Reduction of low-density lipoprotein cholesterol in patients with coronary heart disease and metabolic syndrome: analysis of the Treating to New Targets study

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Summary

Background **Despite the prognostic value of metabolic syndrome for predicting cardiovascular events, few trials have investigated the effects of statin therapy on cardiovascular morbidity and mortality in patients with the metabolic syndrome. Our post hoc analysis of the Treating to New Targets (TNT) study assessed whether intensive lowering of low-density lipoprotein cholesterol with high-dose atorvastatin therapy results in cardiovascular benefits for patients with both coronary heart disease and the metabolic syndrome.**

Methods **The TNT study was a prospective, double blind, parallel-group trial done at 256 sites in 14 countries between April, 1998, and August, 2004, with a median follow-up of 4·9 years. 10 001 patients were enrolled aged 35–75 years with clinically evident coronary heart disease. Our analysis includes 5584 patients with metabolic syndrome based on the 2005 NCEP ATP III criteria. Patients were randomly assigned to receive either atorvastatin 10 mg per day (n=2820) or 80 mg per day (n=2764). The primary outcome measure was time to first major cardiovascular event, defined as death from coronary heart disease, non-fatal non-procedure-related myocardial infarction, resuscitated cardiac arrest, or fatal or non-fatal stroke.**

Findings **In patients with coronary heart disease and metabolic syndrome, mean on-treatment low-density lipoprotein cholesterol concentrations at 3 months were 2·6 mmol/L (99·3 mg/dL) with atorvastatin 10 mg, and 1·9 mmol/L (72·6 mg/dL) with atorvastatin 80 mg. At a median follow-up of 4·9 years, major cardiovascular events occurred in 367 (13%) patients receiving atorvastatin 10 mg, compared with 262 (9·5%) receiving atorvastatin 80 mg (hazard ratio 0·71; 95% CI 0·61–0·84; p<0·0001). Irrespective of treatment assignment, significantly more patients with metabolic syndrome (11·3%) had a major cardiovascular event at a median of 4·9 years than those without metabolic syndrome (8·0%; hazard ratio 1·44; 95% CI 1·26–1·64; p<0·0001). This increased risk was significantly reduced by intensive therapy with atorvastatin 80 mg beyond that achieved with atorvastatin 10 mg.**

Interpretation **These data indicate that patients with coronary heart disease and metabolic syndrome derive incremental benefit from high-dose atorvastatin therapy, irrespective of the presence of diabetes.**

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Introduction

The metabolic syndrome has been identified as the clustering of cardiovascular risk factors including insulin resistance, obesity, hypertension, and dyslipidaemia, and has been closely linked to the development of diabetes and cardiovascular disease.[1–7] Organisations, including the National Cholesterol Education Program Adult Treatment Panel (NCEP ATP)[8,9] and the International Diabetes Federation,[10] have identified the metabolic syndrome as the presence of at least three risk factors including hypertension, raised plasma glucose, raised serum triglycerides, low serum concentrations of high-density lipoprotein cholesterol, and large waist circumference, albeit each with slightly different criteria.

In 2001, the third report of the NCEP ATP recognised the importance of treating metabolic risk factors as a secondary target of cardiovascular risk reduction, after low-density lipoprotein cholesterol reduction.[8] In 2004, based on the results from major clinical trials, the NCEP ATP affirmed its low-density lipoprotein cholesterol goal of less than 2·6 mmol/L (100 mg/dL) in patients with cardiovascular disease or risk equivalents (including multiple risk factors), with an optional low-density lipoprotein cholesterol goal of less than 1·8 mmol/L (70 mg/dL) in high-risk patients (including patients with established coronary heart disease plus other high risk conditions including the metabolic syndrome).[9] The lower goal for low-density lipoprotein cholesterol is consistent with the guidelines on prevention of cardiovascular disease of the Joint British Societies[11] and the recent secondary prevention guidelines of the American Heart Association and American College of Cardiology (endorsed by the National Heart, Lung, and Blood Institute); the former recommends a goal for low-density lipoprotein cholesterol of less than 2·0 mmol/L (80 mg/dL) in high-risk patients whereas the latter states that reduction of concentrations of low-density lipoprotein cholesterol to less than 1·8 mmol/L (70 mg/dL) in any patient with established coronary heart disease is reasonable.[12] Reduction of low-density lipoprotein cholesterol to NCEP ATP III goals was further recommended as the primary target for

the treatment of atherogenic dyslipidaemia in the 2005 scientific statement of the American Heart Association and National Heart, Lung, and Blood Institute on the diagnosis and management of the metabolic syndrome.[13] Joint British Societies' guidelines list the metabolic syndrome as one factor supporting intensified risk-reduction treatment.[11]

The consensus in national and international guidelines for the clinical value of viewing cardiovascular risk as a multifactorial complex and the metabolic syndrome as one multifactorial pattern of risk continues to grow.[12,13] In a recent joint statement, the American Diabetes Association and the American Heart Association reinforced the importance of identifying and treating a core set of risk factors (pre-diabetes, hypertension, dyslipidaemia, and obesity) to reduce the burden of diabetes and cardiovascular disease.[14]

To date, few trials have investigated the effects of statin therapy on cardiovascular morbidity and mortality in patients with the metabolic syndrome. However, there are ample data showing that statin therapy in general reduces cardiovascular risk.[4,15–17] The Treating to New Targets (TNT) study[18] randomly assigned 10 001 patients with coronary heart disease and low-density lipoprotein cholesterol concentrations of less than 3·4 mmol/L (130 mg/dL) to either atorvastatin 80 mg per day or 10 mg per day for a median follow-up of about 5 years. The current post hoc analysis of the TNT study investigates the long-term cardiovascular risk profile of 5584 patients with coronary heart disease and metabolic syndrome and whether significant cardiovascular benefits can be achieved with high-dose intensive statin therapy.

Methods

Study design and participants

The TNT study was a double-blind, parallel-group trial done between April, 1998, and August, 2004, the design of which has been described in detail previously.[18,19] Patients were randomly assigned at 256 sites in 14 countries worldwide (Australia 608 patients; Austria 29; Belgium 300; Canada 1052; France 207; Germany 144; Ireland 53; Italy 75; the Netherlands 788; South Africa 523; Spain 525; Switzerland 91; UK 299; USA 5309). The current analysis investigates whether incremental reduction in cardiovascular risk can be achieved by lowering concentrations of low-density lipoprotein cholesterol beyond minimum targets currently recommended in patients with clinically evident coronary heart disease and metabolic syndrome.

Patients eligible for inclusion were men and women aged 35–75 years with clinically evident coronary heart disease, defined as previous myocardial infarction, previous or present angina with objective evidence of atherosclerotic coronary heart disease, or previous coronary revascularisation procedure. Patients were included in the current analysis if they met criteria for the metabolic syndrome before the open-label run-in period. Metabolic syndrome was defined as the presence of three or more of the following risk factors: body-mass index of 28 kg/m^2 or more, triglycerides 1·7 mmol/L (150 mg/dL) or more, high-density lipoprotein-cholesterol less than 1·0 mmol/L (40 mg/dL) in men or less than 1·3 mmol/L (50 mg/dL) in women, blood pressure 130/85 mm Hg or higher, or fasting glucose 5·6 mmol/L or more (100 mg/dL). This definition was based on that set by the NCEP ATP III,[8] and a recent modification by the American Heart Association and National Heart, Lung, and Blood Institute.[13] Body-mass index of 28 kg/m^2 replaced waist circumference of 102 cm or more in men or 88 cm or more in women, since waist circumference was not recorded at screening. Patients with metabolic syndrome who also had type 2 diabetes mellitus were not excluded from the analysis. Major exclusion criteria for the TNT study included statin hypersensitivity, current liver disease, nephrotic syndrome, pregnancy, or uncontrolled coronary heart disease risk factors (including uncontrolled diabetes mellitus or uncontrolled hypertension as defined by the investigator), coronary heart disease event or revascularisation within a month, congestive heart failure, unexplained creatine phosphokinase concentrations six or more times the upper limit of normal, life-threatening malignancy, or immunosuppressive or lipid-lowering drug treatment.

Any previously prescribed lipid-regulating drugs were discontinued at screening, and all patients required a wash-out period of 1–8 weeks (8 weeks for those patients who had previously received lipid-regulating drugs, and 1 week for those who had not). To ensure that all patients at baseline achieved low-density lipoprotein cholesterol levels consistent with then current guidelines for the treatment of stable coronary heart disease, patients with low-density lipoprotein cholesterol between 3·4 and 6·5 mmol/L (130–250 mg/dL) and triglycerides 6·8 mmol/L or less (600 mg/dL) entered an 8-week open-label period with atorvastatin 10 mg per day. At the end of the run-in phase (baseline), those patients with a mean low-density lipoprotein cholesterol of less than 3·4 mmol/L (130 mg/dL; established at weeks –4 and –2) were randomised to double-blind therapy with either atorvastatin 10 mg or 80 mg per day (figure 1). Cholesterol inclusion and exclusion criteria were selected to achieve an average level of 2·6 mmol/L (100 mg/dL) in the atorvastatin 10 mg per day treatment group. To reach an average low-density lipoprotein cholesterol concentration in the comparator group of about 1·9 mmol/L (75 mg/dL), atorvastatin 80 mg per day was chosen. During the double-blind period, follow-up visits took place at week 12 and at months 6, 9, and 12 in the first year, and every 6 months thereafter. At each visit, vital signs, clinical endpoints, adverse events, and concurrent medication information were obtained. Additionally, on alternating visits (ie, once a year), physical examinations and electrocardiograms were done and laboratory specimens obtained.

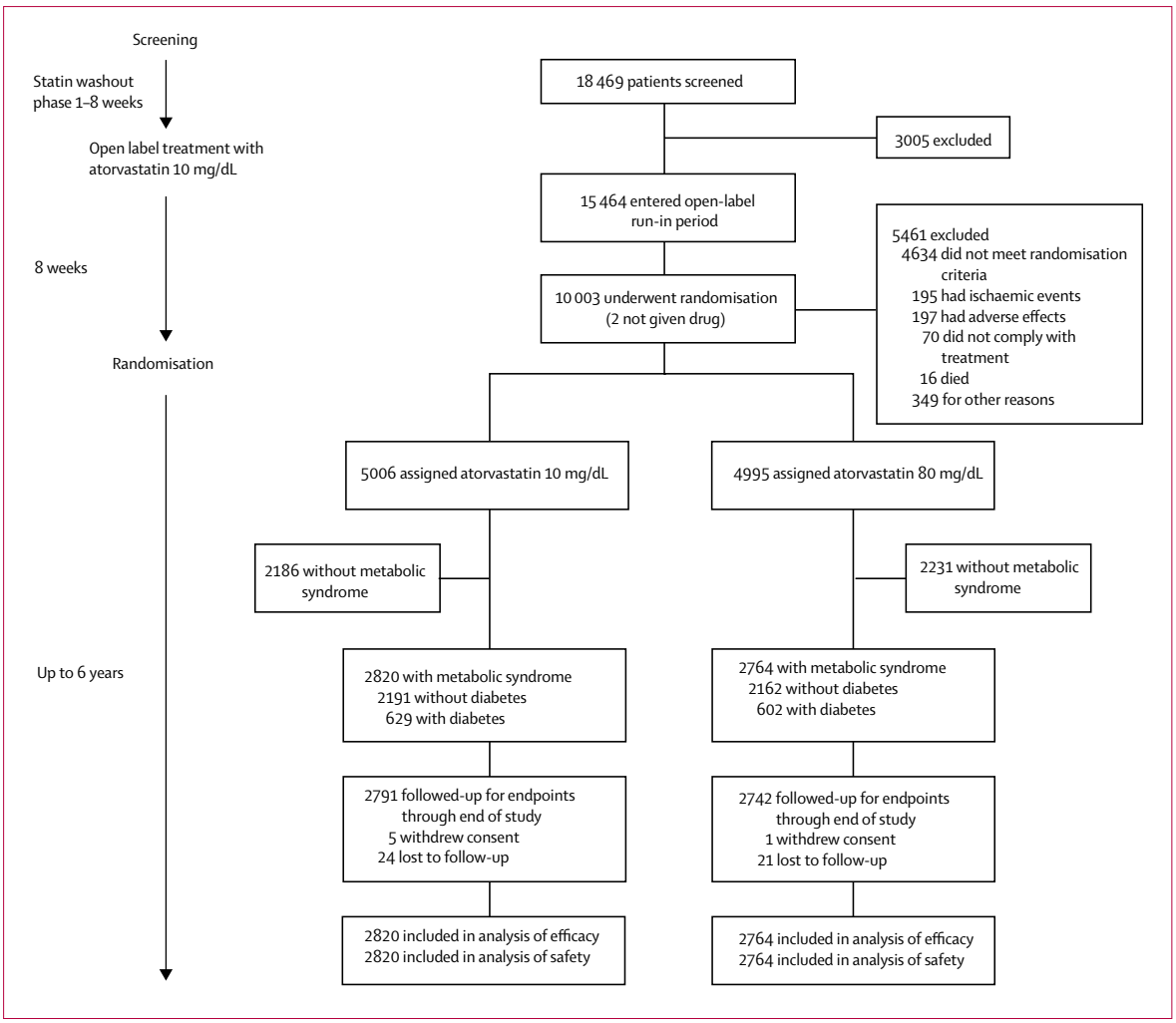


Figure 1: **Trial profile**

The primary outcome measure was the time to first occurrence of a major cardiovascular event, defined as death from coronary heart disease, non-fatal non-procedure-related myocardial infarction, resuscitated cardiac arrest, or fatal or non-fatal stroke. Secondary outcome measures included any cardiovascular event, major coronary event (coronary heart disease death, non-fatal non–procedure-related myocardial infarction, or resuscitated cardiac arrest), any coronary event, cerebrovascular event, peripheral arterial disease, congestive heart failure with hospitalisation, and all-cause mortality.

Statistical analysis

The sample size of the TNT study was based on epidemiological data that suggested that the difference in low-density lipoprotein cholesterol levels between the two treatment groups would reduce the number of 5-year recurrent coronary events in the atorvastatin 80 mg per day treatment group by 20–30% compared with atorvastatin 10 mg per day. The study originally had a target enrolment of around 8600 patients to accumulate 750 major coronary events in an average follow-up time estimated at 5·5 years. A higher than expected recruitment rate afforded the opportunity to increase the sample size in the study; 10 003 patients were randomised and all but two received the study drug.

Analyses were done on the intent-to-treat population, and included all randomised patients who received at least one dose of the study drug. Patients with metabolic syndrome but without a diagnosis of type 2 diabetes before screening were also analysed (the diagnosis of type 2 diabetes was based on history of diabetes at screening). For the current analysis, no data imputation was done for missing values at any particular visit. Between treatment comparisons at a specific visit (eg, 3 months) for changes from baseline in lipids were assessed by an analysis of covariance (ANCOVA) model, with treatment as the major factor and baseline lipid value as the covariate. Overall treatment differences for

changes in lipids across all time points were assessed by repeated measures of the ANCOVA model with the patient as the unit of cluster variable assuming an appropriate variance-covariance structure. The following factors were included in the model: treatment, time, and treatment by time interaction with baseline lipid as the covariate. Differences between the atorvastatin 80 mg and 10 mg treatment groups were based on log rank analyses of the first occurrence of a major cardiovascular event during the 5-year follow-up in each group. Hazard ratios and their 95% CIs were estimated with the Cox proportional hazard regression model. In this model, treatment effect was estimated by a univariate analysis based on treatment as the major factor. The effect of individual characteristics of metabolic syndrome on the risk of cardiovascular events was assessed by a similar univariate Cox proportional hazard model including a binary indicator variable that used the presence or absence of individual metabolic syndrome characteristics as the only factor. The relation between risk of cardiovascular events and the number of metabolic syndrome components was assessed by Cochran-Armitage test for trend in each treatment group. Two-sided p values <0·05 were regarded as significant. All analyses were done with SAS statistical software (version 8.12).

Role of the funding source

The funding source contributed to the design and conduct of the study, the collection, management, analysis, and interpretation of the data, and the preparation, review, and approval of the manuscript. The corresponding author had full access to all of the data in the study and had final responsibility for the decision to submit for publication.

Results

Of the 10 001 patients randomised, 5584 (56%) met the criteria for the metabolic syndrome, of whom 2820 were randomly assigned atorvastatin 10 mg per day and 2764 atorvastatin 80 mg per day (figure 1). Hypertension (66% *vs* 54%) and diabetes (22% *vs* 15%) were more prevalent in this subgroup than in the overall cohort. At baseline (after open-label treatment with atorvastatin 10 mg), mean levels of low-density lipoprotein cholesterol and total cholesterol were similar between patients with metabolic syndrome and the overall population, whereas high-density lipoprotein cholesterol was slightly lower

	All metabolic syndrome patients		Metabolic syndrome patients without diabetes	
	Atorvastatin 10 mg (n=2820)	Atorvastatin 80 mg (n=2764)	Atorvastatin 10 mg (n=2191)	Atorvastatin 80 mg (n=2162)
Men (%)	2210 (78·4%)	2167 (78·4%)	1768 (80·7%)	1741 (80·5%)
Age, years	60·8 (8·8)	61·0 (8·8)	60·3 (8·9)	60·4 (8·9)
White (%)	2650 (94·0%)	2593 (93·8%)	2085 (95·2%)	2050 (94·8%)
Systolic blood pressure, mm Hg	133 (17)	133 (17)	133 (16)	132 (16)
Diastolic blood pressure, mm Hg	79 (10)	79 (10)	79 (9)	79 (9)
Body-mass index, kg/m2	30·5 (4·7)	30·2 (4·5)	30·2 (4·4)	29·9 (4·3)
Fasting plasma glucose, mmol/L	6·4 (2·0)	6·4 (2·0)	5·8 (0·9)	5·7 (0·9)
HbA1c, % (SD)	6·9% (1·3%)	6·9% (1·3%)	6·0% (0·8%)	5·9% (0·7%)
Current smoker (%)	380 (13·5%)	379 (13·7%)	320 (14·6%)	308 (14·3%)
Cardiovascular history				
Angina	2326 (82·5%)	2310 (83·6%)	1815 (82·8%)	1800 (83·3%)
Hypertension	1876 (66·5%)	1820 (65·8%)	1401 (63·9%)	1360 (62·9%)
Myocardial infarction	1631 (57·8%)	1604 (58·0%)	1295 (59·1%)	1249 (57·8%)
Coronary angioplasty	1507 (53·4%)	1515 (54·8%)	1195 (54·5%)	1183 (54·7%)
Coronary artery bypass graft	1373 (48·7%)	1342 (48·6%)	1025 (46·8%)	1019 (47·1%)
Diabetes	629 (22·3%)	602 (21·8%)	0	0
Arrhythmia	543 (19·3%)	518 (18·7%)	415 (18·9%)	389 (18·0%)
Peripheral arterial disease	364 (12·9%)	384 (13·9%)	239 (10·9%)	245 (11·3%)
Congestive heart failure	277 (9·8%)	241 (8·7%)	187 (8·5%)	149 (6·9%)
Cerebrovascular accident	185 (6·6%)	168 (6·1%)	127 (5·8%)	110 (5·1%)
Lipids, mmol/L				
Low-density lipoprotein cholesterol	2·53 (0·46)	2·52 (0·45)	2·54 (0·46)	2·53 (0·45)
Total cholesterol	4·56 (0·63)	4·55 (0·63)	4·56 (0·63)	4·55 (0·62)
Triglycerides	1·97 (0·85)	1·97 (0·84)	1·95 (0·84)	1·94 (0·82)
High-density lipoprotein cholesterol	1·13 (0·24)	1·14 (0·25)	1·13 (0·25)	1·14 (0·25)

Data are mean (SD) or number of participants (%). HbA1c=glycated haemoglobin.

Table: **Baseline characteristics of patients with metabolic syndrome**

(1·1 mmol/L [44 mg/dL] *vs* 1·2 mmol/L [47 mg/dL]) and triglycerides were higher (2·0 mmol/L [175 mg/dL] *vs* 1·7 mmol/L [151 mg/dL]) in patients with metabolic syndrome. Baseline characteristics of patients with metabolic syndrome were similar between the two treatment groups, as were baseline low-density lipoprotein cholesterol, total cholesterol, triglycerides, and high-density lipoprotein cholesterol (table). Within the subgroup with metabolic syndrome, 1231 (22 %) patients had diabetes and 4353 (78%) patients did not. Of the diabetes patients in TNT, 18% (270/1501) did not have metabolic syndrome. Baseline demographics of the subgroup of patients with metabolic syndrome who did not have a diagnosis of diabetes at screening were similar to those of all patients with metabolic syndrome, but consisted of slightly more men, and had a slightly lower prevalence of hypertension, coronary artery bypass graft, peripheral arterial disease, congestive heart failure, and cerebrovascular accident (table).

Figure 2 summarises the changes in lipids during the study for the two treatment groups. From an overall baseline mean of 2·5 mmol/L (97·6 mg/dL), atorvastatin 80 mg lowered the concentration of low-density lipoprotein cholesterol to 1·9 mmol/L (72·6 mg/dL) after 3 months of treatment, compared with 2·6 mmol/L (99·3 mg/dL) in the atorvastatin 10 mg group (p<0·0001). Concentrations of triglyceride were lowered from an overall baseline mean of 2·0 mmol/L (174·5 mg/dL) to 1·7 mmol/L (147·7 mg/dL) in the atorvastatin 80 mg group at 3 months, compared with 2·0 mmol/L (175·8 mg/dL) in the atorvastatin 10 mg group (p<0·0001). There was no significant difference in changes in concentrations of high-density lipoprotein cholesterol after 3 months in either treatment group. Treatment differences, time effect, and treatment by time interaction were significant for changes over time in low-density lipoprotein cholesterol and triglyceride but not for high-density lipoprotein cholesterol. Similar lipid reductions were recorded for the subgroup of patients without diabetes at screening.

After a median follow-up of 4·9 years, 262 patients (9·5%) with metabolic syndrome receiving atorvastatin 80 mg and 367 (13%) receiving atorvastatin 10 mg had a primary event. This finding represented a 29% relative reduction in the risk of major cardiovascular events in favour of the high-dose group (hazard ratio 0·71, 95% CI 0·61–0·84; p<0·0001; figure 3). Significant differences between the groups in favour of atorvastatin 80 mg were also seen for the secondary outcomes of time to any cardiovascular event (0·78, 0·71–0·85; p<0·0001), major coronary event (0·72, 0·60–0·86; p=0·0004), any coronary event (0·75, 0·67–0·83; p<0·0001), cerebrovascular event (0·74, 0·59–0·93; p=0·011), and hospitalisation for congestive heart failure (0·73, 0·55–0·96; p=0·027; figure 4). Consistent with the overall population, there was no significant difference between the treatments for all-cause mortality (figure 4).

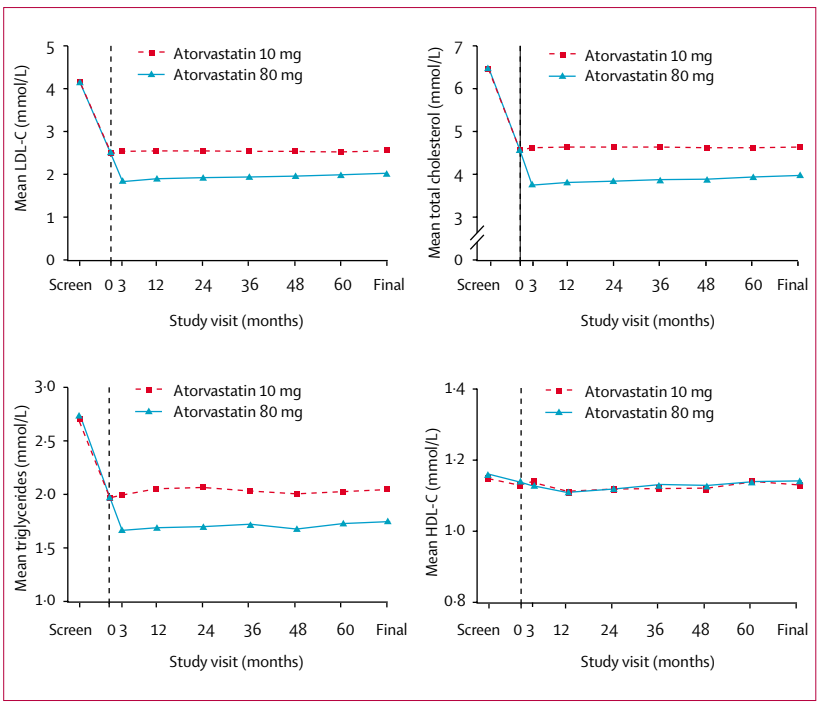
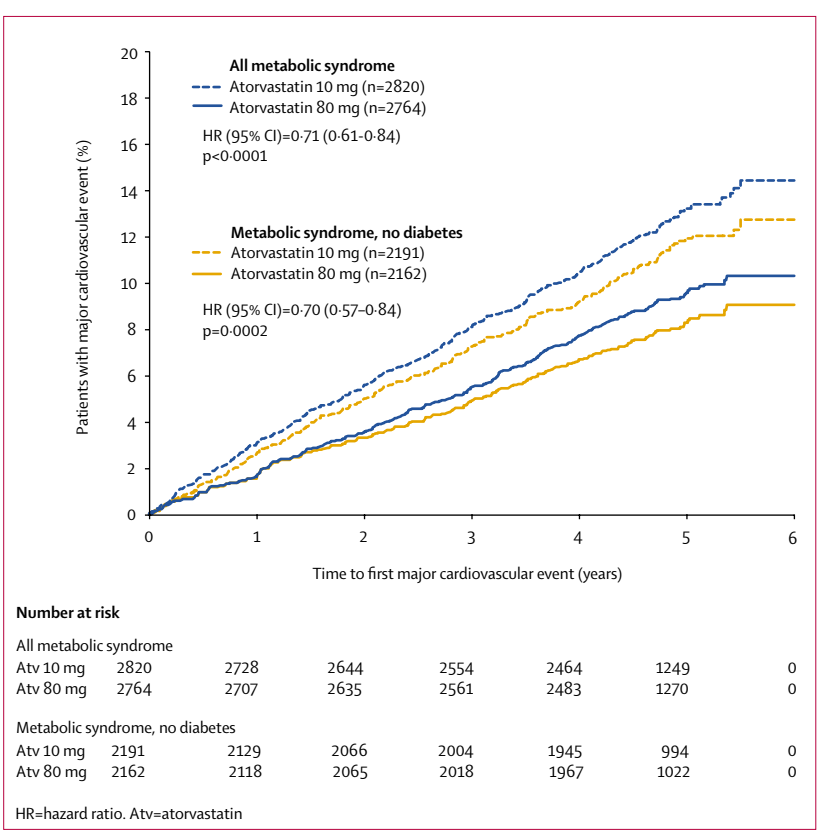


Figure 2: **Mean lipid levels after randomisation in all patients with metabolic syndrome**
LDL-C=low-density lipoprotein cholesterol. HDL-C=high-density lipoprotein cholesterol.



Number at risk

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

HR=hazard ratio. Atv=atorvastatin

Figure 3: **Kaplan-Meier estimates of the proportion of patients with major cardiovascular events by treatment in all patients with metabolic syndrome and in patients with metabolic syndrome without diabetes**

In the subgroup of metabolic syndrome patients without diabetes at screening, 178 (8·2%) receiving atorvastatin 80 mg and 255 (11·6%) receiving atorvastatin 10 mg had a primary event. This finding represented a 30% relative reduction in the risk of a major cardiovascular event in favour of the high-dose group (0·70, 0·57–0·84; p=0·0002; figure 3). The treatment effect of atorvastatin 80 mg compared with 10 mg in patients without diabetes at screening seemed to be at least as great as in all metabolic syndrome patients for most secondary outcomes (figure 4).

Irrespective of treatment assignment, significantly more patients with metabolic syndrome (11·3%) had a major cardiovascular event than those without metabolic syndrome (8·0%; hazard ratio 1·44, 95% CI 1·26–1·64; p<0·0001). Although, patients with metabolic syndrome and diabetes were at the highest risk, significantly more patients with metabolic syndrome but without diabetes (9·9%) had a major cardiovascular event than those without either metabolic syndrome or diabetes (7·5%; figure 5).

Univariate analysis of the individual characteristics of metabolic syndrome revealed a significantly increased

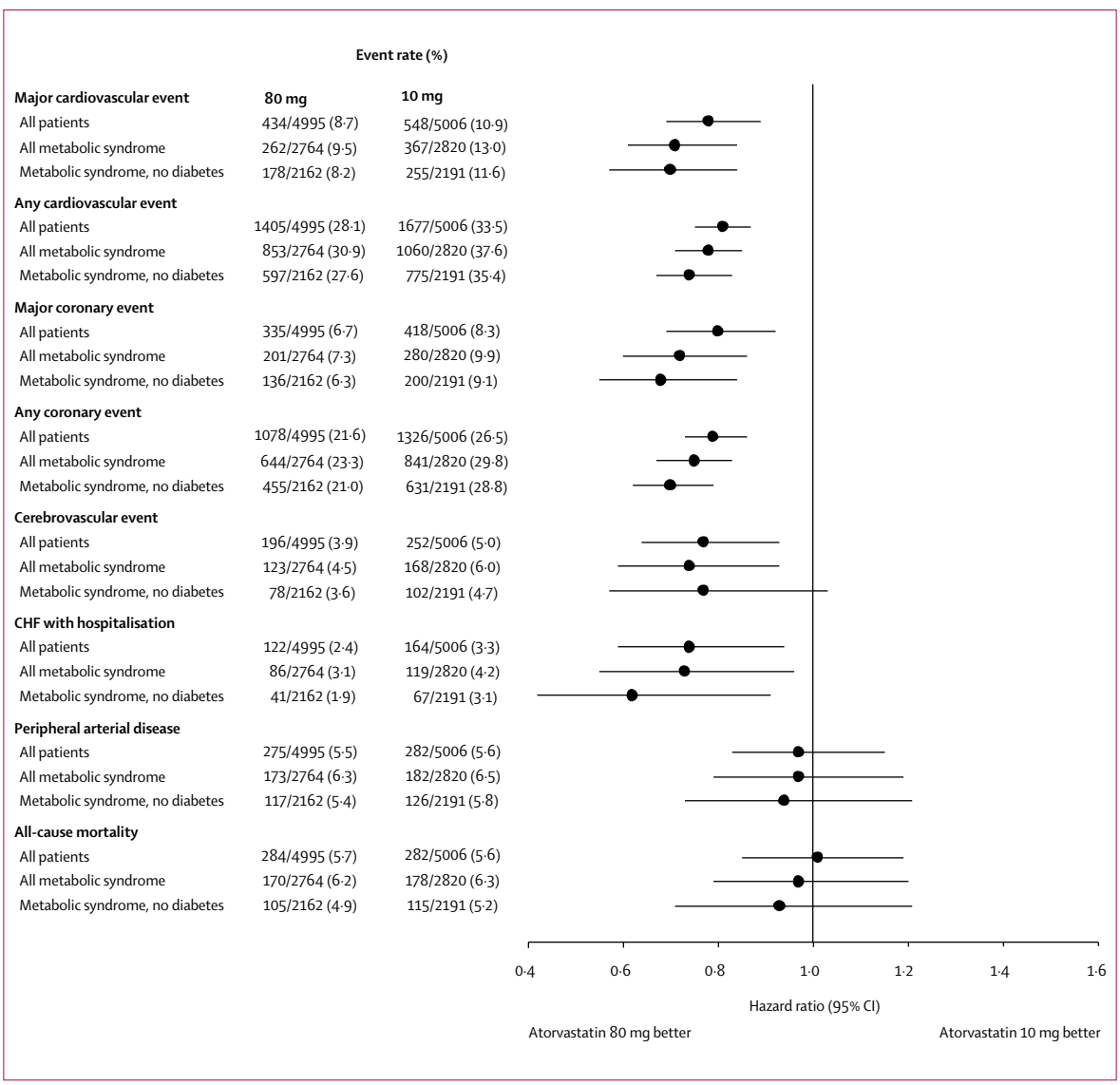


Figure 4: **Hazard ratios for primary and secondary outcomes in all patients recruited in the TNT study (n=10 001), all patients with metabolic syndrome (n=5584), and patients with metabolic syndrome without diabetes (n=4353)**

CHF=congestive heart failure. Major cardiovascular event was defined as death from coronary heart disease, non-fatal non–procedure-related myocardial infarction, resuscitated cardiac arrest, or fatal or non-fatal stroke. Any cardiovascular event indicates cerebrovascular event, congestive heart failure with hospitalisation, death from coronary heart disease, myocardial infarction, resuscitated cardiac arrest, coronary revascularisation, or documented angina. Major coronary event indicates death from coronary heart disease, non-fatal non–procedure-related myocardial infarction, resuscitated cardiac arrest. Any coronary event indicates major coronary event, coronary revascularisation, procedure-related myocardial infarction, documented angina. Cerebrovascular event indicates fatal or non-fatal stroke, or transient ischaemic attack.

risk of major cardiovascular events in patients with the presence of low high-density lipoprotein cholesterol, fasting glucose of 5·6 mmol/L or more (100 mg/dL), body-mass index 28 kg/m² or more, triglycerides 1·7 mmol/L or more (150 mg/dL), or hypertension (figure 6). Furthermore, in an analysis of all patients randomly assigned atorvastatin 10 mg in the TNT study, the risk of major cardiovascular events increased with the presence of each additional component of metabolic syndrome (p<0·0001; figure 7). In patients randomly assigned atorvastatin 80 mg, this incremental increase in cardiovascular risk was attenuated, with greater reduction in absolute risk for each additional component of metabolic syndrome, although the trend remained significant (p<0·0001). A similar result was seen in patients without diabetes (p<0·0001 for atorvastatin 10 mg, p=0·049 for atorvastatin 80 mg; figure 7).

The prevalence of adverse events related to treatment was similar between the two groups. A total of 153 patients (5·4%) randomly assigned atorvastatin 10 mg discontinued because of adverse events related to treatment compared with 178 patients (6·4%) randomly assigned atorvastatin 80 mg. Persistent elevations in liver function enzymes (two measurements of alanine aminotransferase, aspartate aminotransferase, or both, greater than three times or more the upper limit of normal obtained 4–10 days apart) were reported by the central laboratory in 0·2% of patients receiving atorvastatin 10 mg and 1·1% of those receiving atorvastatin 80 mg. No patients in either group had persistent elevations in concentrations of creatine phosphokinase (two measurements greater than 10 times or more the upper limit of normal obtained 4–10 days apart).

Discussion

Patients with coronary heart disease and metabolic syndrome were at significantly higher cardiovascular risk than those with only coronary heart disease. This increased risk was significantly reduced by intensive lowering of low-density lipoprotein cholesterol with atorvastatin 80 mg beyond that achieved with atorvastatin 10 mg. Strikingly, over half of the patients in the TNT study met current clinical criteria for a diagnosis of the metabolic syndrome.[8,13] The present analysis justifies classifying patients with coronary heart disease and metabolic syndrome as being at high risk of future cardiovascular events. Such individuals are therefore good candidates for more intensive lipid-lowering therapy, and consideration for the lower low-density lipoprotein cholesterol goals of 1·8 mmol/L (70 mg/dL) or less cited in updated NCEP ATP III recommendations,[9] and 2·0 mmol/L (80 mg/dL) recommended by the Joint British Societies' guidelines on prevention of cardiovascular disease.[11] In fact, treatment with the higher dose of atorvastatin would be needed to meet these lower targets in most patients with coronary heart disease and the metabolic syndrome. Since the concentration of low-density lipoprotein cholesterol fell from about 2·6 mmol/L (100 mg/dL) with atorvastatin 10 mg to around an average of 1·8 mmol/L (70 mg/dL) with atorvastatin 80 mg, this study provides an opportunity to examine the validity of the lower low-density lipoprotein cholesterol goals for high risk patients who have coronary heart disease and metabolic syndrome.

The primary endpoint of the TNT study was a composite of major cardiovascular events. In TNT patients with the metabolic syndrome, atorvastatin 80 mg reduced the risk

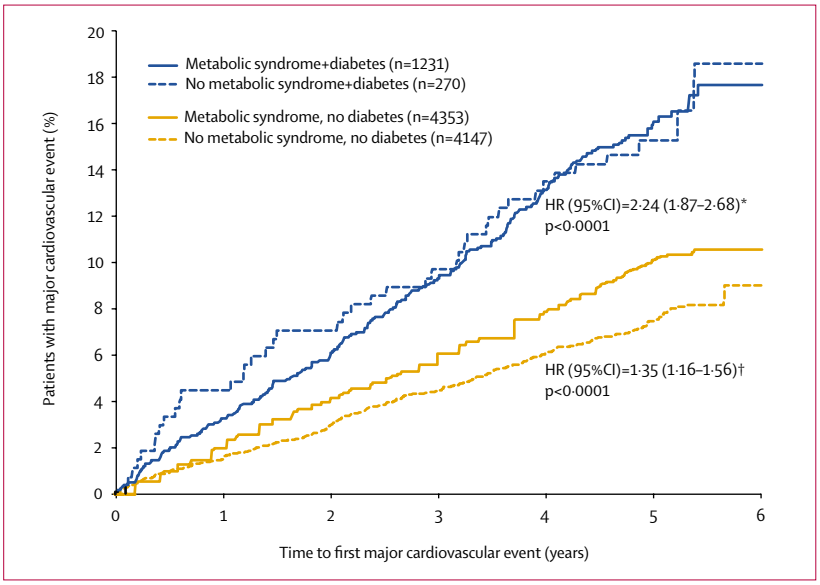


***Figure 5*: Kaplan-Meier estimates of prevalence of patients with major cardiovascular events in all TNT patients by metabolic syndrome and diabetes status**

*Hazard ratio for patients with metabolic syndrome and diabetes versus patients without metabolic syndrome or diabetes. †Hazard ratio for patients with metabolic syndrome without diabetes versus patients without metabolic syndrome or diabetes.

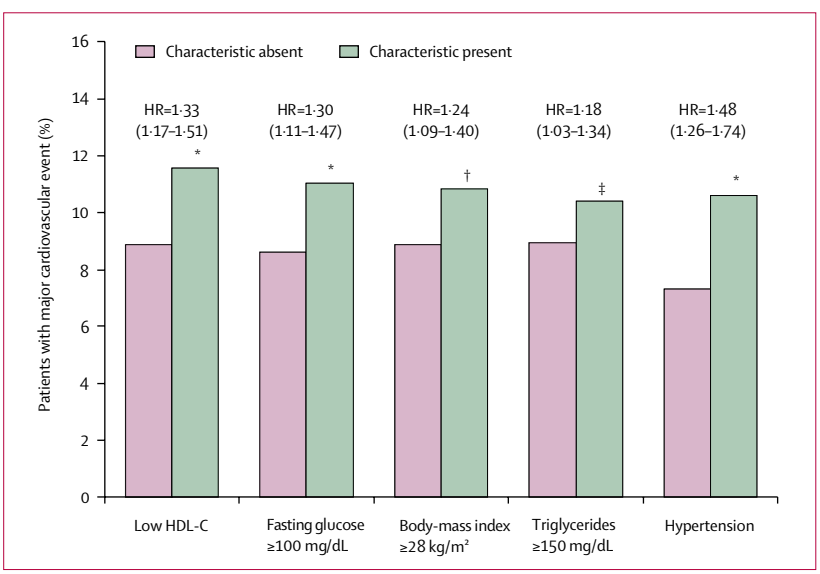


***Figure 6*: Univariate analysis of individual characteristics of metabolic syndrome on risk of major cardiovascular events in all TNT patients (n=10 001)**

HR=hazard ratio. HDL-C=high density lipoprotein cholesterol. Numbers in parentheses represent 95% CI. *p<0·0001. †p=0·0009. ‡p=0·015

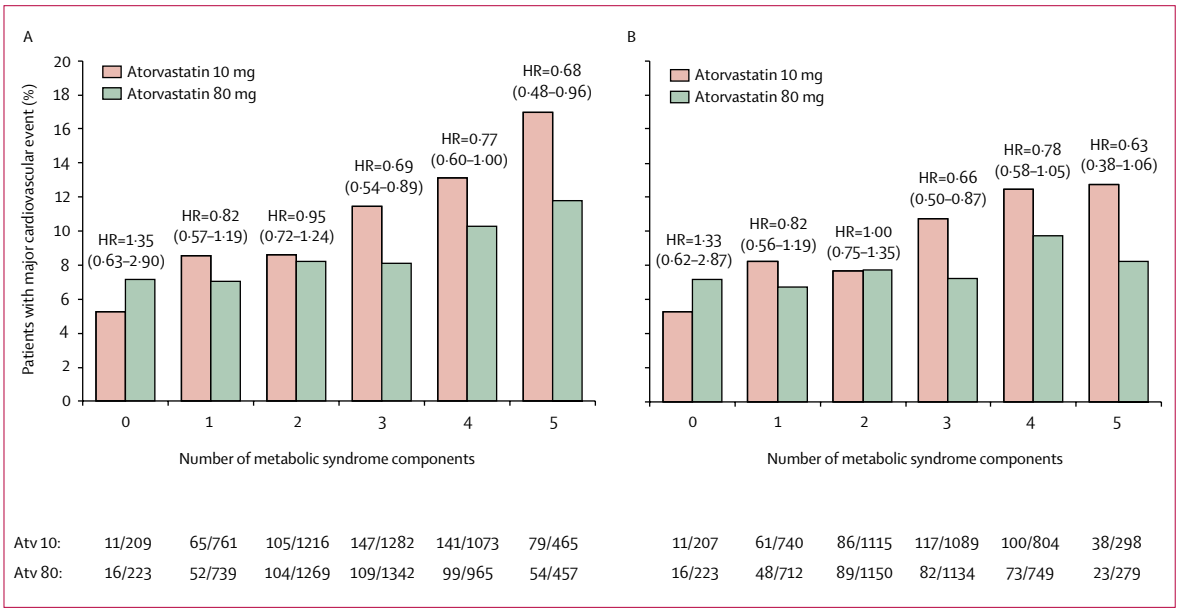


***Figure 7*: Number of patients with major cardiovascular events by presence of metabolic syndrome components in (A) all TNT patients (n=10 001), and (B) all TNT patients without diabetes (n=8500)**

HR=hazard ratio. Numbers in parentheses represent 95% CI. Atv=atorvastatin.

of major cardiovascular events by 29%, a reduction that was over and above that achieved by atorvastatin 10 mg. The study thus provides evidence to suggest that patients with coronary heart disease and metabolic syndrome are good candidates for intensive lipid-lowering therapy.[9,12]

Of patients with coronary heart disease, those with metabolic syndrome are at higher risk than those without because of the presence of multiple risk factors that are not readily reversed by standard therapies. An incremental increase in risk with each additional feature of the metabolic syndrome has also been consistently shown,[4,17,20] as supported by the current study. Thus, even though reduction in relative risk with statin therapy might be similar in patients with and without the metabolic syndrome, the absolute benefit will be greater in those with the metabolic syndrome because of their higher absolute risk. Data from the current study show a 44% increase in absolute risk in coronary heart disease patients with the metabolic syndrome than those without metabolic syndrome, which adds justification for intensive low-density lipoprotein-lowering therapy in these patients.

Moreover, of patients with coronary heart disease and metabolic syndrome, those with diabetes are at the highest risk. Current metabolic syndrome guidelines extend the metabolic syndrome into type 2 diabetes as these patients typically show clustering of multiple risk factors typical of the syndrome.[10,13] However, some investigators prefer to separate metabolic syndrome from type 2 diabetes, which is already well-defined.[21–23] These investigators contend that type 2 diabetes subsumes the metabolic syndrome within itself. A recent analysis of the TNT data indicates that patients with coronary heart disease and diabetes show an incremental benefit during therapy with atorvastatin 80 mg compared with 10 mg.[24] In the current analysis, when patients with diabetes were removed from the analysis, patients with coronary heart disease and metabolic syndrome were still at a 35% higher risk of cardiovascular events than those without metabolic syndrome. Furthermore, a similar benefit was shown for higher-dose atorvastatin, with a 30% reduction in the risk of major cardiovascular events compared with atorvastatin 10 mg.

In this TNT subanalysis, patients with metabolic syndrome, both with and without diabetes had a progressive increase in risk for major cardiovascular events as the number of metabolic syndrome components increased (figure 7). This finding suggests that those at higher risk will show a greater incremental benefit with atorvastatin 80 mg over 5 years. Because of the small number of patients and events, we cannot conclude from this analysis that patients with fewer risk factors will receive no additional risk reduction from atorvastatin 80 mg. Conclusions about the benefits of more intensive intervention per se must be derived from the overall study population which met entrance criteria for the trial; this has been the position of recent guidelines influenced by the TNT study.[11,13] The current findings provide a particularly compelling rationale for more intensive low-density lipoprotein-lowering therapy in coronary heart disease patients with the metabolic syndrome, which is consistent with the findings of the overall TNT study and other statin trials that intensive low-density lipoprotein cholesterol with statins is of benefit in patients with coronary heart disease.[25]

There has been considerable debate about how best to position the metabolic syndrome for clinical practice.[22]

The current study does not resolve the issue about how best to configure the clustering of risk factors that are characteristic of the metabolic syndrome. It does, however, indicate that relative risk for major cardiovascular events rises with an increasing number of components, particularly when three or more cluster together (figure 7); this pattern of clustering is the basis for current clinical definitions for metabolic syndrome.[9,10] The benefit of more intensive atorvastatin therapy was particularly evident in patients of this type (figure 7).

Despite the high enrolment of patients with metabolic syndrome and the robust nature of the TNT study design, there are some limitations to the application of these results. Firstly, the study enrolled only patients with clinically evident coronary heart disease; additional benefits of treating patients with metabolic syndrome beyond the current low-density lipoprotein cholesterol goal of 2·6 mmol/dL (100 mg/dL) for moderately high-risk patients[13] cannot be generalised to metabolic syndrome patients without coronary heart disease. Secondly, there remains no fixed definition of the metabolic syndrome that is universally acknowledged. The current analysis was based on criteria set by the NCEP ATP III,[8] and its modification by the American Heart Association and National Heart, Lung, and Blood Institute,[13] with body-mass index of 28 or more instead of waist circumference. Although waist circumference might be more closely linked to cardiovascular risk factors than body-mass index,[26] the two measures are closely correlated, and a body-mass index of more than 28 in men has shown close agreement with obesity prevalence estimates using waist circumference.[27] Because of discrepancies in the definition, the metabolic syndrome analysis of the TNT study was also run with a definition incorporating a body-mass index of 30 or more, which revealed no differences in the outcome reported.

The Scandinavian Simvastatin Survival Study (4S) compared a standard dose of simvastatin (20 or 40 mg) against placebo in patients with established coronary heart disease.[28] In that trial, simvastatin therapy reduced the risk for various events of coronary heart disease by 30–40% compared with placebo. A subsequent subgroup analysis of 4S showed that patients with the metabolic syndrome benefited from simvastatin therapy by at least as much as those without metabolic syndrome.[15] However, metabolic syndrome patients entered 4S with a mean low-density lipoprotein cholesterol of 4·9 mmol/L (190 mg/dL), which was reduced to around 3·2 mmol/L (120 mg/dL) by simvastatin therapy. In the TNT study, metabolic syndrome patients entered the double-blind treatment phase with a mean low-density lipoprotein cholesterol of 2·5 mmol/L (98 mg/dL), representing a much lower low-density lipoprotein cholesterol level than that achieved in 4S. High-dose atorvastatin therapy further reduced low-density lipoprotein cholesterol to 1·9 mmol/L (73 mg/dL), indicating further significant clinical benefit. Thus, these findings lend support to the idea that greater low-density lipoprotein cholesterol lowering than that achieved with standard doses of statins is warranted in patients with coronary heart disease and the metabolic syndrome.

Contributors

P Deedwania had full access to all of the data in the study, and takes responsibility for the integrity of the data and the accuracy of the analysis. Study concept and design was done by P Barter, J-C Fruchart, S M Grundy, J J P Kastelein, J C LaRosa, J Shepherd, and D D Waters. All authors analysed and interpreted the data, and revised the manuscript.

Conflict of interest statement

P Deedwania has received honoraria for speaking engagements and consulting fees from Pfizer Inc and AstraZeneca. P Barter has received honoraria for speaking engagements and has served on advisory boards for Pfizer, AstraZeneca, FournierPharma, Sanofi-Aventis and Abbott, and has received consulting fees and research support from Pfizer. R Carmena has received honoraria for speaking engagements and consulting fees from Pfizer Inc, AstraZeneca and Merck Sharp & Dohme. J-C Fruchart has received honoraria for speaking engagements, consulting fees, or both from Merck, Fournier, Pfizer, Pierre Fabrie, and AstraZeneca. S M Grundy has been an investigator on research grants awarded to the University of Texas Southwestern Medical Center from Merck, Abbott, and Kos Pharmaceuticals, and has also served as a consultant for Merck, Merck/Schering-Plough, Kos, Pfizer, Eli Lilly, GlaxoSmithKine, Abbott, Fournier, Bristol-Myers Squibb, Sankyo, AstraZeneca, and Sanofi-Aventis. S Haffner has received honoraria for speaking engagements and consulting fees from Pfizer Inc and Merck Sharp & Dohme. J J P Kastelein has received consulting fees, lecture fees and grant support from Pfizer, Merck, Schering-Plough, AstraZeneca, Bristol-Myers Squibb and Sankyo. J C LaRosa has received honoraria for speaking engagements and consulting fees from Pfizer Inc and Bayer. H Schachner is a full-time employee of Pfizer Inc. J Shepherd has received honoraria for speaking engagements and has been a paid consultant for AstraZeneca, Merck Sharp & Dohme/Schering-Plough and Pfizer, and has received funds from AstraZeneca, Merck Sharp & Dohme/Schering-Plough, and Oxford Instruments to do clinical trials. D D Waters has received honoraria for speaking engagements and consulting fees from Pfizer Inc, Merck and Co Inc, Johnson & Johnson, Anthera Pharmaceuticals Inc, Eli Lilly and Company, CSL Ltd, and Atherogenics Inc.

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