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Original Article

The lipid-lowering effect of atorvastatin in Taiwanese diabetic patients with hyperlipidemia

Chwen-Tzuei Chang [a], Jenn-Kuen Lee [b], Jen-Der Lin [c], Yi-Jen Hung [d], Rue-Tsuan Liu [e], Wen-Yi Shau [f], Wayne Huey-Herng Sheu [g,h,*]

[a] Division of Endocrinology and Metabolism, China Medical University Hospital, Taichung, Taiwan
[b] Division of Endocrinology and Metabolism, Kaohsiung Veterans General Hospital, Kaohsiung, Taiwan
[c] Division of Endocrinology and Metabolism, Chang Gung University, Taoyuan, Taiwan
[d] Division of Endocrinology and Metabolism, Tri-Service General Hospital, Taipei, Taiwan
[e] Division of Endocrinology and Metabolism, Chang Gung Memorial Hospital, Kaohsiung, Taiwan
[f] Medical Affairs Division, Pfizer Limited, New Taipei, Taiwan
[g] Division of Endocrinology and Metabolism, Taichung Veterans General Hospital, Taichung, Taiwan
[h] College of Medicine, National Yang Ming University, Taipei, Taiwan

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ABSTRACT

Objective: Patients with diabetes mellitus have an increased risk of coronary heart disease; however, many patients with diabetes remain untreated or undertreated for coronary heart disease risk factors. The incidence of type 2 diabetes is rapidly increasing in Taiwan. The aim of this study was to assess the lipid-lowering effects of atorvastatin in Taiwanese diabetic patients with hyperlipidemia.

Materials and Methods: This 12-week open-label study, conducted at six hospitals in Taiwan, included 157 outpatients (aged 18–80 years old) with type 2 diabetes and concomitant hyperlipidemia. Individuals were randomized (1:1:1) to three dosage groups, as follows: 52 patients received 10 mg of atorvastatin per day; 52 patients received 20 mg of atorvastatin per day; and the remaining 53 patients received 40 mg of atorvastatin per day. Treatment targets were established according to the recommendations of the National Cholesterol Education Program Adult Treatment Panel (NCEP ATP) III. The response was evaluated by Cochran-Mantel-Haenszel tests. The change from the baseline level of all lipid parameters and high-sensitivity C-reactive protein (hs-CRP) was determined through analysis of covariance and was assessed at each time point.

Results: The primary endpoint—a low-density lipoprotein-cholesterol (LDL-C) response of >100 mg/dL at Week 12—was achieved in a dose-dependent manner. The percentage of patients improving to this level was higher in the 20 mg/day group (82%) and 40 mg/day group (82%) than in the 10 mg/day group (56%; $p = 0.002$). The percentage of patients achieving the more aggressive LDL-C goal of >70 mg/dL was 9.6%, 31.4%, and 47.1% in the 10 mg/day, 20 mg/day, and 40 mg/day groups, respectively ($p < 0.001$ in 10 mg/day vs. 20 mg/day; $p < 0.001$ in 10 mg/day vs. 40 mg/day). The co-primary endpoint—the percent change from the baseline LDL-C level—also increased in a dose-dependent manner: by 36.5% in the 10 mg/day group; by 44.7% in the 20 mg/day group, and by 49.3% in the 40 mg/day group. For every 10 mg increase in dose, an estimated 4.0% reduction in LDL-C and 3.5% reduction in total cholesterol could be achieved. Triglyceride levels were also lowered, but there were no clinically meaningful changes in the level of high-density lipoprotein-cholesterol or in hs-CRP. Fasting glucose and glycosylated hemoglobin levels were not affected. Treatment-related adverse events were infrequent and mostly mild.

Conclusion: Atorvastatin is an effective and safe treatment for hyperlipidemia in Taiwanese diabetic patients. Most patients taking the drug are able to achieve NCEP ATP III-recommended treatment targets without any measurable effects on glycemic control.

1. Introduction

Recent studies show that the incidence of type 2 diabetes mellitus (T2DM) is rapidly increasing in Taiwan, particularly in younger age groups [1–4]. Patients with T2DM typically present

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* Corresponding author. Division of Endocrinology and Metabolism, Taichung Veterans General Hospital, 160, Section 3, Chung-Kang Road, Taichung, Taiwan. Tel.: +886 4 2374 1300; fax: +886 4 2374 1318.
E-mail address: whhsheu@vghtc.gov.tw (W.H.-H. Sheu).

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with a dyslipidemic profile and have an increased risk for coronary heart disease (CHD). In fact, up to 80% of patients with diabetes die prematurely from cardiovascular (CV) complications [5]. The degree of CHD risk in diabetes mellitus (DM) patients without a previous history of CHD is similar to that of patients with existing CHD but without diabetes [6,7].

Cardiovascular risk factors for patients with diabetes can be glucose-related (e.g., hyperglycemia and insulin resistance) or related to other risk factors (e.g., dyslipidemia, hypertension, hemostatic abnormalities) [8]. Glycemic control is an integral part of diabetes management; however, improving glycemic control alone does not have a significant impact on the cardiovascular disease risk profile of patients with diabetes [9–11]. Dyslipidemia has emerged as an important, modifiable risk factor for CHD in patients with T2DM or metabolic syndrome, thus highlighting the importance of lipid management [8,12]. Despite strong evidence for the value of lowering lipid levels, dyslipidemia in many patients with DM remains undertreated or untreated [13–15].

Management of dyslipidemia in diabetics requires a well-rounded strategy that takes into account the full lipid profile. The American Diabetes Association (ADA) recognizes low-density lipoprotein cholesterol (LDL-C) as the primary focus of lipid management in DM patients, based on evidence from lipid-lowering clinical trials that demonstrate statistically significant reductions in CHD-related events [16]. The United Kingdom Prospective Diabetes Study found that the LDL-C level is the best predictor of CHD, followed by diastolic blood pressure, smoking, the high-density lipoprotein-cholesterol (HDL-C) level, and glycemic control [17]. The absolute concentrations of LDL-C in patients with diabetes are not significantly different from those in nondiabetic individuals; however, patients with diabetes usually have a greater amount of small, dense, atherogenic LDL particles, and may receive greater reduction in the CHD risk than patients without diabetes [16]. The current ADA and National Cholesterol Education Program—Adult Treatment Panel III (NCEP ATP III)—recommended treatment goal for individuals with diabetes is an LDL-C level of $<$100 mg/dL [16,18]. However, levels $<$70 mg/dL have been advocated of late [19,20].

Overwhelming evidence, including several landmark trials, supports the effective reduction of LDL-C through the use of hydroxymethylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (i.e., statins), which have been proven to reduce the risk and the number of CV events in DM patients [21–26]. Atorvastatin is highly effective in reducing LDL-C concentrations in a dose-dependent manner in T2DM patients, while exerting no influence on glycemic control [27–29].

No study has specifically examined the lipid-lowering potential of atorvastatin in Taiwanese diabetic patients with hyperlipidemia. The purpose of this study was to evaluate the efficacy and safety of a range of atorvastatin doses (10 mg/day, 20 mg/day, or 40 mg/day) in this population, and to determine whether there were any resultant effects on glycemic control. The NCEP ATP III goals for the treatment of dyslipidemia in diabetes and the Taiwanese Bureau of National Health Insurance guidelines were used.

2. Materials and methods

Between December 2, 2003 and October 28, 2004, this study was conducted at six study centers in Taiwan in accordance with the latest version of the Declaration of Helsinki (http://www.wma.net/en/30publications/10policies/b3/) and the International Conference on Harmonization Guideline for Good Clinical Practice (http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6_R1/Step4/E6_R1__Guideline.pdf). Independent ethics committees at each participating center approved the protocol (Pfizer study code: A2581123). Each study participant provided written informed consent as a condition of entry.

2.1. Inclusion criteria

This study included male and female outpatients (aged 18–80 years old) who had T2DM in conjunction with the following: hyperlipidemia; a glycosylated hemoglobin A_{1C} (HbA_{1C}) level of $\leq$10%; a LDL-C level of $\leq$130 mg/dL; and triglyceride (TG) levels of $<$400 mg/dL. Women of childbearing age were required to use a reliable method of birth control. Individuals were not eligible for entry if they had secondary causes of hyperlipoproteinemia; type 1 diabetes mellitus; active liver disease; hypersensitivity to HMG-CoA reductase inhibitors; a creatine kinase (CK) level $>3.0 \times$ the upper limit of normal (ULN), or a body mass index $>$ 30.0 kg/m^2. Prohibited medications included immunosuppressive agents, lipid-regulating or lipid-altering drugs, and other drugs that affect lipid levels (including alternative medications or dietary supplements). Individuals who took lipid-altering drugs were considered for screening after a four-week washout period. The exception was the drug probucol, which must have been discontinued for at least six months prior to considering an individual for screening.

2.2. Study design

This was a randomized, open-label, parallel group study of atorvastatin for the treatment of hyperlipidemia in patients with T2DM. Patients were assessed for five visits. The total duration of the study, including screening, was 13 weeks. At Visit 1 (i.e., screening), study participants presented for eligibility assessment. At Visit 2 (i.e., baseline), eligible participants were randomized (in a ratio of 1:1:1) to 10 mg/day, 20 mg/day, or 40 mg/day atorvastatin regimens. Thereafter, all participants were dosed for 12 weeks (i.e., the active treatment phase). During this period, three follow-up visits were planned at intervals of 4 weeks ($\pm$3 days). The participants were instructed to take the study medication in the evening at the same time every day.

2.3. Measures

The screening included a full medical history that consisted of a physical examination and vital signs, electrocardiography, laboratory testing, and serum lipid analysis. Concomitant medications, compliance, and adverse events were also assessed and monitored at each visit (except during the baseline visit when screening measurements were used). All screening assessments were repeated at the final visit (Week 12). Blood samples were drawn for laboratory testing (e.g., lipid analysis) after a minimum 12-hour fast (water was allowed), and drawn between 6 hours and 18 hours after the last intake of the study drug. Serious adverse events occurring up to 30 days after the end of treatment were tracked.

2.4. Statistical analysis

We determined that this study would require a sample size of 50 individuals per dosage group (i.e., a total of 150 study participants). There were two primary efficacy variables: (1) the response change from the baseline level and (2) the percent change in the LDL-C level from the baseline level. A formal calculation of the sample size was performed after taking both variables into consideration. The study was designed with the assumption that 60%, 75%, and 90% of patients in the 10 mg/day, 20 mg/day, and 40 mg/day groups, respectively, would reach the specified LDL-C target of $<$100 mg/dL. By allowing an attrition rate of 10%, 50 patients per group would be

expected to provide 84% power to detect a difference in response at a two-sided 5% significance level (i.e., Chi-square test). This sample size would also provide 80% power to detect a 5% difference between groups [i.e., with a common standard deviation (SD) of 15%] for a mean percent change in LDL-C when tested at a two-sided 5% significance level [i.e., analysis of variance (ANOVA)].

Efficacy variables were analyzed by using the intent-to-treat (ITT) analysis population. If a post-baseline measure was missing for a defined visit, the last observation measured prior to that visit was used by employing the last observation carried forward (LOCF) methodology. The effect of treatment on the response [i.e., LDL-C level $<$100 mg/dL or total cholesterol (TC) level $<$160 mg/dL] and the trend of response (i.e., an increasing number of responders as the dose increased) were evaluated by using the Cochran-Mantel-Haenszel test (which is stratified by center) at the 5% significance level for each visit. The percent change in the level of lipids (i.e., LDL-C, TC, HDL-C, and TG) and high–sensitivity C-reactive protein (hs-CRP) from baseline to Week 4, Week 8, and Week 12 were analyzed by using an ANOVA model. The treatment group, study center, and baseline values were the explanatory variables. For the primary efficacy variables, pair-wise comparisons were performed between the 10 mg/day and the 20 mg/day groups, and between the 10 mg/day and 40 mg/day groups (at a 2.5% significance level). To further assess the extent of the lipid-lowering effect of the drug, additional *post hoc* analyses were undertaken. The number of patients achieving an LDL-C target of $<$70 mg/dL was measured.

Standard summaries of safety parameters, as defined by the sponsor's worldwide safety standards, were generated for the safety population (i.e., for all patients who took at least one dose of the study medication). Compliance was calculated as the ratio of the dose taken and the planned dose.

3. Results

Two hundred and fifty-four study patients were screened for entry; 155 of the patients were treated with a study medication, and 138 (89%) of the 155 patients completed this study. Fig. 1 presents the patient disposition by dosage group. The mean drug

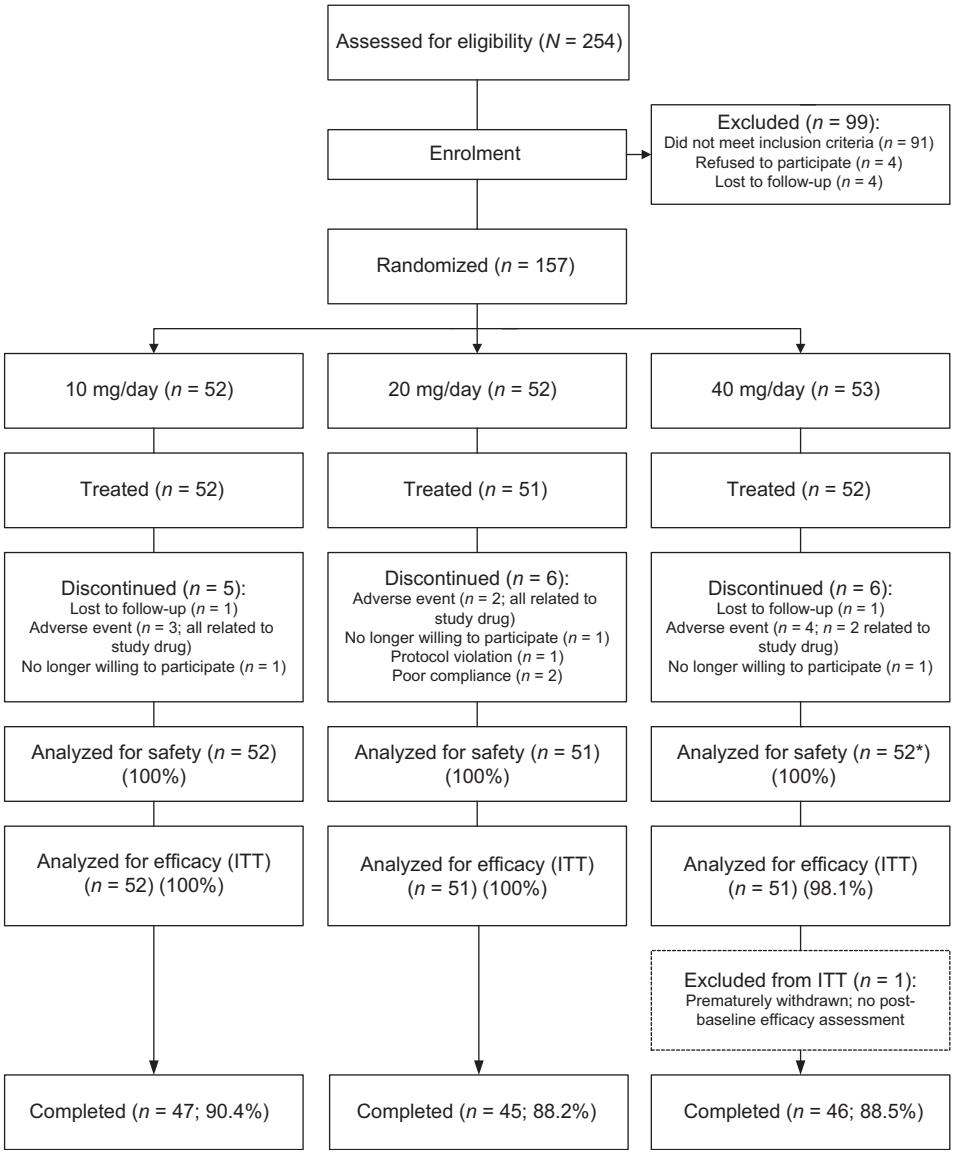

Fig. 1. Patient disposition. Analysis for safety is based on adverse events and laboratory tests. *One study participant was excluded from laboratory test analyses because no post-baseline laboratory assessment was available. ITT = intention-to-treat.

compliance rate was above 96% throughout the study in all three dosage groups.

Groups were well-matched in demographic and baseline characteristics (Table 1). The most common comorbidity present at baseline was hypertension (50.3%), and the most frequently prescribed concomitant medication—apart from drugs used for diabetes (93.5%)—were antihypertensive drugs (43.9%), which consisted primarily of calcium channel blockers (21.3%), angiotensin II receptor blockers (20.0%), and angiotensin-converting enzyme inhibitors (20.0%). At Week 12 (or LOCF), the primary efficacy variable for the LDL-C response (i.e., a target level of <100 mg/dL) was achieved in 55.8%, 82.4%, and 82.4% of patients undergoing the 10 mg/day, 20 mg/day, and 40 mg/day atorvastatin regimen, respectively (Table 2). At each visit, the LDL-C response rate was significantly increased at the higher doses. Table 2 shows the findings of additional *post hoc* analyses of the LDL-C response rates at Week 12 (or LOCF) by baseline subgroups (i.e., LDL-C $\geq$ 150 mg/dL; $HbA_{1c} > 7\%$; and hs-CRP >3 mg/L), and shows the proportion of participants who achieved the more aggressive LDL-C goal of <70 mg/dL. The LDL-C goals were achieved by 9.6% of patients in the 10 mg/day group, by 31.4% of patients in the 20 mg/day group, and by 47.1% of patients in the 40 mg/day group. There was a significant difference in the LDL-C response between the 10 mg/day and the 20 mg/day groups, and between the 10 mg/day and 40 mg/day groups ($p < 0.001$). The mean LDL-C was substantially reduced from baseline to Week 12 (or LOCF; Table 3). A significant trend was established at Week 12. We estimated that, in addition to the reduction with the 10 mg/day dose of atorvastatin, each additional 10-mg dose increase would result in a 4.0% reduction in LDL-C ($p < 0.001$; 95% CI 1.8%–6.2%). This translated into a pair-wise difference of 8.2% between the 10 mg/day and 20 mg/day groups ($p = 0.03$), and a pair-wise difference of 12.7% between the 10 mg/day and 40 mg/day groups ($p < 0.001$).

Similar to the findings for LDL-C, most patients achieved the target TC response (i.e., a level <160 mg/dL). Some patients attained this level as early as Week 4 and sustained it with continued treatment for the remainder of the study. This response was significantly greater at the higher doses, and this trend was true at each visit ($p \leq 0.01$). Substantial reductions in TC occurred at each dose (Table 3). A significant trend was established at Week 12. We surmised that, in addition to the reduction observed with a 10 mg/day dose of atorvastatin, each additional 10-mg dose increase resulted in a 3.5% reduction in TC ($p < 0.001$; 95% CI 1.7%–5.2%).

The mean percent reduction in TG from the baseline level at each visit was significant for all groups ($p < 0.05$). The reduction in the TG level was greater at the higher doses of atorvastatin; however, there were no significant differences or significant trends between the three groups at any visit (Table 3). The changes in the HDL-C and hs-CRP levels varied for each dosage group, but there was no consistent pattern of increase for the HDL-C level within any group.

There were no clinically meaningful changes in HbA_{1C} or fasting glucose levels from the baseline to the end of the study. The levels of HbA_{1C} or fasting glucose were not particularly elevated in this population (Table 3).

The incidence of treatment-related adverse events was 21.2% for the 10 mg/day group, 15.7% for the 20 mg/day group, and 25% for the 40 mg/day group. Thirty-two (20.6%) patients experienced treatment-related adverse events. The most commonly reported events were constipation ($n = 7$) and an increase in the CK level ($n = 6$). Only one treatment-related adverse event (diarrhea) was recorded as severe (Table 4). Of the six (3.9%) patients who had an elevated CK level, two patients from the 40 mg/day group discontinued the study. Seven patients prematurely discontinued treatment as a result of treatment-related adverse events, although all events were mild (increased CK, $n = 2$; dyspepsia, $n = 1$; myasthenia, $n = 1$; dizziness, $n = 1$; flank pain and malaise, $n = 1$; constipation and flatulence, $n = 1$). Three patients experienced serious medical events (e.g., fracture because of a fall, myocardial infarction, and elevated blood pressure). However, these events were not caused by the study drug. Two patients in the 10 mg/day group experienced nontreatment-related mild myalgia. Changes in the level of liver enzymes and in the blood pressure were minimal and clinically comparable among the three groups. Physical examination findings generally showed no new abnormalities.

Table 1
Demographic and baseline characteristics.

Measure	Atorvastatin dosage group		
	10 mg/day	20 mg/day	40 mg/day
	($N = 52$)	($N = 51$)	($N = 52$)
Gender, female (%)	53.8	47.1	51.9
Age (y)	60.8 (11.4)	60.5 (10.5)	60.7 (9.8)
BMI (kg/m^2)	24.8 (3.1)	25.7 (3.0)	25.6 (3.3)
Mean duration of diagnosis:			
Diabetes mellitus type 2, y	7.1 (0.1–22.0)	6.6 (0.1–24.0)	7.9 (0.1–25.0)
Hyperlipidemia, y	3.0 (0.0–10.5)	2.6 (0.0–11.3)	3.2 (0.1–8.3)
Presence of:			
Hypertension	25 (48.1)	25 (49.0)	28 (53.8)
Diabetic retinopathy	4 (7.7)	9 (17.7)	6 (11.5)

Data are presented as *n* (%), mean (SD), or range, unless otherwise indicated.
BMI = body mass index; *n* or *N* = number (for subpopulation or total population, respectively); SD = standard deviation.

Table 2
Low-density lipoprotein cholesterol and total cholesterol response rates in the intention-to-treat analysis population.

Measure	Atorvastatin dosage group		
	10 mg/day	20 mg/day	40 mg/day
LDL-C goal (<100 mg/dL)			
Week 4/LOCF[a]	66 (33/50)	76 (39/51)	90 (45/50)
Week 8/LOCF[a]	63 (33/52)	84 (43/51)	84 (43/51)
Week 12/LOCF[a]	55.8 (29/52)	82.4 (42/51)[b]	82.4 (42/51)[b]
Baseline LDL-C $\geq$ 150 mg/dL[a,c]	36.0 (9/25)	78.8 (26/33)	82.1 (23/28)
Baseline $HbA_{1C} > 7\%$[a,c]	48.6 (18/37)	86.1 (31/36)	88.9 (32/36)
Baseline hs-CRP > 3 mg/L[c]	64.7 (11/17)	70.6 (12/17)	85.7 (18/21)
LDL-C goal (<70 mg/dL)[c]			
Week 12/LOCF[a]	9.6 (5/52)	31.4 (16/51)[b]	47.1 (24/51)[b]
Baseline LDL-C $\geq$ 150 mg/dL[a]	4.0 (1/25)	18.2 (6/33)	39.3 (11/28)
TC goal (<160 mg/dL)			
Week 12/LOCF[a]	42 (22/52)	65 (33/51)	71 (36/51)

Data are presented as % (*n*/*N*).
HbA_{1C} = glycosylated hemoglobin; hs-CRP = high sensitivity C-reactive protein; ITT = intention-to-treat; LDL-C = low-density lipoprotein cholesterol; LOCF = last observation carried forward; *n* or *N* = number (for subpopulation or total population, respectively); TC = total cholesterol.
[a] Indicates the response significantly increased as the dose increased.
[b] Indicates a significant difference ($p < 0.001$) compared to the 10 mg/day group.
[c] Based on *post hoc* analysis.

4. Discussion

Atorvastatin at doses of 10 mg/day, 20 mg/day, or 40 mg/day effectively treated hyperlipidemia in Taiwanese patients with T2DM. Most patients achieved NCEP ATP III-recommended targets. Glycemic control was not affected. The lipid parameters for LDL-C, TC, and TG were significantly reduced from the baseline level. Most patients achieved a lipid-lowering response as early as Week 4 and sustained this response with continued treatment for the remainder of the 12 week study. Treatment-related adverse events were infrequent and safety was not compromised with increasing doses.

Table 3
Change from baseline levels for lipids, high-sensitivity C-reactive protein, glycosylated hemoglobin, and fasting glucose in the intention-to-treat analysis population.

Measure	Atorvastatin dosage group		
	10 mg/day	20 mg/day	40 mg/day
	$N = 52$	$N = 51$	$N = 51$
LDL-C (mmol/L)			
Baseline	4.1 (0.62)	4.1 (0.46)	4.0 (0.51)
Week 12/LOCF	2.6 (0.68)	2.2 (0.75)	2.0 (0.68)
Percent change[a] (95% CI)	36.5 (31.9 − 41.2)[b]	44.7 (40.0 − 49.4)[b]	49.3 (44.6 − 54.0)[b]
TC (mmol/L)			
Baseline	6.1 (0.70)	6.0 (0.63)	6.0 (0.64)
Week 12/LOCF	4.5 (0.88)	4.0 (0.92)	3.7 (0.83)
Percent change[a] (95% CI)	26.5 (22.7 − 30.2)[b]	33.3 (29.5 − 37.0)[b]	37.5 (33.7 − 41.2)[b]
TG (mmol/L)			
Baseline	1.8 (0.78)	1.7 (0.59)	1.6 (0.72)
Week 12/LOCF	1.5 (0.71)	1.3 (0.49)	1.1 (0.43)
Percent change[a] (95% CI)	11.7 (4.2 − 19.3)[b]	18.0 (10.4 − 25.6)[b]	21.6 (14.0 − 29.2)[b]
HDL-C (mmol/L)			
Baseline	1.2 (0.26)	1.2 (0.31)	1.2 (0.26)
Week 12/LOCF	1.2 (0.24)	1.2 (0.25)	1.2 (0.29)
Percent change[a] (95% CI)	3.2 (−2.6 − 8.9)[c]	1.4 (−4.4 − 7.1)[c]	−3.5 (−9.3 − 2.3)[c]
hs-CRP (mg/L)			
Baseline	2.9 (3.7)	4.0 (9.3)	3.3 (3.5)
Week 12/LOC	2.6 (4.5)	2.1 (2.5)	3.1 (6.1)
Percent change[a] (95% CI)	60.6 (−62.0 − 183.2)[c]	−4.3 (−128.1 − 119.5)[c]	107.8 (−15.8 − 231.4)[c]
HbA_{1c} (%)[d]			
Baseline	8.9 (1.7)	8.7 (1.3)	9.0 (1.3)
Week 12/LOCF	8.7 (1.7)	8.9 (1.5)	9.4 (1.7)
Fasting glucose (mmol/L)[d]			
Baseline	8.9 (2.8)	8.6 (2.1)	8.7 (2.0)
Week 12/LOCF	8.1 (2.3)	8.9 (2.6)	9.1 (2.4)

Data are presented as mean (SD) unless otherwise indicated.
CI = confidence interval; HbA_{1C} = glycosylated hemoglobin; HDL-C = high-density lipoprotein cholesterol; hs-CRP = high sensitivity C-reactive protein; ITT = intention-to-treat; LDL-C = low-density lipoprotein cholesterol; LOCF = last observation carried forward; SD = standard deviation; TC = total cholesterol; TG = triglyceride.
[a] Least squares estimates of the presented mean percent change.
[b] Changes are significant compared to baseline.
[c] Changes are not significant compared to baseline.
[d] Based on *post hoc* analysis.

The combined overall treatment response among all three treatment groups was 73% (i.e., 113 of 154 patients); this portion of the ITT population achieved the NCEP ATP III LDL-C goal of <100 mg/dL with a portion of patients achieving the target at higher doses. As treating to target is the recommended standard of care, it is significant that atorvastatin helped patients achieve targets across the dose range. Our findings are particularly meaningful because only 35.3% of diabetic individuals ($n = 7541$) reached goals of total cholesterol (i.e., <160 mg/dL) or LDL-C (i.e. <100 mg/dL) in a national diabetes quality survey conducted in 2006 [14]. In the Diabetes Atorvastatin Lipid Intervention (DALI) study [27] 71.2% of patients in the atorvastatin 10 mg/day group and 84.7% of patients in the atorvastatin 80 mg/day group achieved ADA treatment goals after 30 weeks. The 10 mg/day dose of atorvastatin was not as successful in our study; however, over a shorter period of time, the 40 mg/day dose in our patients achieved similar results as the 80 mg/day group in the DALI study. In the Collaborative Atorvastatin Diabetes Study (CARDS) [30]—the first and largest primary prevention study to assess statins solely in patients with T2DM ($n = 2838$)—an impressive 75% of patients randomized to atorvastatin (at 10 mg/day) achieved LDL-C levels of <2.5 mmol/L with 25% of the patients reaching levels of <1.7 mmol/L during the 3.9-year treatment phase of the study.

Table 4
Treatment-related adverse events in the safety analysis population.

Measure	Atorvastatin dosage group		
	10 mg/day	20 mg/day	40 mg/day
	$N = 52$	$N = 51$	$N = 52$
Total no. of treatment-related adverse events (n)	15	8	15
Total no. of patients with treatment-related adverse events	11 (21.2)	8 (15.7)	13 (25.0)
Adverse events experienced by more than one patient			
Alanine aminotransferase increased	1 (1.9)	1 (2.0)	2 (3.8)
Aspartate aminotransferase increased	1 (1.9)	1 (2.0)	1 (1.9)
Constipation	3 (5.8)	1 (2.0)	3 (5.8)
Creatine kinase increased	2 (3.8)	—	4 (7.7)
Dyspepsia	—	2 (3.9)	—
Diarrhea	1 (1.9)	—	1 (1.9)[a]

Data are presented as n (%).
[a] Recorded as severe; however, the patient recovered.

When treating to target, starting with lower doses and titrating up to achieve the target may be a better approach. However, it has been recommended that lipid-lowering treatment should adopt a more aggressive approach to prevent CHD. In the Atorvastatin Goal Achievement Across Risk Levels (ATGOAL) study conducted in Thailand ($n = 242$), most study participants (88.8%) achieved LDL-C goals at Week 8, and nearly all patients reached LDL-C target levels by Week 2 and Week 4 (81.6% and 87.1%, respectively) [29].

A *post hoc* analysis revealed that 29% (45 of 154) of the patients in the ITT population reached the more stringent LDL-C goal of <70 mg/dL. This response was greater at the higher doses of atorvastatin. A substantial number of patients who had a baseline LDL-C level of ≥150 mg/dL reached this goal. The NCEP ATP III and ADA

guidelines both agree that a LDL-C level of less than 100 mg/dL is the minimum goal, and should not be considered the level needed to achieve the maximum benefit of reducing the LDL-C level. Recent updates to these guidelines suggest aggressive therapy to achieve a LDL-C level of <70 mg/dL [16,20]. However, this has not been investigated thoroughly. The Pravastatin or Atorvastatin Evaluation and Infection Therapy—Thrombolysis in Myocardial Infarction 22 (PROVE-IT TIMI 22) study adopted the more stringent goal of lowering the LDL-C level to approximately 70 mg/dL, and indicated a relative risk reduction of 16% at 2 years ($p = 0.05$; 95% CI, 5%–26%) at the primary endpoint (i.e., death, myocardial infarction, documented unstable angina requiring hospitalization, coronary revascularization, or stroke); 37% of the study participants in the PROVE IT TIMI 22 study had diabetes [31]. This may serve as a reference for future studies and clinical practice.

In the current study, we surmised that—in addition to the reduction in LDL-C occurring with the administration of 10 mg/day atorvastatin—each additional 10-mg increase in the dose would result in a further 4% reduction in the LDL-C level. The combined overall reduction in the LDL-C level for the entire population moreover was 44%. Irrespective of specified targets, the absolute reduction in the LDL-C level is a crucial component in lipid-lowering treatment because it has been proven that any reduction in the LDL-C level results in a comparable reduction in CHD risk, irrespective of the baseline LDL-C level [19,20]. Because of a significant risk of CV events in patients with diabetes, statin therapy is warranted as part of the first-line therapy, even when LDL-C levels are only mildly elevated.

The CARDS study provided convincing support for previous evidence indicating potential CV benefits with statin therapy in patients who have T2DM but no history of CHD. The study found a 37% relative risk reduction in the incidence of CV events with an overall 40% reduction in the LDL-C level from the baseline level [30].

In the PROVE IT study, intensive atorvastatin (80 mg) lipidlowering therapy resulted in a 17% risk reduction in the diabetes subgroup ($n = 770$) [32]. The Treating to New Targets (TNT) study similarly found that a daily dose of 10 mg atorvastatin reduced the LDL-C level by 34% and a daily dose of 80 mg atorvastatin reduced the LDL-C level by 49%. Both doses subsequently resulted in a 22% reduction in CV morbidity [33]. The Anglo-Scandinavian Cardiac Outcomes Trial–Lipid Lowering Arm (ASCOT-LLA) study furthermore found an insignificant 16% reduction in CHD in 2532 patients with diabetes and hypertension who had no previous CHD [26]. There have been similar findings with other statins [23]. All studies validate the concept that a greater reduction in the LDL-C level significantly reduces CV morbidity.

There was minimal, if any, increase in the HDL-C level over the 12-week treatment period. A low HDL-C level has been associated with a greater risk of vascular events (31.1% greater risk, compared to a placebo) , suggesting that strategies targeting low HDL-C levels may have a CV benefit [23].

However, results for HDL-C vary from study to study. Only a 1% increase in the HDL-C level was observed during the CARDS study [30]. By contrast, the HDL-C level was significantly increased in the DALI study: 6% of study participants receiving the 10 mg/day dose of atorvastatin and 5.2% receiving the 80 mg/day dose of atorvastatin had a marked elevation in their HDL-C levels [27]. If HDL-C levels are lower than 0.9 mmol/L, adding a selective cholesterol inhibitor (e.g., ezetimibe), or a low-dose bile acid sequestrant is a useful strategy because these therapies increase the HDL-C level and induce a greater reduction in the LDL-C level. Ezetimibe can induce an additional 15–20% reduction in the LDL-C level [34]. The HDL–Atherosclerosis Treatment Study (HATS) found that simvastatin plus niacin increased the HDL-C level by 26% in patients with diabetes whose baseline HDL-C levels were <0.9 mmol/L [35]. However, there may be increased safety risks in regard to myopathy and liver toxicity when such combination strategies are used [18].

Inflammation is a pivotal final step in acute coronary syndrome. Several studies show that measuring hs-CRP (a nonspecific but sensitive marker of underlying systemic inflammation) in stable individuals is highly predictive of CV events [36]. Patients with diabetes and metabolic syndrome reportedly have elevated hs-CRP levels [37]. Concentrations of hs-CRP of <1 mg/L indicate a low risk for future CV events; concentrations of 1–3 mg/L indicate a moderate risk; and concentrations > 3 mg/L indicate a high risk [38]. In our study, we found that most patients on entry had hs-CRP concentrations indicating a moderate to high risk for future CV events: 55 patients were at high risk, 54 patients were at moderate risk, and 45 patients were at low risk. The mean hs-CRP concentration for the entire population was 3.4 mg/L. Despite the evidence that atorvastatin can lower hs-CRP to <1 mg/L, we found that the change in the hs-CRP level was minimal, although there was a trend towards reduction. However, no statistical significance was observed. The hs-CRP data for this study was indeed extremely variable. Other factors that have an effect on inflammation (e.g., hypertension, retinopathy, smoking, obesity) may need to be considered when interpreting serum hs-CRP levels in patients with diabetes.

Adverse events were infrequent and mostly mild in this study. No patient experienced an extreme elevation of the CK level (prespecified at >10× the ULN), and there were no cases of rhabdomyolysis or myopathy reported during the study. Statins are associated with a small increased risk of elevating liver enzyme levels and an increased frequency of myopathy. However, adverse events were generally mild and infrequent [23,30]. Periodic monitoring of liver function tests and CK is recommended, particularly when high-dose statin therapy is used. However, it is widely accepted that the longterm benefits of statin therapy outweigh the reasonably low risk of adverse events [19].

For the most part, patients with diabetes are less than optimally treated for the management of CV risk. Dyslipidemia is asymptomatic until a CV event occurs; therefore compliance with lipid-lowering regimens is a challenge because of poor awareness of the threat. Leiter reported that only 59% of physicians aim for the target LDL-C level of <100 mg/dL in patients with no previous CVD, compared with 84% for patients with CVD [13]. Because CVD is a top priority risk concern for patients with diabetes, the overall risk of CVD events should be the key consideration when making decisions about aggressively treating diabetic dyslipidemia with statin therapy. When baseline LDL-C levels are mildly above the current goal (115–125 mg/dL), a 30–40% reduction in LDL-C should be a prudent target. More stringent goals (e.g., <70 mg/dL) are warranted in diabetic patients with CVD, based on the CV risk. The choice of high-dose statin therapy should therefore depend principally on the LDL-C reduction needed to reach the target level, on the initial LDL-C level, and on the judgment of the physician in charge.

The current study has some limitations. First, it used an open-label design, which is not as rigorous as a blinded design. However, the primary endpoint for this study was based on the objective measure of lipid sampling. A longer study may be necessary to determine the longterm CV benefits of atorvastatin in this population. The link between lipid-lowering treatment and CV outcomes is nevertheless well documented in many patient populations. Second, all secondary endpoints were tested at an unadjusted 5% level of significance, the purpose of which was to supplement evidence from confirmatory primary analysis to fully characterize the clinical effects of treatment. All findings should therefore be interpreted in this context. In conclusion, because the incidence of diagnosed T2DM has markedly increased in Taiwan in recent years, the findings from this study can provide useful information for

reference when managing hyperlipidemia in Taiwanese patients with T2DM.

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References

[1] Amos AF, McCarty DJ, Zimmet P. The rising global burden of diabetes and its complications: estimates and projections to the year 2010. Diabet Med 1997;14(Suppl. 5):S1–85.
[2] Laakso M, Lehto S, Penttilä I, Pyörälä K. Lipids and lipoproteins predicting coronary heart disease mortality and morbidity in patients with non-insulin-dependent diabetes. Circulation 1993;88:1421–30.
[3] Tseng CH, Tseng CP, Chong CK, Huang TP, Song YM, Chou CW, et al. Increasing incidence of diagnosed type 2 diabetes in Taiwan: analysis of data from a national cohort. Diabetologia 2006;49:1755–60.
[4] Chang CH, Shau WY, Jiang YD, Li HY, Chang TJ, Sheu WH, et al. Type 2 diabetes prevalence and incidence among adults in Taiwan during 1999-2004: a national health insurance data set study. Diabet Med 2010;27:636–43.
[5] Hsueh WA, Law RE. Diabetes is a vascular disease. J Investig Med 1998;46:387–90.
[6] Haffner SM, Lehto S, Rönnemaa T, Pyörälä K, Laakso M. Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without prior myocardial infarction. N Engl J Med 1998;339:229–34.
[7] Schramm TK, Gislason GH, Køber L, Rasmussen S, Rasmussen JN, Abildstrøm SZ, et al. Diabetes patients requiring glucose-lowering therapy and nondiabetics with a prior myocardial infarction carry the same cardiovascular risk: a population study of 3.3 million people. Circulation 2008;117:1945–54.
[8] Betteridge J. Benefits of lipid-lowering therapy in patients with type 2 diabetes mellitus. Am J Med 2005;118(Suppl. 12A):10–5.
[9] UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet 1998;352:837–53.
[10] Action to Control Cardiovascular Risk in Diabetes Study Group, Gerstein HC, Miller ME, Byington RP, Goff Jr DC, Bigger JT, et al. Effects of intensive glucose lowering in type 2 diabetes. N Engl J Med 2008;358:2545–59.
[11] ADVANCE Collaborative Group, Patel A, MacMahon S, Chalmers J, Neal B, Billot L, et al. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. N Engl J Med 2008;358:2560–72.
[12] Sheu WH, Jeng CY, Lee WJ, Lin SY, Pei D, Chen YT. Simvastatin treatment on postprandial hypertriglyceridemia in type 2 diabetes mellitus patients with combined hyperlipidemia. Metabolism 2001;50:355–9.
[13] Leiter LA. Diabetic dyslipidaemia: effective management reduces cardiovascular risk. Atheroscler Suppl 2005;6:37–43.
[14] Yu NC, Su HY, Tsai ST, Lin BJ, Shiu RS, Hsieh YC, et al. ABC control of diabetes: survey data from National Diabetes Health Promotion Centers in Taiwan. Diabetes Res Clin Pract 2009;84:194–200.
[15] Santos RD, Waters DD, Tarasenko L, Messig M, Jukema JW, Ferrières J, et al. Low- and high-density lipoprotein cholesterol goal attainment in dyslipidemic women: the Lipid Treatment Assessment Project (L-TAP) 2. Am Heart J 2009;158:860–6.
[16] American Diabetes Association. Standards of medical care in diabetes–2006. Diabetes Care 2006;29(Suppl. 1):S4–42.
[17] Turner RC, Millns H, Neil HA, Stratton IM, Manley SE, Matthews DR, et al. Risk factors for coronary artery disease in non-insulin dependent diabetes mellitus: United Kingdom Prospective Diabetes Study (UKPDS: 23). BMJ 1998;316:823–8.
[18] Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive summary of the third report of the National Cholesterol Education Program (NCEP) Expert Panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III). JAMA 2001;285:2486–97.
[19] Irons BK, Kroon LA. Lipid management with statins in type 2 diabetes mellitus. Ann Pharmacother 2005;39:1714–9.
[20] Grundy SM, Cleeman JI, Merz CN, Brewer Jr HB, Clark LT, Hunninghake DB, et al. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines. Circulation 2004;110:227–39.
[21] The Scandinavian Simvastatin Survival Study. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). Lancet 1994;344:1383–9.
[22] The Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group. Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. N Engl J Med 1998;339:1349–57.
[23] Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. Lancet 2002;360:7–22.
[24] Downs JR, Clearfield M, Weis S, Whithney E, Shapiro DR, Beere PA, et al. Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels: results of AFCAPS/TexCAPS. Air Force/Texas Coronary Atherosclerosis Prevention Study. JAMA 1998;279:1615–22.
[25] Sacks FM, Pfeffer MA, Moye LA, Rouleau JL, Rutherford JD, Cole TG, et al. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. Cholesterol and Recurrent Events Trial investigators. N Engl J Med 1996;335:1001–9.
[26] Sever PS, Dahlöf B, Poulter NR, Wedel H, Beevers G, Caulfield M, et al. Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than-average cholesterol concentrations, in the Anglo-Scandinavian Cardiac Outcomes Trial–Lipid Lowering Arm (ASCOT-LLA): a multicentre randomised controlled trial. Lancet 2003;361:1149–58.
[27] Diabetes Atorvastin Lipid Intervention (DALI) Study Group. The effect of aggressive versus standard lipid lowering by atorvastatin on diabetic dyslipidemia: the DALI study: a double-blind, randomized, placebo-controlled trial in patients with type 2 diabetes and diabetic dyslipidemia. Diabetes Care 2001;24:1335–41.
[28] Aguilar-Salinas CA, Gómez-Pérez FJ, Posadas-Romero C, Vázquez-Chávez C, Meaney E, Gulías-Herrero A, et al. Efficacy and safety of atorvastatin in hyperlipidemic, type 2 diabetic patients. A 34-week, multicenter, open-label study. Atherosclerosis 2000;152:489–96.
[29] Deerochanawong C, Buranakitjaroen P, Nitiyanant W, Suwantamee J, Piamsomboon C, Vongthavaravat V, et al. The Atorvastatin goal achievement across risk levels: (ATGOAL) study in Thailand. J Med Assoc Thai 2007;90:72–81.
[30] Colhoun HM, Betteridge DJ, Durrington PN, Hitman GA, Neil HA, Livingstone SJ, et al. Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomised placebo-controlled trial. Lancet 2004;364:685–96.
[31] Rouleau J. Improved outcome after acute coronary syndromes with an intensive versus standard lipid-lowering regimen: results from the Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction 22 (PROVE IT-TIMI 22) trial. Am J Med 2005;118(Suppl. 12A):28–35.
[32] Cannon CP, Braunwald E, McCabe CH, Rader DJ, Rouleau JL, Belder R, et al. Intensive versus moderate lipid lowering with statins after acute coronary syndromes. N Engl J Med 2004;350:1495–504.
[33] LaRosa JC, Grundy SM, Waters DD, Shear C, Barter P, Fruchart JC, et al. Intensive lipid lowering with atorvastatin in patients with stable coronary disease. N Engl J Med 2005;352:1425–35.
[34] Gagné C, Gaudet D, Bruckert E, Ezetimibe Study Group. Efficacy and safety of ezetimibe coadministered with atorvastatin or simvastatin in patients with homozygous familial hypercholesterolemia. Circulation 2002;105:2469–75.
[35] Brown BG, Zhao XQ, Chait A, Fisher LD, Cheung MC, Morse JS, et al. Simvastatin and niacin, antioxidant vitamins, or the combination for the prevention of coronary disease. N Engl J Med 2001;345:1583–92.
[36] Rifai N, Ridker PM. High-sensitivity C-reactive protein: a novel and promising marker of coronary heart disease. Clin Chem 2001;47:403–11.
[37] Pickup JC. Inflammatory markers and type 2 diabetes. Diabetes Technol Ther 2006;8:1–6.
[38] Pearson TA, Mensah GA, Alexander RW, Anderson JL, Cannon 3rd RO, Crigui M, et al. Markers of inflammation and cardiovascular disease: application to clinical and public health practice: a statement for healthcare professionals from the Centers for Disease Control and Prevention and the American Heart Association. Circulation 2003;107:499–511.