Effects of patient-tailored atorvastatin therapy on ameliorating the levels of atherogenic lipids and inflammation beyond lowering low-density lipoprotein cholesterol in patients with type 2 diabetes

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ABSTRACT

Aims/Introduction: Recently, patient-tailored statin therapy was proven effective for achieving target low-density lipoprotein (LDL) cholesterol levels. It is unclear, however, whether this therapeutic modality would be effective for atherogenic lipid profiles and inflammation in patients with type 2 diabetes.

Materials and Methods: The present study was an 8-week, multicenter, single-step titration trial of patient-tailored atorvastatin therapy (10, 20 and 40 mg) according to baseline LDL cholesterol levels in 440 patients with type 2 diabetes. We measured the LDL particle size by polyacrylamide gel electrophoresis, and used high-sensitivity C-reactive protein (hsCRP) and adiponectin as surrogate markers of inflammation.

Results: In the intention-to-treat analysis, 91% of the patients achieved their LDL cholesterol targets (<2.6 mmol/L) at week 8. There were significant reductions at week 8 in total cholesterol, triglycerides, non-high-density lipoprotein cholesterol (HDL) cholesterol, and the total cholesterol:HDL cholesterol ratio compared with the baseline values for all of the doses. The mean LDL particle size was significantly increased, and the small, dense LDL cholesterol levels were decreased in a dose-dependent manner over the study period. In addition, the hsCRP levels were decreased in those high-risk patients with baseline hsCRP levels over 3 mg/L ($P < 0.001$), and the adiponectin levels tended to increase with all of the doses ($P = 0.004$) at 8 weeks.

Conclusions: Patient-tailored atorvastatin therapy based on LDL cholesterol at baseline was effective in ameliorating atherogenic LDL particle size and inflammation, in addition to achieving the target LDL cholesterol level without an undesirable effect on glycemic control in patients with type 2 diabetes. This trial was registered with ClinicalTrials.gov (no. NCT01239849). (J Diabetes Invest, doi: 10.1111/jdi.12074, 2013)

KEY WORDS: Atorvastatin, Low-density lipoprotein cholesterol, Type 2 diabetes mellitus

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INTRODUCTION

Type 2 diabetes is associated with multiple concomitant factors, which interact to increase the risk for cardiovascular disease (CVD)[1,2]. Among modifiable risk factors, the association between dyslipidemia and cardiovascular risk is well established in patients with type 2 diabetes[3–6]. Current guidelines highlight the need for aggressive management of dyslipidemia to reduce cardiovascular risk in patients with type 2 diabetes. However, the overall number of type 2 diabetic patients who achieve their low-density lipoprotein (LDL) cholesterol target goals is far below the expectations[7,8]. Thus, a more intensive lipid-lowering therapy is warranted to improve the suboptimal metabolic outcomes, including the option to tailor the starting dose of the statins in accordance with the individual LDL cholesterol reduction requirements. Recently, several studies have shown that patient-tailored statin therapy that is customized to the individual's cardiovascular risk or their baseline LDL cholesterol values allowed for a greater proportion of patients, either with or without type 2 diabetes, to achieve their target LDL cholesterol levels[9–12].

Although it is important to achieve lipid goals, it is also known that approximately half of CVD events occur in patients with normal LDL levels[13,14]. Growing evidence indicates that additional risk factors, including atherogenic lipid profiles and a pro-inflammatory status, might be implicated in the pathogenesis of CVD in patients with type 2 diabetes. Patients with type 2 diabetes are characterized by elevated serum triglyceride levels, low serum high-density lipoprotein (HDL) cholesterol levels and a preponderance of small, dense LDL (sd-LDL) cholesterol particles, which are likely atherogenic[15]. The increased residence time of sd-LDL particles contributes to an increased cardiovascular risk because of their pro-inflammatory properties, and to an increased susceptibility to oxidation[16–19]. Type 2 diabetes also predisposes individuals to elevated C-reactive protein (CRP) and low adiponectin levels, which is strongly associated with low-grade inflammation in the vascular wall and a risk of atherosclerosis[20–22]. Despite beneficial reductions in LDL cholesterol levels, controversy remains regarding whether statin has beneficial metabolic and anti-inflammatory actions in patients with type 2 diabetes[23]. In particular, concern was recently raised in patients with type 2 diabetes, because long-term statin therapy was associated with an undesirable effect on glycemic control. Therefore, assessing the effects of a patient-tailored therapy in patients with type 2 diabetes who are at high risk for coronary heart disease (CHD), is an important component of clinical care. However, limited data are available regarding the effects of a tailored approach to statin therapy on components of atherogenic lipid profiles, inflammatory properties and glycemic control in patients with type 2 diabetes. In particular, it is unclear whether statin treatment reduces sd-LDL cholesterol levels as effectively as it reduces large buoyant LDL particle levels, because sd-LDL particles have a weaker affinity to the LDL receptor than large buoyant LDL particles[24,25]. Furthermore, no studies have examined the quantitative change in LDL particle size by a tailored approach to statin therapy in patients with type 2 diabetes. Most previous studies carried out subgroup analyses for type 2 diabetes and did not include an adequate number of patients with type 2 diabetes, especially in the Asian population.

To address this issue, we carried out an 8-week, multicenter, single-step titration, open-label study to assess whether the individualization of starting doses of atorvastatin (10, 20 and 40 mg) according to baseline LDL cholesterol levels led to an achievement of LDL cholesterol target levels, improvements of the atherogenic LDL particle size and low-grade inflammation, as observed by the levels of high-sensitivity C-reactive protein (hsCRP) and adiponectin, and an undesirable effect on glycemic control in patients with type 2 diabetes.

MATERIALS AND METHODS

Patients

The participants, aged 18–80 years, included male and female patients with type 2 diabetes who had glycated hemoglobin (HbA_{1c}) levels of 10% or lower. The American Diabetic Association's criteria for the diagnosis of type 2 diabetes were commonly used in the present study[3]. The main inclusion criteria were a fasting LDL cholesterol level between 2.6 mmol/L and 5.7 mmol/L, and a fasting triglyceride level lower than 4.5 mmol/L. The study patients were eligible for the study if they were statin-free for at least 1 month before the start of the run-in phase. Patients were excluded if they had a history of CHD, cerebrovascular disease or peripheral vascular disease, impaired hepatic or renal function, elevation of creatinine kinase levels, uncontrolled hypertension, uncontrolled hypothyroidism, alcohol or any other drug abuse, a history of hypersensitivity to statins or were women who were pregnant or lactating. Medications known to affect lipid levels or to interact with the medications used in this trial were prohibited for the duration of the study.

Study Design

This was a multicenter, 8-week, single-step titration, open label study with an atorvastatin (starting dose 10, 20 or 40 mg) assessment of the percentage of Korean patients with diabetes mellitus and dyslipidemia who achieved the LDL cholesterol target levels. The patients were assigned to 4 weeks of open-label treatment with atorvastatin (10, 20 or 40 mg) according to a their baseline LDL cholesterol levels, followed by an additional 4-week open-label treatment during which, when possible, the participants who had not reached their target LDL cholesterol levels were titrated to the next highest dose of atorvastatin (20, 40 or 80 mg). The LDL cholosterol concentration in mg/dL was used to determine the initial dose assignment and to decide dose titration at week 4. Patients with baseline LDL cholesterol levels of 100–129 mg/dL, 130–159 mg/dL and 160–220 mg/dL were assigned to 10, 20 and 40 mg of atorvastatin, respectively (Figure S1). We validated if the participants' drug compliance was more than 80% at weeks 4 and 8. The

study was carried out using a common protocol at 18 clinical sites. Blood samples were obtained at the screening, and at week 4 and week 8 for the assessment of efficacy and safety. All laboratory measurements were carried out by a central laboratory (Seoul Clinical Laboratories, Seoul, Korea). Written informed consent was obtained from all participants. The study protocol was carried out in compliance with the principles of the Declaration of Helsinki, as revised in 2000, and was approved by the local institutional review board.

Laboratory Assessments

All of the participants fasted for 12 h before the blood sampling. The total cholesterol and triglyceride levels were measured using an enzymatic calorimetric test, and the HDL cholesterol level was measured using the selective inhibition method. HbA_{1c} was determined by high-performance liquid chromatography. A direct LDL cholesterol measurement was carried out. The LDL particle size was estimated by polyacrylamide gel electrophoresis, as described in the Lipoprint LDL System product insert (Quantimetrix Corporation, Redondo Beach, CA, USA). Briefly, a patient's serum sample (25 μL) was applied to the 'ready to use' polyacrylamide gel tube along with 200 μL of a loading gel solution containing a Sudan black B. The sample loading gel mixture was photopolymerized before electrophoresis at a constant of 3 mA per tube for 1 h. Using the Lipoprint method, HDL migrated the fastest, whereas very low-density lipoprotein (VLDL) migrated the slowest to the top of gel. Mid-band and seven LDL subfractions were detected between the HDL and VLDL. The LDL subtypes 1–2 were larger, buoyant LDLs, which have been designated as 'phenotype A'; subtypes 3–7 were predominantly smaller and denser LDLs, which have been designated as 'phenotype B'. The LDL particle size cut-off was greater than 26.8 nm for phenotype A, and less than 26.8 nm for phenotype B. The concentration for small, dense LDL cholesterol (subtypes 3–7) was calculated as follows: total cholesterol × fractions (%) of small dense LDL cholesterol. The serum levels of hsCRP were measured using a latex microparticle-enhanced immunoturbidimetric assay (Denka-seiken Ltd, Tokyo, Japan), and the total circulating levels of adiponectin were determined using a human adiponectin radioimmunoassay kit (Linco Research, St Charles, MO, USA).

Clinical Efficacy and Safety

The primary outcome evaluated was the proportion of patients in each category who achieved their target LDL cholesterol levels (<2.6 mmol/L) after 8 weeks of treatment. The secondary outcomes evaluated were the mean change from the baseline levels for the total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides and non-HDL cholesterol, the mean change in sd-LDL cholesterol, adiponectin and hsCRP, and the mean change in HbA_{1c} levels at 8 weeks. The safety variables included the all-causality adverse events and treatment-related adverse events, which were reported after the administration of at least one dose of the study medication. Safety laboratory tests, physical examinations and vital sign measurements were carried out at all follow-up visits, and all adverse events were recorded at each study visit.

Statistical Analyses

A sample size of approximately 440 patients was considered for enrolment to provide a precise estimate of the overall treatment response rate. The precision in our measurements of the response rate was measured by the width of the 95% confidence interval (CI). The planned total sample size gave a 95% CI of less than 3.3% in width, which was based on an estimated 10% dropout rate and an observed overall response rate of 85%. This sample size adequately addressed the study hypothesis that atorvastatin treatment would enable the patients to achieve their LDL cholesterol target level with either no or only a single titration step. All data were analyzed by the intention-to-treat and per-protocol analyses, with the last observation carried forward being used for any missing data. Because of the right-skewed distribution of the triglyceride, sd-LDL cholesterol, hsCRP and adiponectin levels, log-transformed values were used for the analysis, but were back-transformed when presenting the results for ease of interpretation. Paired *t*-tests were used to compare the data between the baseline and week 8 values in the study patients. A repeated measures analysis of variance was used to test for differences within the levels of sd-LDL cholesterol, hsCRP and adiponectin among the three intervention groups. All statistical analyses were carried out using SAS 9.1 for Windows (SAS Institute Inc., Cary, NC, USA).

RESULTS

Between January 2009 and February 2010, 579 participants were screened from 18 clinical sites in Korea, and 474 patients were assigned to the treatment. An additional 15 patients were excluded because of no post-baseline data, and 19 did not receive the study medication. Among the intention-to-treat population (n = 440), 185 (42.0%), 181 (41.1%) and 74 (16.8%) were assigned according to their baseline LDL cholesterol levels to a treatment with 10, 20 and 40 mg of atorvastatin, respectively. The proportions of patients who completed the study were 177 (95.6%), 161 (88.9%) and 65 (87.8%) for the 10-, 20- and 40-mg doses, respectively (Figure 1). Thus, the per-protocol population comprised 403 participants. The baseline characteristics of the study patients are shown in Table 1. The participants were predominantly women (61%), with a mean age of 59 years. Overall, 13% were current smokers, 20% had hypertension and 3% had a family history of CVD. The mean duration of diabetes was 6.0 ± 6.5 years, the mean HbA_{1c} level was 7.2 ± 0.9% and the mean LDL cholesterol level was 3.55 ± 0.57 mmol/L.

The proportion of patients who achieved their target LDL cholesterol level at each initial dose is presented in Figure S2. Among the intention-to-treat population, 91% of the patients

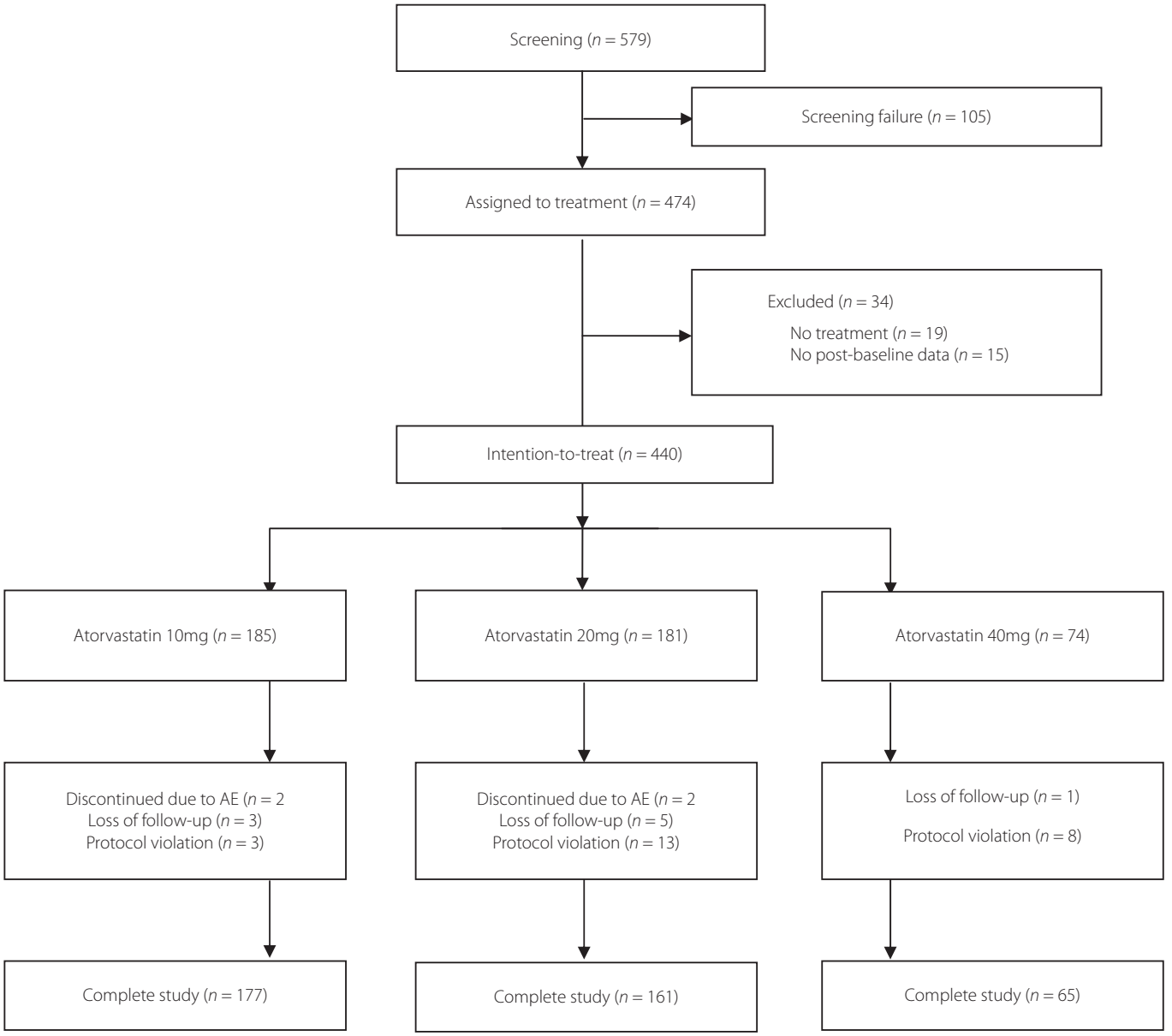

Figure 1 | Flow diagram. AE, adverse events.

achieved their LDL cholesterol target by week 8 (94% of those treated with 10 mg, 93% of those treated with 20 mg and 81% of those treated with 40 mg). Among the intention-to-treat patients who achieved their target goal (n = 403), 92% achieved their LDL cholesterol target level with the initial dose (94%, 91% and 88% for the 10-, 20- and 40-mg doses, respectively). The mean percent changes in the LDL cholesterol levels from the baseline until the end of the study were significant for all of the doses. Similarly, significant changes from the baseline for the total cholesterol, the total cholesterol : HDL cholesterol ratio, triglycerides, mean LDL particle size and non-HDL cholesterol were observed with all of the doses. Changes in the HDL cholesterol were only significant when compared to the baseline with the 10-mg dose. We observed a non-significant change in HbA_{1c} levels during statin therapy (Table 2). In addition, 90% of the patients in the intention-to-treat population achieved a total cholesterol : HDL cholesterol target of <4.0 at week 8 (data not shown).

There was a significant reduction in the sd-LDL cholesterol levels at week 8 compared with the baseline levels for all of the doses (10 mg: −0.13, 95% CI −0.12—0.14; 20 mg: −0.20, 95% CI −0.19—0.21; 40 mg: −0.19, 95% CI −0.18—0.21; $P < 0.001$), and this significance was dose-dependent ($P = 0.006$; Figure 2). In addition, the adiponectin levels tended to increase over the study period with all of the doses ($P = 0.004$; Figure 3, Table S1). This difference was not significant among the three

Table 1 | Baseline characteristics of the intention-to-treat population

Variables	10 mg (n = 185)	20 mg (n = 181)	40 mg (n = 74)	P
Age (years)	58.47 ± 11.20	59.37 ± 9.51	58.87 ± 9.09	0.7142
Men (%)	45.65	38.33	29.17	0.0455
Duration of diabetes (years)	6.45 ± 6.77	6.32 ± 6.57	4.54 ± 5.81	0.1029
Current smoker, yes (%)	16.28	10.65	10.77	0.4773
Hypertension, yes (%)	20.54	19.34	22.97	0.8073
Family history of CHD, yes (%)	4.32	2.76	0.00	0.1749
Weight (kg)	66.38 ± 11.80	64.94 ± 11.07	65.81 ± 11.36	0.4875
BMI (kg/m^2)	25.41 ± 3.49	25.75 ± 4.92	25.97 ± 3.27	0.5607
Waist circumference (cm)	87.99 ± 10.02	87.54 ± 9.14	88.34 ± 9.56	0.8139
Systolic BP (mmHg)	125.58 ± 15.04	125.47 ± 13.28	124.97 ± 11.55	0.9502
Diastolic BP (mmHg)	77.09 ± 10.32	77.68 ± 8.99	77.27 ± 8.09	0.8308
HbA_{1c} (%)	7.37 ± 1.01	7.22 ± 0.89	7.25 ± 0.99	0.3321
Total cholesterol (mmol/L)	4.98 ± 0.43	5.75 ± 0.44	6.37 ± 0.37	<0.001
Triglyceride (mmol/L)	1.41 ± 0.89	1.45 ± 0.92	1.34 ± 0.62	0.5006
HDL cholesterol (mmol/L)	1.20 ± 0.28	1.25 ± 0.29	1.20 ± 0.23	0.2353
LDL cholesterol (mmol/L)	3.02 ± 0.20	3.73 ± 0.21	4.49 ± 0.27	<0.0001
TC/HDL cholesterol ratio	4.32 ± 0.96	4.81 ± 1.05	5.47 ± 1.00	<0.0001
Non-HDL cholesterol (mmol/L)	3.77 ± 0.42	4.50 ± 0.43	5.16 ± 0.36	<0.0001
Oral hypoglycemic agents, n (%)	164 (88.65)	150 (82.87)	56 (75.68)	0.0303
Insulin ± OHA, n (%)	11 (5.95)	15 (8.29)	6 (8.11)	0.6584

Data are expressed as the means ± standard deviation or percentage. BMI, body mass index; BP, blood pressure; CHD, coronary heart disease; HDL, high-density lipoprotein; HbA_{1c}, glycated hemoglobin; LDL, low-density lipoprotein; OHA, oral hypoglycemic agents; TC, total cholesterol.

Table 2 | Change from the baseline values for the lipid profiles at the end of the 8-week study

Variables	10 mg (n = 185)	20 mg (n = 181)	40 mg (n = 74)
Total cholesterol (mmol/L)			
Baseline	4.97 ± 0.43	5.74 ± 0.44	6.36 ± 0.38
Week 8	3.59 ± 0.54	3.75 ± 0.58	3.83 ± 0.87
Change (95% CI)	−1.38 (−1.46 to −1.30)	−1.99 (−2.08 to −1.91)	−2.53 (−2.72 to −2.35)
Triglyceride (mmol/L)			
Baseline	1.41 ± 0.90	1.45 ± 0.92	1.34 ± 0.62
Week 8	1.10 ± 0.69	1.08 ± 0.58	1.06 ± 0.70
Change (95% CI)	−0.31 (−0.42 to −0.22)	−0.37 (−0.49 to −0.29)	−0.28 (−0.47 to −0.15)
HDL cholesterol (mmol/L)			
Baseline	1.21 ± 0.28	1.25 ± 0.30	1.20 ± 0.23
Week 8	1.23 ± 0.27	1.26 ± 0.30	1.18 ± 0.29
Change (95% CI)	0.03 (0.003 to 0.05)	0.01 (0.01 to 0.02)	0.02 (0.02 to 0.07)
LDL cholesterol (mmol/L)			
Baseline	3.02 ± 0.20	3.73 ± 0.21	4.49 ± 0.27
Week 8	1.23 ± 0.27	1.26 ± 0.30	1.18 ± 0.29
Change (95% CI)	−1.78 (−1.32 to −1.18)	−2.46 (−1.86 to −1.73)	−3.30 (−2.55 to −2.24)
Mean LDL particle size (nm)			
Baseline	26.55 ± 0.53	26.40 ± 0.60	26.43 ± 0.49
Week 8	26.81 ± 0.44	26.80 ± 0.46	26.68 ± 0.51
Change (95% CI)	0.27 (0.19 to 0.35)	0.39 (0.31 to 0.48)	0.25 (0.12 to 0.37)
Non-HDL cholesterol (mmol/L)			
Baseline	3.77 ± 0.43	4.49 ± 0.44	5.16 ± 0.37
Week 8	2.36 ± 0.49	2.49 ± 0.50	2.65 ± 0.80
Change (95% CI)	−1.41 (−1.49 to −1.33)	−2.00 (−2.08 to −1.92)	−2.51 (−2.68 to −2.34)
HbA_{1c} (%)			
Baseline	7.37 ± 1.01	7.22 ± 0.89	7.25 ± 0.99
Week 8	7.29 ± 1.01	7.32 ± 1.07	7.26 ± 1.00
Change (95% CI)	0.08 (−0.03 to 0.19)	−0.10 (−0.22 to 0.02)	−0.01 (−0.16 to 0.13)

Repeated measured ANOVA with adjusting for sex. Data are expressed as the means ± standard deviation or percent change with the 95% confidence interval (CI). HbA_{1c}, glycated hemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

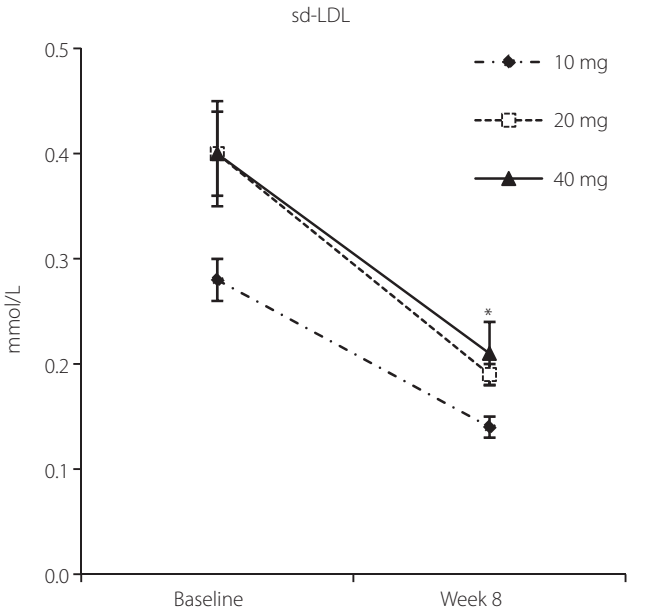

Figure 2 | The change from the baseline values for the small, dense low-density lipoprotein (sd-LDL) levels over the study period. Separate lines are plotted for the groups with 10 mg of atorvastatin (dashed-dot line), 20 mg of atorvastatin (dashed line) and 40 mg of atorvastatin (solid line). The bars indicate standard errors, and *$P < 0.05$.

intervention groups. When the participants were divided in two subgroups according to whether their baseline hsCRP levels were greater than or less than 3 mg/dL, the reductions in the hsCRP levels were significant compared with the baseline levels for all of the doses in the groups with hsCRP levels greater than 3 mg/dL ($n = 63$), but not in the groups with hsCRP levels of less than 3 mg/dL ($n = 377$; Figure 3, Table S1).

The adverse events are summarized in Table S2. The safety population comprised 455 participants who were treated at least once with the trial medication. The severity of most of the events was mild to moderate. There was no difference in the number of adverse events among the three groups. Just two participants discontinued the atorvastatin use as a result of treatment-related adverse events, including dyspepsia ($n = 1$) and anorexia ($n = 1$). Furthermore, the atorvastatin therapy did not affect the overall glycemic control at any dose. The results of the physical examinations and vital signs remained stable throughout the study period.

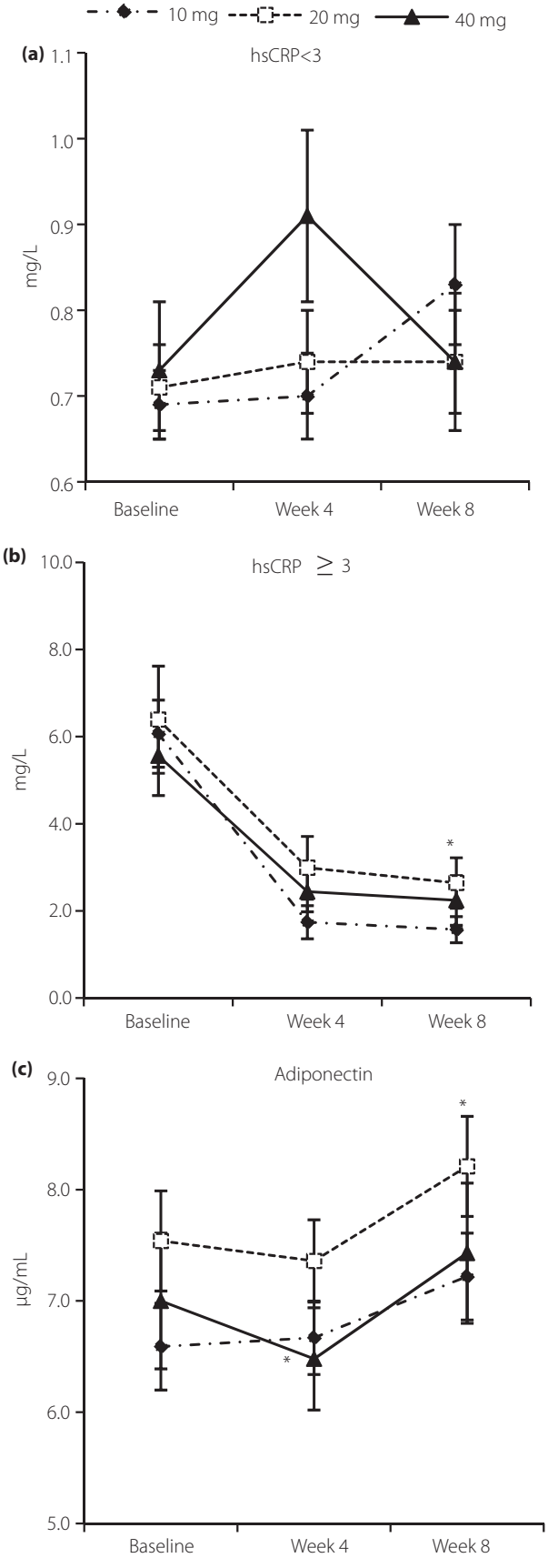

Figure 3 | The change from the baseline values for the (a) high-sensitivity C-reactive protein (hsCRP), stratified according to the (b) baseline hsCRP category and (c) adiponectin levels. Separate lines are plotted for the groups with 10 mg of atorvastatin (dashed-dot line), 20 mg of atorvastatin (dashed line) and 40 mg of atorvastatin (solid line). The bars indicate standard errors, and *$P < 0.05$.

DISCUSSION

In the present study, we confirmed that treatment with atorvastatin at the appropriate starting dose according to the baseline LDL cholesterol levels effectively achieved the LDL cholesterol targets and reduced the sd-LDL cholesterol levels in patients with type 2 diabetes. By using our algorithm, 91% of all patients studied achieved their target LDL levels by the end of the study. The majority of participants achieved their LDL cholesterol target level without the need for titration. In addition, a patient-tailored atorvastatin therapy conferred significant reductions in the hsCRP levels among patients with elevated hsCRP levels (≥3 mg/L) at baseline, and promoted increases in the adiponectin levels within 8 weeks, which were independent of the LDL cholesterol-lowering effects.

Recent trials that were undertaken specifically to determine the optimum starting atorvastatin dose support the use of individualized statin dosing for achieving the LDL cholesterol goals. In the Atorvastatin Goal Achievement Across Risk Levels (ATGOAL) study, 81.1% (533/657) of the high-risk groups, including a subgroup of 309 patients with type 2 diabetes, reached their LDL cholesterol target by using an algorithm based on their risk factors and baseline LDL cholesterol levels at week 8[11]. The Achieve Cholesterol Targets Fast with Atorvastatin Stratified Titration (ACTFAST) study also showed that by initiating the therapy at doses selected in accordance with the baseline LDL cholesterol levels, 72% of the participants with CHD or CHD equivalents achieved their target LDL cholesterol level[10]. In ACTFAST-2, a study that was mainly carried out in European countries, the proportion of participants with diabetes (n = 196) who achieved their LDL cholesterol targets was similar to the proportion in the overall group (70.9% and 68.0%, respectively)[26]. Similar to the present findings, the high-risk, statin-free participants in the ACTFAST trial showed better results with even lower starting doses (10 mg and 20 mg), because their baseline LDL cholesterol levels were taken into account. Compared with the aforementioned studies, the proportion of patients who achieved their target levels was greater in the present study. This result might have been influenced by the rather low mean baseline LDL cholesterol level (3.5 mmol/L) and the relatively small number of patients in the high-dose group (74/440; 16.8%) at baseline in this population.

With respect to the sd-LDL cholesterol levels in the present study, the individualized starting doses of atorvastatin had a strong effect on the mean LDL particle size, and markedly reduced the sd-LDL cholesterol levels with all of the doses. These findings are in agreement with previous small studies, which have shown that atorvastatin is effective in reducing the levels of sd-LDL cholesterol particles and improving the abnormal LDL particle distribution in patients with or without diabetes[27,28]. Notably, the changes in the sd-LDL cholesterol levels were proportionately greater based on the baseline LDL cholesterol levels, which supports the idea that a higher starting dose based on a treatment algorithm was advantageous for patients with type 2 diabetes[9–11,26]. The presence of sd-LDL cholesterol was mainly associated with hypertriglyceridemia, and lowering the triglyceride levels might be necessary for improving the LDL particle size. As expected, we found an independent association between the reductions in triglyceride levels and the sd-LDL cholesterol levels after adjusting for the age, sex and body mass index (data not shown).

In addition to the LDL-lowering effects, the present study was strengthened by the reciprocal changes of hsCRP and adiponectin, which indicate the anti-inflammatory properties in the development of atherosclerosis. There is a significant reduction of the hsCRP levels in high-risk patients and an elevation of adiponectin levels with all of the doses at 8 weeks, although no significance was found earlier, at 4 weeks. In the present study, the statin-mediated changes in hsCRP and adiponectin were independent of the changes in LDL cholesterol and total cholesterol, which suggests that hsCRP and adiponectin might be connected to the pleiotropic effects of statins, such as the improvement of insulin resistance or the pro-inflammatory state. Similar to our findings, in the ACTFAST study, the hsCRP levels were significantly reduced by 35–47% with atorvastatin doses of 10–80 mg, respectively, among patients with baseline hsCRP levels ≥3 mg/L, and this significance was not different in patients with type 2 diabetes in the subgroup analysis[29]. With respect to adiponectin, the effect of statin treatment on increased adiponectin levels is still controversial. A prior study showed that the adiponectin levels were significantly increased at 4 weeks, with further increases at 6 months with a long-term atorvastatin treatment in high-risk cardiovascular disease patients[30]. A more recent study showed that the median serum concentration of high molecular weight adiponectin increased significantly, whereas the median total adiponectin levels were not significantly altered by the atorvastatin therapy in patients with type 2 diabetes[31]. On the contrary, in the ACTFAST study, which included 102 patients with a high CVD risk, there was no significant effect of atorvastatin on the adiponectin levels in a subgroup of 23 patients with type 2 diabetes, although the total adiponectin levels increased in the total study population[32]. Therefore, the present data add to the current body of literature by showing a significant elevation of adiponectin, and the converse properties of hsCRP and adiponectin by using a patient-tailored atorvastatin therapy in patients with type 2 diabetes.

The limitations of the present study include its short-term observational design, which limited any conclusions regarding the influences of statins on cardiovascular end-points in patients with type 2 diabetes. In addition, the improvement of the atherogenic lipid profiles and low-grade inflammation might be partially explained by the statin-induced attenuation of insulin resistance and increased lipoprotein lipase activity. However, we did not assess the degree of lipoprotein lipase activity or the degree of insulin resistance in our participants. Finally, one limitation was the lack of a high molecular weight (HMW) adiponectin measurement in the present study. HMW adiponectin might be the active form of this protein. In recent

studies, the HMW:total adiponectin ratio showed a strong relationship to CVD in type 2 diabetes. Although it is still controversial, measuring the total and HMW adiponectin in the serum to calculate the ratio is preferable to measuring the total or HMW adiponectin alone. Determining the HMW adiponectin during statin therapy might have clinical importance in patients with type 2 diabetes. Additional clinical trials and experimental studies should be considered to clarify the impact of the present results.

In conclusion, a patient-tailored approach to atorvastatin therapy, as determined by the baseline LDL cholesterol levels, is an effective strategy for achieving the target LDL cholesterol levels without undesirable effect on glycemic control, and contributes to the attenuation of the atherogenic risk by reducing the sd-LDL cholesterol levels within 8 weeks of the initial dose in patients with type 2 diabetes. Furthermore, the present findings show the additional pleiotropic effects of individualized atorvastatin therapy in improving pro-inflammatory properties by reducing the hsCRP levels in high-risk patients and increasing the adiponectin levels quickly in patients with type 2 diabetes. These results support that a patient-tailored atorvastatin therapy might be effective in terms of reducing the cardiovascular disease risk in patients with type 2 diabetes. Further studies with cardiovascular endpoints are required to elucidate the clinical implications of the present study.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Figure S1 | Study design and initial dose assignment according to baseline low-density lipoprotein cholesterol levels.
Figure S2 | The proportion of participants who achieved their low-density lipoprotein cholesterol targets of lower than 2.6 mmol/L at the end of the 8-week study in the intention-to-treat (ITT) population and the per-protocol (PP) population.
Table S1 | Change from the baseline for high-sensitivity C-reactive protein levels, according to the baseline high-sensitivity C-reactive protein category, and adiponectin levels over the study period
Table S2 | Adverse events