellitus and/or metabolic syndrome. In primary prevention, CARDS (Collaborative Atorvastatin Diabetes Study) showed that atorvastatin 10 mg/day (vs placebo) reduced relative risk of the composite primary endpoint (acute coronary heart disease [CHD] events, coronary revascularisation, or stroke) by 37% ($p = 0.001$). This decrease was similar to decreases in major cardiovascular events in the ASCOT-LLA (Anglo-Scandinavian Cardiac Outcomes Trial-Lipid Lowering Arm) trial and HPS (Heart Protection Study). However, in CARDS, atorvastatin efficacy was evident as early as 6 months after starting treatment, whereas in HPS, simvastatin efficacy was noticeable only from about 15–18 months after starting treatment. In the ASCOT-LLA trial, in 2226 hypertensive diabetic patients without previous cardiovascular disease, atorvastatin (vs placebo) reduced the relative risk of all cardiovascular events and procedures by 25% ($p = 0.038$).

In secondary prevention, substudies of the GREACE (GREek Atorvastatin and Coronary-heart-disease Evaluation), TNT (Treating to New Targets) and PROVE-IT (PRavastatin Or atorVastatin Evaluation and Infection Therapy) trials reported results for the approximately 15–25% of study participants who had diabetes. In the GREACE substudy, atorvastatin (vs physicians' standard care) significantly reduced the relative risk of total mortality by 52% ($p = 0.049$), coronary mortality by 62% ($p = 0.042$), coronary morbidity by 59% ($p < 0.002$) and stroke by 68% ($p = 0.046$). In the TNT substudy, incidence of the primary endpoint was significantly lower in diabetic patients treated with atorvastatin 80 mg/day rather than 10 mg/day (13.8% vs 17.9%; relative risk 0.75; $p = 0.026$). In the PROVE-IT substudy, a significantly lower incidence of acute cardiac events was reported for atorvastatin versus pravastatin recipients (21.1% vs 26.6%; $p = 0.03$) and, therefore, an absolute risk reduction of 5.5% was associated with atorvastatin therapy.

ASPEN (Atorvastatin Study for Prevention of coronary heart disease Endpoints in Non-insulin-dependent diabetes mellitus) – a mixed primary and secondary prevention trial in diabetic patients – found that a 29% lower low-

density lipoprotein-cholesterol level was seen with atorvastatin than placebo at endpoint ($p < 0.0001$); however, the reduction in composite primary endpoint of major cardiovascular events (cardiovascular mortality, nonfatal major cardiovascular event or stroke, and unstable angina requiring hospitalisation) with atorvastatin (13.7% vs 15.0% with placebo), and reduction in acute myocardial infarction relative risk of 27% with atorvastatin were not statistically significant.

In CHD patients with metabolic syndrome (n = 5584) in a sub-analysis of the TNT trial, intensive versus lower-dosage atorvastatin therapy reduced the relative risk of major cardiovascular and cerebrovascular events by 29% ($p < 0.0001$). The analysis also revealed that CHD patients with, rather than those without, metabolic syndrome had a 44% greater level of absolute cardiovascular risk, thus clearly underscoring the clinical feasibility of administering intensive lipid-lowering therapy to CHD patients with metabolic syndrome.

In summary, several patient populations, from definitive, large-scale studies, are now available to corroborate the integral place of atorvastatin – in line with various regional and internationally accepted disease management guidelines – in the primary and secondary prevention of cardiovascular events in patients with diabetes and/or metabolic syndrome.

Type 2 diabetes mellitus is a major, independent, risk factor for cardiovascular disease – coronary heart disease (CHD) and stroke – as indeed are conditions such as hypertension and dyslipidaemia that frequently coexist with diabetes.[1] Cardiovascular disease is the major cause of mortality in patients with diabetes.[1] Most diabetic patients have high levels of cardiovascular risk – approximately 2-fold that of nondiabetics – even when established CHD is absent; indeed, in high-risk populations, type 2 diabetic patients have cardiovascular risk levels similar to those in nondiabetic patients with established cardiovascular disease.[2] Furthermore, when it occurs in diabetic patients, cardiovascular disease is associated with a poor prognosis, both when acute events manifest and in the post-event setting.[2] Patients with type 2 diabetes have an increased prevalence of lipid abnormalities contributing to the increased risk of cardiovascular disease, and risk of cardiovascular events is increased further in diabetic patients who have experienced previous coronary or cerebrovascular events.[1]

Treatment of dyslipidaemia, in particular elevated low-density lipoprotein-cholesterol (LDL-C), is a major part of the management of diabetes. In 2004, an update to the 2001 National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) high blood cholesterol treatment guidelines was published based on newly published clinical evidence[2] confirming the benefit of achieving LDL-C <100 mg/dL in high-risk patients, and showing that additional reductions in cardiovascular risk may be possible with more stringent LDL-C goals. Thus, the updated guidelines propose an optional therapeutic goal of LDL-C <70 mg/dL in patients deemed to be at 'very high risk' – i.e. established cardiovascular disease plus multiple risk factor (especially diabetes).[2] The 2005 American Diabetes Association (ADA) guidelines concur, and recommend optional use of aggressive high-dose statin therapy to achieve an LDL-C goal of <70 mg/dL in patients with diabetes and overt cardiovascular disease.[1]

Several large-scale studies have assessed the efficacy of atorvastatin in the primary and secondary prevention of cardiovascular events in patients with diabetes.[3-9] CARDS (Collaborative Atorvastatin Diabetes Study)[3] was the first randomised, double-blind, placebo-controlled, multicentre trial to exclusively enrol type 2 diabetic patients with no history of CHD or stroke, and can therefore be considered the first major primary prevention study of statin therapy in type 2 diabetes.

Regarding secondary prevention, a subgroup of patients with type 2 diabetes from the original GREACE (GREek Atorvastatin and Coronary-heart-disease Evaluation) study[10] were randomised to receive atorvastatin 10–80 mg/day (n = 161) or conventional therapy (n = 152) for a mean of 3 years (see section 2.1).[7] Moreover, the original TNT (Treating to New Targets) trial[11] in patients with stable CHD was designed to determine whether reduction of plasma LDL-C concentration to a target of <75 mg/dL (high-dosage atorvastatin 80 mg/day), compared with <100 mg/dL (atorvastatin 10 mg/day), would produce an additional decrease in the incidence of major cardiovascular events. A TNT diabetes sub-trial[4] was designed to more closely evaluate the efficacy of high-dosage atorvastatin in patients with type 2 diabetes and CHD. Furthermore, among diabetic patients, the risks of additional cardiovascular morbidity and mortality are greatest in patients with acute coronary syndrome (ACS).[12] Thus, a PROVE-IT (PRavastatin Or atorVastatin Evaluation and Infection Therapy) sub-analysis[5] assessed, over 18–36 (mean 24) months, the approximately 25% of PROVE-IT participants (n = 978) who had ACS and diabetes; the presence of diabetes was identified from medical records, and/or from a fasting plasma glucose concentration ≥126 mg/dL, or haemoglobin (Hb)A_{1c} value >7%.

ASPEN (Atorvastatin Study for Prevention of coronary heart disease Endpoints in Non-insulin-dependent diabetes mellitus)[8] evaluated cardiovascular risk in atorvastatin-treated diabetic patients versus placebo. Unlike the previously mentioned studies, ASPEN was a study of both primary and secondary prevention, since the efficacy of atorvastatin was compared with that of placebo in type 2 diabetic patients with and without a previous history of cardiovascular illness.[8]

Metabolic syndrome is defined by the NCEP ATP III as a cluster of three or more of the following cardiovascular risk factors: central obesity, fasting hyperglycaemia, hypertension, hypertriglyceridaemia and/or low levels of plasma high-density lipoprotein-cholesterol (HDL-C).[13]

While much epidemiological evidence indicates that, like diabetes, metabolic syndrome also increases cardiovascular risk,[13,14] only a few clinical trials have actually assessed the efficacy of statins in reducing cardiovascular morbidity and mortality in patients with metabolic syndrome. Thus, a *post hoc* analysis of the TNT trial[6] was designed to determine whether intensive atorvastatin therapy (80 mg/day) would reduce the incidence of cardiovascular events to a greater extent than lower-dosage therapy (10 mg/day) in CHD patients with metabolic syndrome; this analysis comprised the largest database of patients with metabolic syndrome (n = 5584) ever included in a statin trial.

This review details and discusses data from all the abovementioned primary and secondary prevention studies of atorvastatin in patients with diabetes and/or metabolic syndrome.

1. Atorvastatin in Primary Prevention

The CARDS trial[3] randomised 2838 patients with type 2 diabetes, but only slightly elevated plasma LDL-C (116 mg/dL), to atorvastatin 10 mg/day (n = 1428) or placebo (n = 1410) for a median duration of 3.9 years. Importantly, the trial was stopped 2 years earlier than planned because of the marked efficacy of atorvastatin. That is, atorvastatin reduced relative risk of the composite primary endpoint (i.e. time to a first occurrence of acute CHD events, coronary revascularisation or stroke) by 37% (95% CI 17, 52; p = 0.001; figure 1). This was associated with 40% reduction of plasma LDL-C concentration in the atorvastatin group compared with the placebo group. Atorvastatin also markedly reduced the relative risks of each component of the primary endpoint: acute CHD events (−36%), coronary revascularisation (−31%) and stroke (−48%). Effects of atorvastatin on each component of the primary endpoint remained statistically significant in subgroup analyses according to age, albuminuria, baseline systolic blood pressure and lipidaemia, gender, retinopathy and smoking status. The all-cause mortality rate was 4.3% in atorvastatin-treated patients compared with 5.8% in placebo recipients, thus representing a risk reduction of only borderline

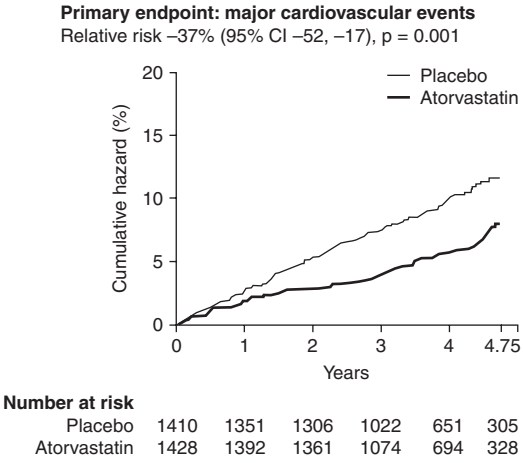


Fig. 1. Atorvastatin efficacy against the composite primary endpoint in CARDS (Collaborative Atorvastatin Diabetes Study). The primary endpoint comprised time to a first occurrence of acute coronary heart disease events, coronary revascularisation or stroke (reproduced from Colhoun et al., [3] with permission).

statistical significance (−27%; p = 0.059). However, the early cessation of the CARDS trial led to a lower number of 'in-study' deaths than originally anticipated and, thus, to a reduced chance to confirm a statistically significant effect for atorvastatin (vs placebo) on all-cause mortality. A rational interpretation of study data would seem to be that atorvastatin markedly reduces total mortality, but that the precise magnitude of this effect remains unclear.[3]

The atorvastatin-induced risk reduction in the primary endpoint in the CARDS trial (−37%; p = 0.001)[3] is similar to overall risk reductions in diabetes substudies of the HPS (Heart Protection Study) trial of simvastatin,[15] and the ASCOT-LLA trial.[9] That is, in diabetic patients without baseline occlusive arterial disease in the HPS trial, simvastatin reduced the relative risk (vs placebo) of major cardiovascular events by 33% (p = 0.0003) over 5 years,[15] and in diabetic patients in ASCOT-LLA, atorvastatin reduced the relative risk (vs placebo) of major cardiovascular events or procedures by 23% (p = 0.036) over a median of 3.3 years.[9]

In the CARDS study,[3] the effect of atorvastatin on the primary study endpoint was evident as early as 6 months after starting treatment, when Kaplan-Meier primary endpoint curves for atorvastatin and placebo started to diverge; a clear difference between the curves was noted 12 months after starting treatment.[16,17] Conversely, in the HPS substudy of diabetic patients,[15] who had higher levels of cardiovascular risk than diabetic patients in the CARDS trial,[3] simvastatin versus placebo Kaplan-Meier curves for major cardiovascular events started to diverge only about 15–18 months after beginning treatment.[17] Furthermore, the CARDS trial[3] revealed that atorvastatin had favourable early effects on the following secondary endpoints: CHD events, stroke and total mortality (figure 2).[16] Regarding CHD events, the risk reduction after 6 months' treatment with atorvastatin was similar to that after 4.5 years, and after 18 months the confidence interval for the hazard ratio was <1. For stroke, the atorvastatin-induced relative risk reduction after 18 months was similar to the final decrease, and after 2 years the confidence interval for the hazard ratio was <1. Overall, atorvastatin (vs placebo) reduced the relative risk of all-cause mortality by 27%; this reduction was evident from 6 months onwards, even though the decrease at the final study visit was only of borderline statistical significance (p = 0.059).[16]

After 1 year of follow-up in diabetic patients in the ASCOT-LLA trial, mean plasma total cholesterol and LDL-C levels were each about 46 mg/dL lower, and plasma triglyceride levels about 27 mg/dL lower, in atorvastatin recipients than in those receiving placebo. At the end of follow-up, total cholesterol and LDL-C levels were approximately 35 mg/dL lower, and triglyceride levels approximately 16 mg/dL lower, in the atorvastatin group than in the placebo group.[9] Plasma HDL-C concentrations were similar in both groups throughout the study. After 3 years' follow-up, 84% of diabetic patients originally randomised to atorvastatin were still receiving the drug, and 14% of initial placebo 'randomees' were receiving concurrent, open-label statin therapy. In the diabetic population, atorvastatin (vs placebo) reduced the risk of all cardiovascular events and procedures by 23% (95% CI 2, 39; p = 0.036); this was similar to the decrease in ASCOT-LLA participants without diabetes (−20%; 95% CI 6, 32). Excluding 306 patients with previous cardio-

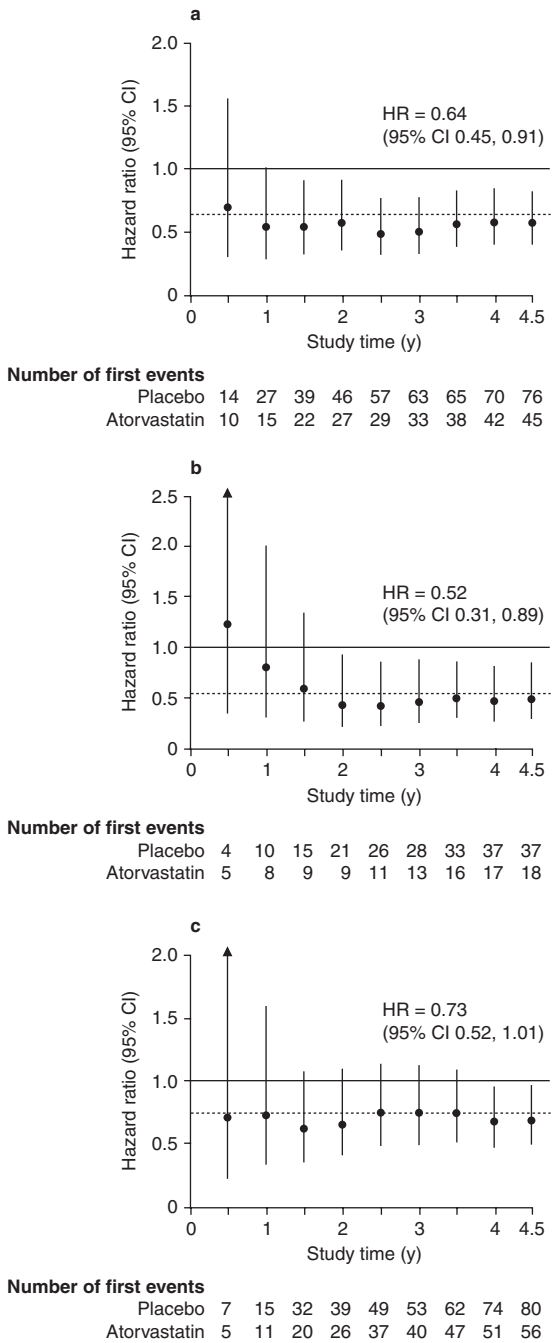


Fig. 2. Atorvastatin efficacy against various secondary endpoints in CARDS (Collaborative Atorvastatin Diabetes Study): (**a**) coronary heart disease (CHD) events; (**b**) stroke; (**c**) total mortality (reproduced from Colhoun et al.,[16] with permission). **HR** = hazard ratio.

vascular disease from the diabetic subgroup, atorvastatin still reduced the relative risk of total cardiovascular events and procedures by 25% (95% CI 1, 43; p = 0.038) in the remaining 2226 diabetic patients. Baseline plasma total cholesterol levels did not affect atorvastatin efficacy against the primary study endpoint: i.e. atorvastatin produced relative risks of 0.72, 0.74 and 0.84 in patients with baseline levels of <193 mg/dL (<5 mmol/L), 193–232 mg/dL (5–6 mmol/L) and ≥232 mg/dL (≥6 mmol/L), respectively. In addition, despite the small number of actual coronary or cerebrovascular events detected in the diabetic population, atorvastatin reduced the relative risk of nonfatal (including silent) myocardial infarction (MI) and fatal CHD by 16%, and that of nonfatal and fatal stroke by 33%.[9]

The ASPEN trial[8] was a median 4-year, double-blind study involving a total of 2410 patients with type 2 diabetes randomised to atorvastatin 10 mg/day (n = 1211) or placebo (n = 1199). In this mixed primary and secondary prevention trial, patients with MI or an interventional procedure in the 3 months before screening were required to have an LDL-C value ≤140 mg/dL (secondary prevention), whereas other patients were required to have an LDL-C value ≤160 mg/dL (primary prevention). Approximately 80% of patients were involved in the primary prevention arm, and approximately 20% in the secondary prevention arm. Overall, at treatment completion mean plasma LDL-C concentration was significantly lower in atorvastatin than in placebo recipients (79 vs 113 mg/dL; p < 0.0001). While the composite primary endpoint (cardiovascular mortality, nonfatal or silent MI, nonfatal stroke, revascularisation procedures, cardiac arrest and resuscitation, deteriorating or unstable angina necessitating hospitalisation) occurred less often in atorvastatin than placebo recipients in the overall study population (13.7% vs 15.0%), this difference was not statistically significant (p = 0.341). In the primary prevention arm, the proportion of patients experiencing a primary endpoint was similar (10.4% with atorvastatin and 10.8% with placebo). In the overall population, the risk of nonfatal or fatal MI, a secondary endpoint, was 27% lower in atorvastatin than in

placebo recipients, although this difference was again not statistically significant (p = 0.1). Adverse events occurred with a similar frequency in the atorvastatin and placebo groups in the overall, primary and secondary prevention arms.[8]

The ASPEN trial had several methodological limitations,[8] in that the trial was originally designed as a secondary prevention study, but because clinical guidelines for the management of CHD patients changed, the study protocol was altered 2 years after trial commencement to include diabetic patients without previous MI or revascularisation procedures (i.e. primary prevention). Similarly, during the trial, new guidelines were produced for the management of diabetes,[1,2] such that the ASPEN study protocol was again amended: patients in the primary prevention 'arm' who experienced cardiovascular events, and all those in the secondary prevention 'arm' who discontinued study medication (i.e. atorvastatin or placebo) received standard care in line with regional guidelines.[8] Only about 60–70% of study participants completed the trial, although all patients were included in the efficacy analysis. Thus, several patients initially randomised to atorvastatin were subsequently treated with another statin, and several placebo recipients were subsequently given statin therapy.[8] Moreover, 15% of atorvastatin and 27% of placebo recipients received concurrent lipid-lowering therapy, which, as shown in the ALLHAT-LLT trial,[18] can have a major influence on study outcomes.[8] Another important aspect of the ASPEN trial is that 42% of cardiovascular events in the atorvastatin group occurred in patients who had discontinued atorvastatin >1 year earlier, thus potentially decreasing the benefit of the statin.[8] All the abovementioned factors are likely to have contributed to the lack of a statistically significant atorvastatin-placebo difference regarding the composite primary endpoint in the ASPEN trial.[8] However, subsequent re-evaluation of ASPEN study results reveals that the cardiovascular risk reduction associated with atorvastatin is in line with that noted in other primary and secondary prevention studies of statins in diabetic patients (figure 3).[3,4,9,15,19,20]

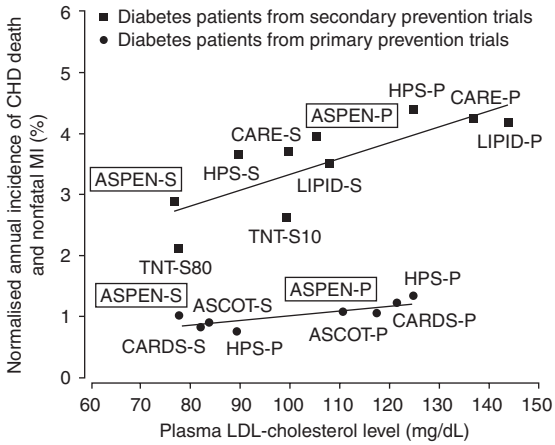


Fig. 3. Incidence of coronary heart disease mortality and nonfatal myocardial infarction, in relation to low-density lipoprotein-cholesterol (LDL-C) levels, in primary and secondary prevention studies of statins in diabetic patients (adapted from Kastelein,[21] with permission). **ASCOT** = Anglo-Scandinavian Cardiac Outcomes Trial; **ASPEN** = Atorvastatin Study for Prevention of coronary heart disease Endpoints in Non-insulin-dependent diabetes mellitus; **CARDS** = Collaborative Atorvastatin Diabetes Study; **CARE** = Cholesterol And Recurrent Events; **CHD** = coronary heart disease; **HPS** = Heart Protection Study; **LIPID** = Long-term Intervention with Pravastatin in Ischaemic Disease; **MI** = myocardial infarction; **P** = placebo-treated; **S** = statin-treated; **TNT** = Treating to New Targets trial.

2. Atorvastatin in Secondary Prevention

2.1 Patients with Diabetes Mellitus

Several large-scale studies have evaluated atorvastatin efficacy in the secondary prevention of cardiovascular events in patients with diabetes.[4,5,7,8]

The GREACE trial enrolled a total of 1600 patients with established CHD.[10] Included in a diabetic substudy were 313 patients with type 2 diabetes, 161 of whom were randomised to intensive therapy with atorvastatin 10–80 mg/day, and 152 to 'usual' care (i.e. physicians' standard care), for a mean of 3 years.[7] Almost all patients in the atorvastatin group (97%) received a mean dosage of 23.7 mg/day during the trial, and 93% attained the NCEP LDL-C target of <100 mg/dL. Conversely, only 17% of patients in the usual-care group received long-term lipid-lowering therapy, and only 4% attained the LDL-C goal of <100 mg/dL. Atorvastatin (vs usual-

care) produced statistically significant relative risk reductions in the following primary endpoints: all-cause mortality (−52%; p = 0.049); coronary mortality (−62%; p = 0.042); coronary morbidity (−59%; p < 0.002); and stroke (−68%; p = 0.046). In addition, atorvastatin reduced the relative risk of major cardiovascular events or death by 58% (p < 0.0001). Atorvastatin treatment benefits were evident as early as 6 months after starting treatment, when Kaplan-Meier event curves for atorvastatin and usual-care started to diverge.[7] Although this substudy involved only a small number of diabetic patients, it nonetheless indicates that atorvastatin – administered at dosages sufficient to attain the NCEP LDL-C goal of <100 mg/dL – has major clinical benefits in diabetic patients with established CHD.

The TNT diabetes substudy[4] involved a total of 1501 patients with diabetes, CHD and plasma LDL-C levels <130 mg/dL. They were randomised to double-blind administration of atorvastatin 10 mg/day (n = 753) or 80 mg/day (n = 748) for a median follow-up period of 4.9 years. During open-label treatment, LDL-C levels dropped from 160.3 mg/dL in both groups to 96.2 mg/dL (2.5 mmol/L) for all patients with diabetes. At treatment completion, mean plasma LDL-C concentration had increased by 3% to 98.6 mg/dL in the lower-dosage group, while a further reduction of 19% (from 95.6 to 77.0 mg/dL; p < 0.0001) was observed in the high-dosage group. Similarly, mean plasma total cholesterol concentration had increased by 2% (lower-dosage) or decreased by 13% (high-dosage); corresponding changes in mean plasma triglyceride levels were +11% and −10%, respectively. Importantly, over 5 years, incidence of the primary endpoint (a composite of CHD death, nonfatal MI [unrelated to procedures], cardiac arrest and resuscitation, and nonfatal or fatal stroke) was significantly lower in patients treated with atorvastatin 80 mg/day rather than 10 mg/day (13.8% vs 17.9%), thus representing a relative risk reduction of 25% (p = 0.026; figure 4). The benefit of intensive atorvastatin therapy on the primary endpoint was irrespective of patient age, duration of diabetes, glycaemic control (i.e. HbA_{1c} ≤7% vs >7%), and pre-baseline (i.e. initial screening) plasma LDL-C level.[4]

As in the TNT main trial,[11] the TNT diabetes substudy revealed favourable trends for intensive atorvastatin therapy against constituents of the composite primary endpoint: i.e. high-dosage atorvastatin reduced the relative risk of CHD death by 26% (p = 0.203), nonfatal MI (unrelated to procedures) by 21% (p = 0.202), and nonfatal or fatal stroke by 33% (p = 0.075).[4] Regarding the latter three 'constituent' endpoints, the overall number of events documented in the diabetic population was insufficient to demonstrate a statistically significant effect for intensive atorvastatin therapy. Concerning secondary endpoints, however, high-dosage atorvastatin reduced the relative risk of cerebrovascular events by 31% (p = 0.037), and that of any cardiovascular events by 15% (p = 0.044).[4] As in the main TNT trial,[11] the TNT diabetes substudy showed no difference between the two atorvastatin schedules regarding total mortality, although the high- versus lower-dosage regimen was associated with a lower incidence of cardiovascular mortality (5.2% vs 6.5%); nevertheless, the substudy was not

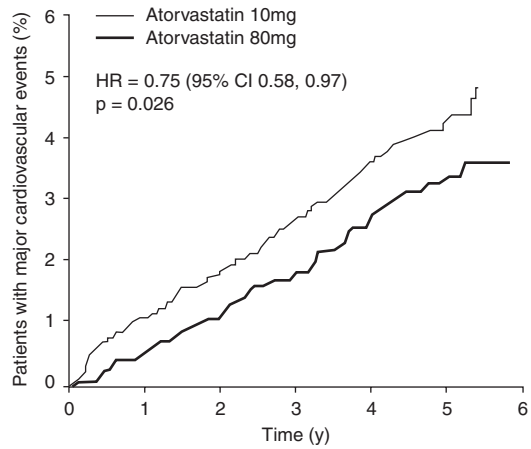


Fig. 4. Incidence of the primary endpoint (major cardiovascular events) in diabetic patients in the TNT (Treating to New Targets) trial. Major cardiovascular events comprised a composite of coronary heart disease death, nonfatal myocardial infarction (unrelated to procedures), cardiac arrest and resuscitation, and nonfatal or fatal stroke (reproduced from Shepherd et al.,[4] with permission). **HR** = hazard ratio.

sufficiently powered to identify statistically significant, between-group differences in mortality.[4]

Findings from the TNT diabetes substudy[4] corroborate and, to some extent, extend what is already known about cardiovascular risk levels, and their management, in diabetic populations. Notably, not all diabetic populations have the same degree of cardiovascular risk; indeed, in the TNT sub-trial,[4] the level of cardiovascular risk was substantially lower than that noted in the statin 'arms' of other secondary prevention studies, such as 4S (Scandinavian Simvastatin Survival Study),[22] CARE (Cholesterol And Recurrent Events),[19] HPS,[15] and LIPID (Long-term Intervention with Pravastatin in Ischaemic Disease).[20] Nevertheless, diabetic patients in the TNT sub-trial[4] had a greater incidence of all primary and secondary outcomes than in the overall TNT population,[11] thus indicating the extremely high level of cardiovascular risk in diabetic patients with CHD.[4] Importantly, the reduced event rate associated with intensive versus lower-dosage atorvastatin therapy in the TNT substudy, irrespective of age, diabetes duration, glycaemic control and pre-study LDL-C level, confirms the additional benefit of such intensive intervention in diabetic patients with CHD. Furthermore, it is possible to attain a LDL-C target of <100 mg/dL with intensive versus lower-dosage statin therapy, without compromising drug safety or tolerability.[4]

In view of the findings from HPS and PROVE-IT, the 2004 NCEP ATP III updated guidelines on the treatment of high blood cholesterol levels suggested an optional therapeutic goal of LDL-C <70 mg/dL in patients with established cardiovascular disease and diabetes.[2] In 2005, the ADA[1] also updated its recommendations about standards of medical care in diabetes to incorporate data from recent randomised controlled studies of intensive versus moderate lipid-lowering therapy in high-risk patients, albeit without diabetes.[23,24] Thus, the ADA suggested that aggressive high-dose statin therapy could be used to attain a LDL-C target of <70 mg/dL in patients with diabetes and overt CHD.[1] To some extent, results from the TNT diabetes substudy[4] also support the optional LDL-C goal of <70 mg/dL.[1,2]

A sub-analysis[5] of the PROVE-IT trial[23] included 978 patients with ACS and diabetes, and compared these patients with 3184 without diabetes. Atorvastatin 80 mg/day versus pravastatin 40 mg/day reduced mean plasma LDL-C levels to 57 mg/dL (−44%) and 81 mg/dL (−18%), respectively, 30 days after randomisation;[5] similar statistically significant decreases (i.e. to 57 and 91 mg/dL, respectively) were also noted in patients without diabetes. Moreover, mean plasma C-reactive protein (CRP) concentrations in diabetic patients were 2.0 mg/dL (atorvastatin) and 2.6 mg/dL (pravastatin) 30 days after randomisation; these values were slightly higher than corresponding values in nondiabetic patients (1.6 and 2.2 mg/dL, respectively).[5]

The primary endpoint in this PROVE-IT subanalysis of diabetic patients was a composite of total mortality, acute MI, unstable angina requiring hospitalisation, revascularisation procedures >30 days after randomisation and stroke.[5] In addition, treatment efficacy was evaluated against a triple endpoint of acute cardiac events (i.e. death, MI or unstable angina requiring hospitalisation). Both the primary endpoint (figure 5) and the triple endpoint occurred more frequently in diabetic than nondiabetic patients. In the diabetic population, the incidence of the primary endpoint was 28.4% in atorvastatin-treated patients, compared with 31.8% in

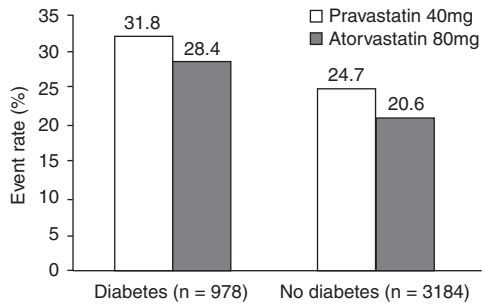


Fig. 5. Primary endpoint frequency in a PROVE-IT (PRavastatin Or atorVastatin Evaluation and Infection Therapy) sub-analysis of diabetic versus nondiabetic patients. The primary endpoint was a composite of total mortality, acute myocardial infarction, unstable angina requiring hospitalisation, revascularisation procedures >30 days after randomisation and stroke (reproduced from Ahmed et al.,[5] with permission).

pravastatin recipients (relative risk 0.88; p = 0.28); corresponding values for the much larger nondiabetic population were 20.6% and 24.7%, respectively (figure 5). No significant interaction (p = 0.62) was noted between diabetes and intensive atorvastatin therapy, thus indicating that the marked benefits of atorvastatin were similar in the diabetic and nondiabetic populations.[5]

The triple endpoint of acute cardiac events occurred significantly less frequently in atorvastatin than pravastatin recipients in both the diabetic (21.1% vs 26.6%; p = 0.03) and nondiabetic (14% vs 18%; p = 0.002) populations in the PROVE-IT trial.[5] Thus, intensive atorvastatin therapy prevented 55 events per 1000 diabetic patients treated, and 44 events per 1000 nondiabetic patients treated; atorvastatin-induced absolute risk reductions regarding the triple endpoint were therefore 5.5% in diabetic patients and 4.4% in nondiabetic patients.[5] Similarly, the A to Z (AGGRASTAT® to Zocor™)[1] study,[25] like the PROVE-IT trial,[23] revealed additional clinical benefit associated with intensive rather than 'standard' lipid-lowering therapy in ACS patients with diabetes. In the A to Z trial, intensive simvastatin therapy also reduced the absolute risk of cardiovascular mortality, MI, re-hospitalisation for ACS, or stroke by 2%.[25]

Returning to the PROVE-IT analysis,[5] an assessment was made of the proportions of diabetic and nondiabetic patients attaining the dual clinical goal of plasma LDL-C level <70 mg/dL and plasma CRP concentration <2 mg/dL. Among diabetic patients who attained this 'dual goal', the frequency of the triple endpoint was significantly lower than in diabetic patients who did not (17.7% vs 24.7%; relative risk 0.66; p = 0.021). A similar finding was evident in patients without diabetes (12.8% vs 16.7%; relative risk 0.72; p = 0.003) [figure 6]. These results underscore the clinical importance of attaining the abovementioned LDL-C and CRP goal in ACS patients with diabetes, since one in four such diabetic patients who do not attain this goal experience acute cardiac events.[5]

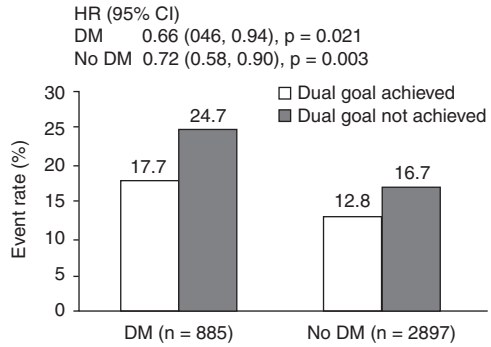


Fig. 6. Incidence of acute cardiac events in diabetic and nondiabetic patients in the PROVE-IT (PRavastatin Or atorVastatin Evaluation and Infection Therapy) trial. Acute cardiac events comprised death, myocardial infarction, and unstable angina requiring hospitalisation. The dual goal refers to a plasma low-density lipoprotein cholesterol level <70 mg/dL and a plasma C-reactive protein concentration <2 mg/dL (reproduced from Ahmed et al.,[5] with permission). **DM** = diabetes mellitus; **HR** = hazard ratio.

Unlike the previously mentioned secondary prevention trials with atorvastatin, which all revealed favorable effects in diabetic patients, the secondary prevention arm of the ASPEN trial[8] failed to reveal a statistically significant decrease in cardiovascular risk in atorvastatin-treated patients with CHD. In fact, the composite primary endpoint (cardiovascular mortality, nonfatal or silent MI, nonfatal stroke, revascularisation procedures, cardiac arrest and resuscitation, deteriorating or unstable angina necessitating hospitalisation) occurred less often in atorvastatin than placebo recipients (26.2% vs 30.8%), but this was not statistically significant.[8] Also, the incidence of fatal/nonfatal MI was 27% lower with atorvastatin than with placebo (p < 0.10) but the difference was not significant. Limitations of the ASPEN study are discussed in section 1.

2.2 Patients with Metabolic Syndrome

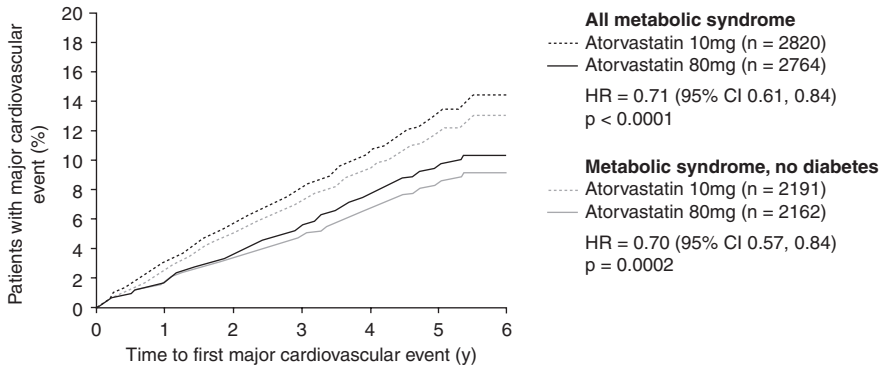
A TNT study sub-analysis[6] involved a total of 5584 CHD patients with metabolic syndrome, as defined by NCEP ATP III[13] and National Heart, Lung, and Blood Institute criteria:[14] that is, the presence of three or more risk factors, such as body mass index ≥28 kg/m^2, triglycerides ≥150 mg/dL,

1 The use of trade names is for product identification purposes only and does not imply endorsement.

HDL-C <40 mg/dL (men) or <50 mg/dL (women), blood pressure ≥130/85mm Hg, or fasting glucose ≥100 mg/dL.[6] After an 8-week run-in period of atorvastatin 10 mg/day, patients with plasma LDL-C concentrations <130 mg/dL were randomised, in double-blind fashion, to receive atorvastatin 80 mg/day (n = 2764) or continue with 10 mg/day (n = 2820), for a median follow-up period of 4.9 years. High-dosage atorvastatin reduced mean LDL-C concentration from 97.6 mg/dL at baseline to 72.6 mg/dL after 3 months' treatment, and the value was maintained at <80 mg/dL for the remainder of the trial (i.e. up to and including the final study visit); at 3 months, mean LDL-C level in the lower-dosage atorvastatin group was 99.3 mg/dL ($p < 0.0001$ vs high-dosage therapy). At 3 months, the mean plasma triglyceride level was 147.7 mg/dL in the high-dosage group, compared with 175.8 mg/dL in the lower-dosage group ($p < 0.0001$).[6]

Overall, in the main TNT trial,[11] and regardless of the assigned study schedule, the incidence of major cardiovascular events was significantly greater in patients with, versus those without, metabolic syndrome (11.3% vs 8.0%; relative risk 1.44; $p < 0.0001$).[6] However, among the subpopulation with metabolic syndrome, intensive versus lower-dosage atorvastatin therapy reduced the relative risks of cardiovascular, coronary and cerebrovascular events, and the risk of congestive heart failure requiring hospitalisation, in a manner similar to that in the entire TNT population. That is, with the exception of total mortality and peripheral arterial disease, risk reductions were generally >20%, and confidence intervals for specific hazard ratios were <1, in patients with metabolic syndrome and in the overall study population.[6]

In TNT study participants with metabolic syndrome (n = 5584), high- versus lower-dosage atorvastatin was associated with a significantly lower incidence over 4.9 years of the primary study endpoint (i.e. CHD death, nonfatal MI [unrelated to procedures], cardiac arrest and resuscitation, or nonfatal or fatal stroke; 9.5% vs 13.0%), thus indicating a relative risk reduction of 29% ($p < 0.0001$; figure 7).[6] High-dosage atorvastatin also significantly reduced relative risks of the following secondary endpoints: any cardiovascular events (−22%; $p < 0.0001$); major coronary events (i.e. CHD mortality, nonfatal MI [unrelated to procedures], or cardiac arrest and resuscitation; −28%; $p = 0.0004$); any



Number at risk

All metabolic syndrome							
Atorvastatin 10mg	2820	2728	2644	2554	2464	1249	0
Atorvastatin 80mg	2764	2707	2635	2561	2483	1270	0
Metabolic syndrome, no diabetes							
Atorvastatin 10mg	2191	2129	2066	2004	1945	994	0
Atorvastatin 80mg	2162	2118	2065	2018	1967	1022	0

Fig. 7. Rates of major cardiovascular events in TNT (Treating to New Targets) study participants with metabolic syndrome (reproduced from Deedwania et al.,[6] with permission). **HR** = hazard ratio.

coronary events (−25%; p < 0.0001); cerebrovascular events (−26%; p = 0.011); and congestive heart failure requiring hospitalisation (−27%; p = 0.027). Among the 4353 patients who had metabolic syndrome, but without diabetes, high- versus lower-dosage atorvastatin was again associated with a significantly lower incidence of the primary study endpoint (8.2% vs 11.6%), thus indicating a relative risk reduction of 30% (p = 0.0002; figure 7). Among all TNT study participants with metabolic syndrome, the atorvastatin regimens produced similar rates of treatment-related adverse events, and similar rates of study discontinuation because of such events (high-dosage, 6.4% of patients; low-dosage, 5.4%). More patients in the high- versus lower-dosage group had persistently raised plasma hepatic enzyme levels (i.e. AST, ALT, or both, >3 × the upper limit of normal on two separate occasions 4–10 days apart; 1.1% vs 0.2% of patients), but no patients had persistently raised creatine phosphokinase concentrations.[6]

Findings from this TNT sub-analysis suggest that intensive lipid-lowering therapy is a particularly viable therapeutic option for CHD patients with metabolic syndrome; indeed, the analysis revealed that CHD patients with, rather than those without, metabolic syndrome had a 44% greater level of absolute cardiovascular risk.[6] Furthermore, the previous suggestion is in line with findings from the main TNT trial, and from various other studies of intensive lipid-lowering therapy with statins in CHD patients.[6,26]

3. Conclusions

A broad range of clinical trial data now confirm the important degree of cardiovascular risk reduction that can be attained with atorvastatin therapy in patients with diabetes and/or metabolic syndrome. In this respect, relevant, major trials comprise the CARDS and ASCOT-LLA studies of atorvastatin 10 mg/day in primary prevention, and the GREACE, TNT, and PROVE-IT trials of atorvastatin, up to 80 mg/day, in the secondary prevention of cardiovascular events. Clearly, several patient populations, from definitive, large-scale studies, are now available to corroborate the integral place of atorvastatin – in line with various regional and internationally accepted disease management guidelines – in the primary and secondary prevention of cardiovascular events in patients with diabetes and/or metabolic syndrome.

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