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Effect of individualizing starting doses of a statin according to baseline LDL-cholesterol levels on achieving cholesterol targets: The Achieve Cholesterol Targets Fast with Atorvastatin Stratified Titration (ACTFAST) study

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Abstract

Aims: To investigate whether selecting the starting dose of atorvastatin according to baseline and target (<2.6 mmol/L) LDL-cholesterol (LDL-C) values would allow high-risk subjects to achieve target LDL-C concentration within 12 weeks, with the initial dose or a single uptitration.

Methods and results: Twelve-week, prospective, open-label trial that enrolled 2117 high-risk subjects (statin-free [SF] or statin-treated [ST]). Subjects with LDL-C >2.6 mmol/L (100 mg/dL) but ≤5.7 mmol/L (220 mg/dL) were assigned a starting dose of atorvastatin (10, 20, 40 or 80 mg/day) based on LDL-C and status of statin use at baseline, with a single uptitration at 6 weeks, if required. There was no washout for ST subjects. At study end, 80% of SF (82%, 82%, 83% and 72% with 10, 20, 40 and 80 mg, respectively) and 59% of ST (60%, 61% and 51% with 20, 40 and 80 mg, respectively) subjects reached LDL-C target. In the ST group, an additional 21–41% reduction in LDL-C was observed over the statin used at baseline. Atorvastatin was well tolerated.

Conclusion: This study confirms that individualizing the starting dose of atorvastatin according to baseline and target LDL-C values (i.e. the required LDL-C reduction), allows a large majority of high-risk subjects to achieve target safely, within 12 weeks, with the initial dose or with a single titration.

Keywords: Statins; HMG CoA reductase inhibitors; Atorvastatin; Low density lipoprotein-cholesterol; Coronary heart disease; Diabetes

1. Introduction

Most current guidelines for the treatment of dyslipidemia in adults recommend more aggressive lipid-lowering targets for subjects who are at high risk for cardiovascular events. This includes subjects with established coronary heart dis-

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[1] See Appendix A for complete list.

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ease (CHD) or CHD-equivalents such as diabetes, and those asymptomatic subjects with a 10-year CHD risk greater than 20%. HMG Co-A reductase inhibitors (statins) are recommended as the initial drug of choice [1–4].

Despite the widespread availability of effective statins, many patients do not reach their LDL-C targets, and thus, may not achieve the degree of reduction in cardiovascular events observed in landmark trials. Surveys reveal that under-treatment of dyslipidemia remains a significant healthcare concern worldwide. A survey conducted in the USA revealed that although primary care physicians claimed a good level of awareness of lipid management guidelines, only 18% of subjects with CHD achieved a LDL-C target of 2.6 mmol/L (<100 mg/dL) [5]. A European survey of subjects with CHD conducted in 1999–2000, observed that the number of subjects with a total cholesterol ≥5.0 mmol/L (193 mg/dL) had dropped from 86% to 59% and that the proportion of subjects using lipid-lowering therapy had increased from 32% to 63% (from 19% to 58% for statins, specifically) since the previous survey conducted 5 years earlier [6]. Although, as a consequence of the increased use of statins, the proportion of subjects reaching a total cholesterol target of less than 5.0 mmol/L (193 mg/dL) increased from 21% to 49%, this level of goal attainment is still sub-optimal [6,7]. More recently, the ALLIANCE study, conducted in a managed-care setting, reported that only 40% of secondary prevention subjects assigned to usual care achieved a LDL-C target of <2.6 mmol/L (100 mg/dL) compared to 72% in those assigned to aggressive management with atorvastatin ($P < 0.001$), leading to a 17% reduction in the incidence of major cardiovascular events ($P = 0.02$) [8]. Under-usage of statins has also been reported in subjects with diabetes and acute coronary syndromes [9–11].

Factors which may prevent achievement of targets include: lack of follow-up for uptitration, lack of adherence to therapy, miscommunication between patient and physician, complacency with sub-optimal cholesterol values achieved, confusion around recommended lipid targets, patient or physician preferences, and selection of an inappropriate starting dose. It is a widespread medical practice to initiate statin treatment at the lowest dose. Unfortunately, it is also common that doses are not titrated up in order to reach the recommended LDL-C goal [12–14]. Tailoring the starting dose according to individual LDL-C reduction requirements may aid in the achievement of target LDL-C levels [12,15]. There is evidence to suggest that baseline LDL-C levels impact overall LDL-C reduction, [16–18] and that treatment with intensive lipid lowering therapy results in greater reductions in LDL-C and a higher proportion of subjects achieving targets compared with more moderate regimens [19–29]. Thus, selecting an initial starting dose calculated to achieve the required LDL-C reduction, may allow more patients to reach targets more quickly, reducing the need for dose increases, thus improving clinical outcomes and being more cost-effective in the long term [30,31].

Atorvastatin has been shown to reduce LDL-C levels by up to 60% and is well tolerated [32]. No additional safety or tolerability concerns were observed when LDL-C levels were reduced to <2.1 mmol/L (80 mg/dL) [33,34]. Atorvastatin has been shown to halt the progression of atherosclerosis [35–37], and to reduce the incidence of cardiovascular events in both primary and secondary prevention of CHD [8,38–40].

The Achieve Cholesterol Targets Fast with Atorvastatin Stratified Titration (ACTFAST) trial was designed to assess whether using atorvastatin at starting doses appropriate for the degree of LDL-C reduction required would achieve LDL-C targets quickly with either no titration or just one titration step, regardless of statin use at baseline.

2. Methods

2.1. Patient population

ACTFAST is a 12-week, multicenter, prospective, open-label trial assessing the effectiveness of using starting doses of atorvastatin that are selected based on the baseline LDL-C value and on the required LDL-C reduction to reach target. Men and women aged at least 18 years old were eligible for inclusion if they had been diagnosed with dyslipidemia defined as LDL-C of >2.6 mmol/L (100 mg/dL) and ≤5.7 mmol/L (220 mg/dL) at screening, had a triglyceride level ≤6.8 mmol/L (600 mg/dL), and had a history of CHD, a CHD-equivalent (diabetes, cerebrovascular disease or peripheral vascular disease) or an estimated 10-year CHD risk >20% as per the Framingham tables [2]. Subjects could be either statin-free or statin-treated at baseline. The subject also had to be willing to follow the NCEP III multifaceted lifestyle approach (or local equivalent) [2].

Subjects were considered ineligible for the study if they were receiving therapy with any statin at a dose >40 mg/day,[2] atorvastatin, fibrates, niacin or resins that could not be discontinued a minimum of 2 months prior to enrolment, or received drugs that are strong inhibitors of CYP3A4 or were likely to receive such treatment during the study period. Subjects who used atorvastatin at screening were not eligible since the study aimed at assessing the potential benefits of switching over from the statin used at baseline to a flexible starting dose of atorvastatin. Subjects were also excluded if they had participated in any other study, suffered from specific systemic diseases including impaired hepatic (defined as aspartate aminotransferase (AST) or alanine aminotransferase (ALT) ≥2 times the upper limit of normal) or renal function (creatinine ≥181 μmol/L), uncontrolled diabetes (HbA1c > 10%), uncontrolled hypertension (>160/100 mmHg), uncontrolled primary hypothyroidism (thyroid stimulating hormone ≥1.5 times the upper limit of normal), evidence of gastrointesti-

[2] Rosuvastatin became commercially available in Canada and the UK during the trial and the Steering Committee allowed subjects on 10mg to be enrolled in the study.

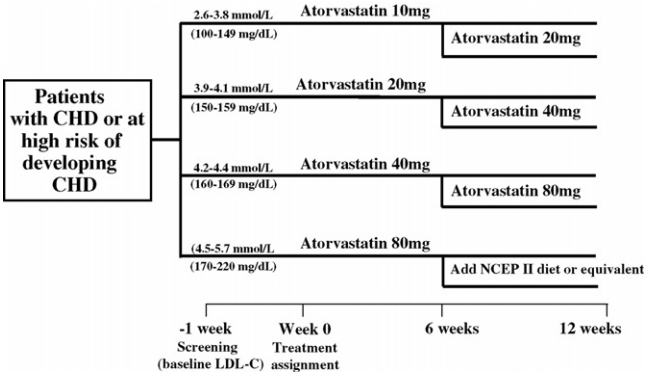

Fig. 1. Study design and dose assignment based on baseline LDL-C levels for statin-free subjects (no prior statin therapy within 2 months of screening). Statin-treated subjects (current statin therapy but LDL-C above target values) received double the atorvastatin dose for the same baseline LDL-C levels (subjects with LDL-C 4.5–5.7 mmol/L all received the 80 mg dose).

nal disease limiting drug absorption or partial ileal bypass, elevation of creatine kinase (CK) level (defined as >3 times the upper limit of normal), alcohol and/or any other drug abuse, history of intolerance or hypersensitivity to statins, any severe disease or surgical procedure within 3 months prior to screening, or were women who were pregnant or lactating or of childbearing potential not using an acceptable method of contraception.

The following medications were prohibited for the duration of the study: all other lipid-lowering medications, psyllium (>2 tablespoons/day), orlistat, fish oils, terfenadine, strong CYP3A4 inhibitors such as macrolide antibiotics, systemic azole antifungals, or cyclosporine.

2.2. Treatment

Subjects were assigned to 6 weeks of open-label treatment with atorvastatin 10, 20, 40, or 80 mg according to their baseline LDL-C level and prior statin use, followed by an additional 6-week open-label treatment during which subjects who had not reached target LDL-C levels, where possible, were titrated to the next highest dose of atorvastatin (Fig. 1). Subjects initially allocated to atorvastatin 80 mg who did not reach LDL-C targets, were continued at that dose and a more intense therapeutic lifestyle intervention (NCEP II step 2 diet or equivalent) was recommended [2].

One week after the screening visit, subjects who had not received statin therapy within 2 months of screening were allocated to an atorvastatin dose in arm 1 (statin-free) according to their baseline LDL-C level (Fig. 1). A subject's LDL-C concentration in mg/dL was used to determine initial dose assignment and for decision-making regarding dose titration at week 6. Subjects who had received prior statin therapy (excluding atorvastatin) but who's LDL-C remained above target values were allocated to arm 2 (statin-treated), and received double the atorvastatin dose for the same baseline LDL-C level as compared to their untreated counterparts, without any washout period. Subjects with LDL-C between 4.5 and 5.7 mmol/L (170–220 mg/dL) all received the 80 mg dose, regardless of treatment arm.

Blood samples were obtained at screening, weeks 6 and 12 for the measurement of 12 h fasting serum lipid profiles, and routine haematology and chemistry measurements that were part of the safety assessment. All cholesterol assays were performed by a central laboratory. Direct LDL-C measurement was performed, regardless of triglyceride levels. Subjects received dietary counselling at all visits. The relevant institutional review boards approved the protocol, and informed consent was obtained from all subjects. This study was conducted in compliance with the ethical principles of the Declaration of Helsinki [41].

2.3. Efficacy parameters

The primary efficacy outcome was the proportion of subjects achieving NCEP ATP-III target LDL-C levels of <2.6 mmol/L (<100 mg/dL) after 12 weeks of treatment [2]. Secondary efficacy parameters included the proportion of subjects achieving total cholesterol/high density lipoprotein-cholesterol (TC/HDL-C) ratio target (<4.0) at 6 and 12 weeks, and mean percent change from baseline in TC, LDL-C, HDL-C, TC/HDL-C ratio, non-HDL-C, triglycerides and apo-B at 6 and 12 weeks. Safety variables included treatment-emergent adverse events defined as any adverse event reported after administration of at least one dose of study medication or that worsened in intensity or frequency after therapy began. Serious adverse events were defined as death or events that were life-threatening, that required or prolonged hospitalization, that resulted in persistent or significant disability, and congenital anomalies.

2.4. Lipid assays

Direct measurement of LDL-C was performed using a homogeneous enzymatic colorimetric assay (LDL-C plus second generation, Roche Diagnostics GmbH) by a central laboratory accredited for lipid assays by the CDC/NHLBI. This assay is reliable with TG plasma values up to 1200 mg/dL (13.5 mmol/L).

2.5. Statistical analysis

Based on the results of NASDAC (15), where 69% of high-risk subjects achieved LDL-C target, the dose assignment table of ACTFAST was expected to allow 70% of subjects to reach target. Although an ambitious target based on current evidence of sub-optimal management of dyslipidemia in high-risk subjects (5–11), this value of 70% of subjects reaching LDL-C target was determined to be clinically meaningful. With a sample size of 2020 subjects, a two-sided 95% confidence interval for a single proportion using the large sample normal approximation will extend 2% from the observed proportion for an expected proportion of 70% overall. Based on an estimated 3% dropout rate, enrolment of 2080 subjects was

determined. This sample size adequately addressed the study hypothesis that atorvastatin treatment would enable subjects to achieve their LDL-C target with either no, or just a single titration step.

Data were analyzed on an intent-to-treat (ITT) and *per-protocol* basis. If data for a given visit were missing, this was resolved by carrying forward the most recent non-missing on-treatment data (last observation carried forward; LOCF). The ITT population consisted of all subjects who were assigned a starting dose, took at least one dose of study medication, and who had at least one subsequent assessment. The *per-protocol* population consisted of those subjects who completed the study as per protocol, were exempt of major protocol violations and who were compliant with study treatment. The safety population consisted of all subjects who took at least one dose of study medication.

Categorical efficacy variables are presented as counts and percentages. Continuous variables are summarized as mean, standard deviation and 95% confidence intervals for the mean. No inferential statistical tests were performed. Although allocation of doses was not randomized, data were summarized by initial dose allocation, as well as for all doses combined, where appropriate. Safety parameters were summarized overall and by initial dose allocation. The Steering Committee designed the trial in collaboration with the sponsor, oversaw the conduct of the trial and led the preparation of the manuscript. Data co-ordination and production of data tables were performed by Pfizer Canada Inc. The Steering Committee and the sponsor performed the data analysis jointly. Statistical analysis was performed using SAS Version 8.2.

3. Results

Between January and November 2003, 2859 subjects were screened from 138 sites in Canada, Italy, Spain and the United Kingdom (Appendix A) and 2187 were assigned to study drug. Of the 672 screening failures, 91% were due to the subject not meeting entry criteria. Thirty-three subjects did not provide a post-baseline assessment of blood cholesterol and 37 did not receive study medication. Consequently, the safety population comprised 2150 subjects, and 2117 subjects (96.8%) were included in the ITT population (686 on 10 mg (32.4%), 773 on 20 mg (36.5%), 234 on 40 mg (11.1%) and 424 on 80 mg (20.0%)). The proportion of subjects who

Table 1
Baseline characteristics—ITT population

Characteristics	Statin-free ($N = 1345$)	Statin-treated ($N = 772$)	All subjects ($N = 2117$)
Male (*N*, %)	877 (65.2)	552 (71.5)	1429 (67.5)
Caucasian (*N*, %)	1254 (93.2)	724 (93.8)	1978 (93.4)
Mean age (y) (mean ± S.D.)	63.0 ± 11.0	63.5 ± 10.1	63.2 ± 10.7
Weight (kg) (mean ± S.D.)	82.3 ± 16.9	80.5 ± 14.7	81.6 ± 16.1
Body mass index (kg/m^2) (mean ± S.D.)	29.3 ± 5.4	28.6 ± 4.6	29.0 ± 5.1
Waist circumference (cm) (mean ± S.D.)	100.4 ± 13.7	99.2 ± 12.6	99.9 ± 13.3
Systolic/diastolic blood pressure (mmHg) (mean ± S.D.)	136.7 ± 16.3/79.4 ± 10.0	133.4 ± 16.9/76.9 ± 10.1	135.5 ± 16.6/78.5 ± 10.1
Smoking (*N*, %)	308 (22.9)	146 (18.9)	454 (21.4)
Diabetes (*N*, %)	611 (45.4)	217 (28.1)	828 (39.1)
Proportion of type 2 diabetes (*N*, %)	594 (97.2)	211 (97.2%)	805 (97.2)
CHD (*N*, %)	675 (50.2)	625 (81.0)	1300 (61.4)
Cerebrovascular disease (*N*, %)	126 (9.4)	77 (10.0)	203 (9.6)
Peripheral vascular disease (*N*, %)	108 (8.0)	67 (8.7)	175 (8.3)
10-year CHD risk >20%[a] (*N*, %)	103 (7.7)	15 (1.9)	118 (5.6)
Metabolic syndrome (*N*, %)	667 (49.6)	315 (40.8)	982 (46.4)
Hypertension (*N*, %)	930 (69.1)	509 (65.9)	1439 (68.0)
Family history of premature CHD (*N*,%)	292 (21.7)	197 (25.5)	489 (23.1)
Current statin used at baseline[b] (*N*, %)	Fibrates 11 (0.8)[c], statins 3 (0.2)[c], resins 1 (0.07)[c]	Fluvastatin 56 (7.3), lovastatin 42 (5.4), pravastatin 238 (30.8), rosuvastatin 6 (0.8), simvastatin 427 (55.3), other LLT 10 (1.3)[d]	
Concomitant medications (*N*, %)			
ASA and other antiplatelet agents	838 (62.3)	691 (89.5)	1522 (71.9)
Oral anticoagulants	93 (6.9)	37 (4.8)	130 (6.1)
Beta-blockers	495 (36.8)	433 (56.1)	928 (43.8)
ACE inhibitors	567 (42.2)	399 (51.7)	966 (45.6)
Angiotensin II receptor antagonists	206 (15.3)	105 (13.6)	311 (14.7)

ACE: angiotensin converting enzyme; LLT: lipid lowering therapy.

[a] Subjects without CHD, CHD-equivalent or diabetes who qualified solely based on a 10-year CHD risk >20%.

[b] In the statin-treated group, the distribution of the various statins was approximately the same across the 20, 40 and 80 mg doses of atorvastatin.

[c] These subjects were not eligible since any LLT at baseline was prohibited in the statin-free group. These subjects were included in intention-to-treat analyses.

[d] These 10 subjects were using other LLT (ezetimibe, fibrates, cholestyramine and niacin) at baseline and thus, were not eligible for the study. These subjects were included in intention-to-treat analyses.

Table 2
Baseline laboratory values—ITT population (mean (S.D.))

Value	Statin-free ($N=1345$)	Statin-treated ($N=772$)	All subjects ($N=2117$)
Fasting glucose (mmol/L)	6.7 (2.4)	6.3 (2.0)	6.5 (2.3)
HbA1C (%)	6.4 (1.2)	6.3 (1.1)	6.4 (1.1)
Total cholesterol (mmol/L)	5.8 (0.9)	5.4 (0.8)	5.7 (0.8)
LDL-C (mmol/L)	3.9 (0.7)	3.5 (0.6)	3.7 (0.7)
HDL-C (mmol/L)	1.3 (0.3)	1.3 (0.3)	1.3 (0.3)
TC/HDL ratio	4.8 (1.2)	4.4 (1.0)	4.7 (1.2)
Triglycerides (mmol/L)	1.9 (1.0)	1.9 (0.9)	1.9 (0.9)
Apo-B (g/L)	1.1 (0.2)	1.1 (0.2)	1.1 (0.2)
Non-HDL-C	4.6 (0.8)	4.1 (0.7)	4.4 (0.8)

completed the study was 95%, 95%, 94% and 90% for the 10, 20, 40 and 80 mg doses, respectively.

Participants were mainly Caucasians (93%) and male (68%), with a mean age of 63 years. Overall, 21% were current smokers, 39% had diabetes, and 61% had prior CHD (Table 1). There was a lower prevalence of diabetes and higher prevalence of CHD in the statin-treated group. The mean baseline laboratory values are illustrated in Table 2. As expected from the dose assignment scheme based on baseline LDL-C and status of statin use at baseline, the mean baseline TC, LDL-C, non-HDL-C and TC/HDL-C differed between groups.

Using the LOCF analysis, the primary efficacy parameter, the proportion of subjects achieving LDL-C targets of <2.6 mmol/L (100 mg/dL) after 12 weeks of treatment, was 72.0% overall, and 79.6% and 58.7% for statin-free and statin-treated subjects, respectively. Fig. 2 illustrates the proportion of subjects achieving LDL-C target on each initial dose for both the statin-free and statin-treated groups. When considering the per protocol population, the proportions of subjects achieving targets were slightly higher, most notably in the statin-free group (Fig. 3).

Among statin-free subjects who achieved target ($N=1071$), over 90% achieved their LDL-C target with the initial dose (91%, 90%, 90% and 96% for the 10, 20, 40 and 80 mg doses, respectively). Among the statin-treated subjects who achieved target ($N=453$), the proportions of subjects who accomplished this at initial dose were 72%, 64% and 96% with the 20, 40 and 80 mg doses, respectively.

Considering statin-free subjects who required titration at week 6 from the 10 mg ($N=106$), 20 mg ($N=30$) and 40 mg ($N=17$) doses, 80%, 80% and 94% of these, respectively, were uptitrated. Of these, 58%, 67% and 69% reached target at week 12 with 10, 20 and 40 mg, respectively. Considering statin-treated subjects who required uptitration at week 6 from the 20 mg ($N=260$) and 40 mg ($N=33$) doses, 90% and 88% of these, respectively, were uptitrated. Of these, 42% and 52% achieved target at week 12 on 20 and 40 mg, respectively. Overall, in subjects assigned to 10, 20 or 40 mg doses, the lack of uptitration in eligible subjects ($N=58$) was due to failure of the investigator to uptitrate as required by protocol ($N=23$; 40%), failure of the patient to follow the dosing instructions ($N=28$; 48%) or to adverse events ($N=7$; 12%).

Within each treatment group, the proportion of subjects reaching target at weeks 6 and 12 was not significantly different (Table 3). Since this result may have been biased by subjects who did not adhere to study medication or who did not attend the two study-assessment visits at least 3 weeks apart, an additional post hoc analysis was conducted, excluding these subjects from the per protocol analysis. Despite this adjustment, no difference was observed between the weeks 6 and 12 achievement of LDL-C target in each treatment group (Table 3).

Mean percent changes in LDL-C were significant versus baseline for all doses in both statin-free and statin-treated subjects. Similarly, significant change from baseline in TC, TC/HDL-C ratio, triglycerides, non-HDL-C and apo-B were observed with all doses in both statin-free and statin-treated

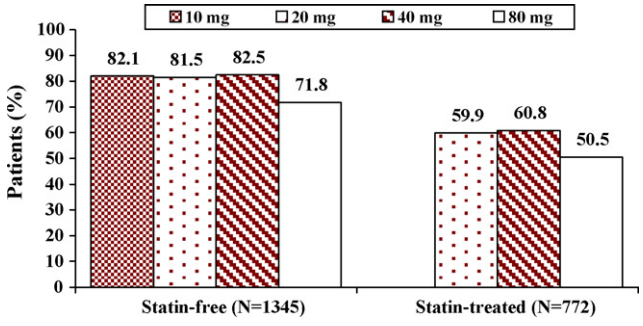

Fig. 2. Proportion of subjects reaching LDL-C target of <2.6 mmol/L (100 mg/dL) by starting dose in the statin-free and statin-treated groups (intention to treat ($N=2117$); last observation carried forward).

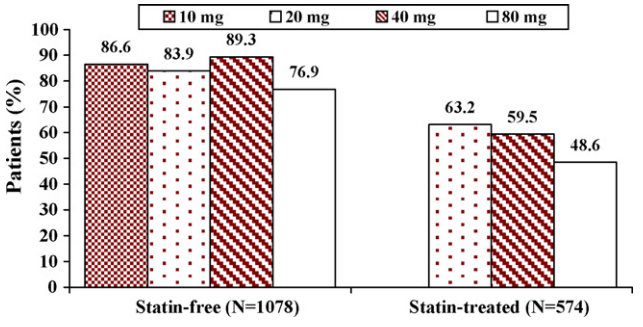

Fig. 3. Proportion of subjects reaching LDL-C target of <2.6 mmol/L (100 mg/dL) by starting dose in the statin-free and statin-treated groups (per protocol population ($N=1652$); last observation carried forward).

Table 3
Proportion of subjects achieving LDL-C target at weeks 6 and 12, in statin-free and statin-treated groups—ITT population and the subset of per protocol subjects[a] who attended both weeks 6 and 12 assessments

Statin-free	ITT ($N=1345$) (%) (95% CI)		Per protocol subjects who attended both visits[a] ($N=1012$) (%) (95% CI)	
	Week 6	Week 12	Week 6	Week 12
10 mg	84.3 (81.5–87.0)	83.1 (80.3–86.0)	88.6 (85.9–91.3)	87.1 (84.3–90.0)
20 mg	83.4 (78.0–88.8)	80.7 (74.9–86.5)	86.3 (80.6–92.0)	84.2 (78.1–90.2)
40 mg	88.9 (83.9–93.9)	82.2 (76.2–88.2)	90.3 (85.1–95.5)	89.5 (84.1–94.9)
80 mg	79.9 (75.3–84.4)	72.1 (67.0–77.2)	82.4 (77.3–87.4)	78.3 (72.8–83.7)
All doses	83.7 (81.7–85.7)	80.1 (78.0–82.3)	87.2 (85.1–89.2)	85.1 (82.9–87.3)
Statin-treated	**ITT ($N=772$) (%) (95% CI)**		**Compliant subjects who attended both visits[a] ($N=552$) (%) (95% CI)**	
	Week 6	Week 12	Week 6	Week 12
20 mg	55.1 (51.0–59.2)	60.3 (56.3–64.3)	57.4 (52.8–62.0)	63.0 (58.5–67.5)
40 mg	55.4 (44.1–66.7)	60.3 (49.1–71.5)	57.1 (42.2–72.1)	59.5 (44.7–74.4)
80 mg	58.1 (48.7–67.5)	50.9 (41.5–60.4)	53.6 (41.9–65.4)	47.8 (36.0–59.6)
All doses	55.5 (52.0–59.1)	59.0 (55.5–62.5)	56.9 (52.8–61.0)	60.9 (56.8–64.9)

LOCF data is illustrated in Fig. 2.
[a] Subjects included in this sub-population, had to have their assessment visits for weeks 6 and 12 at least 21 days apart. ITT: intention-to-treat.

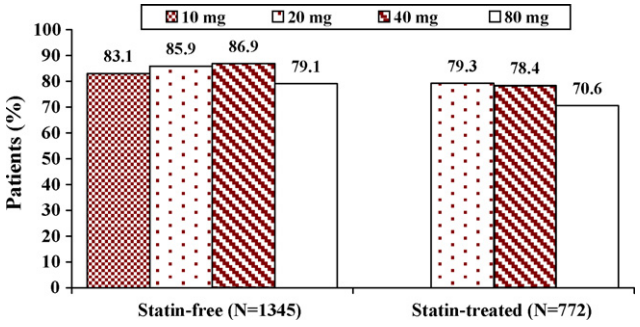

Fig. 4. Proportion of subjects reaching TC/HDL-C target of <4.0 by starting dose in the statin-free and statin-treated groups (intention to treat ($N=2117$); last observation carried forward).

subjects (Table 4). Overall, 83% and 78% of statin-free and statin-treated subjects, respectively, achieved a TC/HDL-C target of <4.0 (Fig. 4). This result was improved slightly in the per protocol population (87% and 80% for statin-free and statin-treated subjects, respectively). Changes in HDL-C were minor and only significant compared to baseline with the 10 mg dose in statin-free subjects, and with the 20 and 80 mg doses in the statin-treated group. In order to clarify the HDL-C effect, the study population was analyzed according to baseline HDL-C < or ≥1.03 mmol/L (40 mg/dL), the cut-off point defined by NCEP-III for 'low' HDL-C (Fig. 5) [2]. The results show that, at any dose, an increase in HDL-C occurs almost exclusively in subjects with a low baseline HDL-C. Data on subjects with intermediate HDL-C (40–45 mg/dL) at baseline show an intermediate response, more closely related to the HDL-C response of subjects with a baseline HDL-C ≥40 mg/dL (data not shown).

3.1. Safety

The incidence of treatment-related adverse events was 12.1%, across the dose range (Table 5). The most common

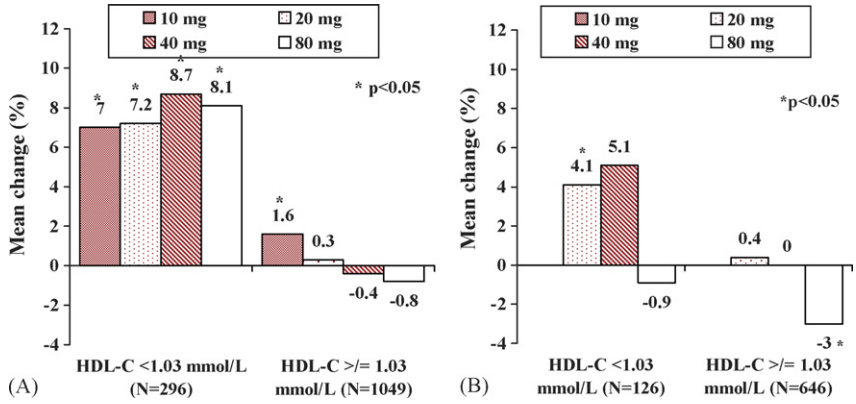

Fig. 5. Percent change from baseline in HDL-C according to baseline HDL-C <1.03 mmol/L (40 mg/dL) vs. ≥1.03 mmol/L in the statin-free (A) and statin-treated arms (B). Intention to treat; last observation carried forward. $^{*}P<0.05$ from baseline.

Table 4
Percent reduction from baseline in lipid parameters at end of 12-week study (ITT, LOCF), mean (95% CI)

	LDL-C	TC	TG	HDL-C	TC/HDL-C	Apo-B	Non-HDL-C
Statin-free							
10 mg	−34.8 (−36.0, −33.7)	−23.9 (−24.8, −23.0)	−13.7 (−16.1, −11.3)	3.1 (2.1, 4.0)	−25.4 (−26.4, −24.4)	−31.5 (−32.5, −30.5)	−32.1 (−33.2, −31.0)
20 mg	−43.3 (−45.4, −41.3)	−31.6 (−33.3, −30.0)	−22.7 (−25.9, −19.4)	1.4 (−0.4, 3.2)	−32.0 (−33.8, −30.1)	−39.4 (−41.2, −37.5)	−41.0 (−43.0, −38.9)
40 mg	−49.8 (−52.0, −47.7)	−37.2 (−38.9, −35.4)	−26.5 (−30.6, −22.3)	1.6 (−0.7, 3.9)	−37.4 (−39.4, −35.5)	−44.8 (−46.6, −42.9)	−47.1 (−49.2, −45.0)
80 mg	−52.7 (−54.3, −51.0)	−39.7 (−41.6, −37.7)	−5.2 (−45.5, 35.1)	0.6 (−1.2, 2.5)	−39.1 (−41.0, −37.1)	−46.8 (−48.2, −45.3)	−48.7 (−50.9, −46.4)
			Median[a]: −31.2				
Statin-treated							
20 mg	−21.4 (−22.7, −20.1)	−15.3 (−16.3, −14.3)	−8.2 (−10.9, −5.4)	1.0 (0.1, 2.0)	−15.4 (−16.5, −14.2)	−21.2 (−22.3, −20.1)	−20.4 (−21.7, −19.1)
40 mg	−37.0 (−40.6, −33.5)	−27.5 (−30.3, −24.8)	−22.8 (−28.2, −17.3)	0.6 (−2.4, 3.5)	−27.3 (−30.1, −24.4)	−34.2 (−37.2, −31.2)	−35.2 (−38.5, −31.9)
80 mg	−41.0 (−44.5, −37.4)	−32.0 (−34.4, −29.6)	−18.9 (−24.3, −13.6)	−2.7 (−4.7, −0.8)	−29.5 (−32.2, −26.7)	−38.0 (−40.7, −35.4)	−39.1 (−42.0, −36.1)

[a] One subject in this dose-group had a 6363% rise in triglycerides reported by the investigator as secondary to excessive alcohol drinking the day before the study visit, and unrelated to atorvastatin. The median is provided to better reflect the true effect of atorvastatin 80 mg on TG. Excluding this subject, the mean decrease in TG was −25.6% (95% CI: −28.9, −22.3).

events reported with a global incidence >1% were: asthenia (1.6%), myalgia (1.4%), constipation (1.1%) and dyspepsia (1.1%). The majority of events were of mild to moderate intensity with severe adverse events reported in only 0.6% of subjects. Overall, only 3.3% and 0.5% of subjects discontinued atorvastatin due to treatment-related adverse events and laboratory abnormalities, respectively. The most frequently reported adverse events leading to discontinuation of atorvastatin were (in decreasing order of frequency): gastrointestinal complaint, musculoskeletal complaint, abnormal laboratory parameter and asthenia. Treatment-related adverse events involving the musculoskeletal system occurred in only 2.3% of subjects. One case of rhabdomyolysis was reported as a mild, non-serious event by an investigator. The rise in CK was modest (peak at 359 IU/L) and the subject completed the study while remaining on the 80 mg dose. Upon review of this case, the Steering Committee determined that it was not consistent with a diagnosis of rhabdomyolysis based on the criteria defined in the ACC/AHA/NHLBI advisory on the use and safety of statins [42]. No treatment-related serious adverse events were reported. Two subjects died during the study, both in the atorvastatin 20 mg group; one of a myocardial infarction and the other of heart failure, neither of which were deemed treatment-related by the investigator. The incidence of any rise in AST/ALT >3 times the upper limit of normal, regardless of causality, was low at 1.2%. There was only one case of CK >10 times the upper limit of normal, which occurred without accompanying muscle symptoms, in a statin-free subject assigned to the 80 mg dose (0.05% overall). In this case, although the investigator reported the event as drug-related, it must be highlighted that the subject had sustained two falls 2 days before due to weak legs (due to degenerative disease of the spine, which was present at baseline and was reported as not related to atorvastatin) and that a swollen right ankle was also documented on the day blood was sampled. The possible contribution of these confounding events cannot be eliminated.

4. Discussion

The ACTFAST study was designed to assess whether using atorvastatin at starting doses appropriate for the degree of LDL-C reduction required would lead to achievement of LDL-C target quickly with either no titration or just one titration step. Traditionally, treatment has involved initiating therapy with the lowest dose of atorvastatin (i.e., 10 mg) and titrating up over time, with more subjects achieving targets with higher doses [12]. Frequent medical visits for dose titration being costly and time-consuming, may lead to frustration for patients and physicians alike [15]. In addition, Foley et al reported that only 45% of high-risk subjects who did not reach goal with initial dose of a statin were uptitrated [14]. It is interesting that, in this study, baseline lipid profile was not associated with a greater likelihood of uptitration. In addition, uptitration was less likely in subjects where the statin

Table 5
Overview of safety

	10 mg (*N* = 698)	20 mg (*N* = 784)	40 mg (*N* = 240)	80 mg (*N* = 428)	All doses (*N* = 2150)
All causality					
Subjects with AE (%)	37.4	34.3	37.1	44.9	37.7
Subjects with musculoskeletal AE (%)	6.2	5.7	6.3	7.0	6.2
AST or ALT >3 times upper limit of normal[a] (%)	0.7	0.5	1.3	3.3	1.2
CK >10 times upper limit of normal[a] (%)	0	0	0	0.2	0.05
Treatment-related AE					
Subjects with AE (%)	10.7	7.9	16.7	19.4	12.1
Subjects with musculoskeletal AE (%)	1.7	1.8	3.3	3.5	2.3
Subjects discontinued due to AE (%)	2.7	2.4	5.0	5.1	3.3
Subjects discontinued due to laboratory abnormality (%)	0.1	0	1.3	1.6	0.5

AE, adverse events; AST: aspartate aminotransferase; ALT: alanine aminotransferase; CK, creatine kinase.
[a] From a normal baseline value.

was initiated at doses above the recommended starting doses and when care was provided by a general practitioner.

Studies on subjects with CHD or diabetes have reported that about 32–59% of subjects will achieve targets with a starting dose of atorvastatin of 10 mg [15,17,18,26,29]. However, an additional 29–51% of subjects will go on to achieve targets when titrated to higher doses of atorvastatin (20–80 mg) [17,18,26,29]. Brown et al reported that 32% of subjects at higher risk achieved LDL-C targets of <2.6 mmol/L (100 mg/dL) after 12 weeks of therapy, and with dose titration up to 80 mg of atorvastatin, 83% were able to achieve this target [26]. In the NASDAC trial, there was a greater likelihood of subjects with CHD or CHD-equivalents to reach targets with higher starting doses (80.9% with 40 mg dose, 80.3% with 80 mg dose) than with lower starting doses (46.5% with 10 mg dose, 66.2% with 20 mg dose) [15]. ACTFAST showed that by initiating therapy at doses selected according to baseline LDL-C levels, 72% of all subjects, whether statin-free or statin-treated, achieved a target LDL-C of <2.6 mmol/L (100 mg/dL) as early as within 6 weeks. Interestingly, significant additional LDL-C reductions of 21–41% were observed at each dose when subjects treated with another statin at baseline were switched to a given dose of atorvastatin defined by the dose assignment table.

Changes in HDL-C concentrations were small and similar to those observed in other studies [38,39,48]. As suggested by these studies, our results might have been influenced by the rather high mean baseline HDL-C (1.3 mmol/L [50 mg/dL]) observed in our subjects. Our data confirm the results of other studies, which reported that a significant rise in HDL-C occurs almost exclusively in subjects with a low baseline HDL-C (<1.03 mmol/L (40 mg/dL)) [43–45]. In this subgroup, HDL-C increased by 7–9% in a non-dose-related fashion.

ACTFAST confirms that initiating treatment with a dose of atorvastatin selected to provide the required LDL-C reduction could bring a large proportion of high-risk subjects to LDL-C targets within 12 weeks. Despite the high cardiovascular risk in this subject group and the low LDL-C target levels (<2.6 mmol/L (100 mg/dL)), 80% of statin-free, and 59% of statin-treated subjects, achieved targets within 12 weeks. In an 8-week, open-label study using a similar treatment algorithm, 81.1% of high-risk statin-free subjects achieved LDL-C target [48]. In contrast, in the NASDAC study, subjects were randomized to a starting dose of 10–80 mg of atorvastatin, regardless of their baseline LDL-C value [15]. The proportion of subjects with 0–1 risk factors and with CHD/CHD-equivalent who achieved LDL-C targets (defined as <4.1 mmol/L (160 mg/dL) and <2.6 mmol/L (100 mg/dL), respectively) with 10, 20, 40 and 80 mg were 85%, 88%, 98% and 95%, and 47%, 66%, 81% and 80%, respectively. This demonstrates that, as the LDL-C target is lowered, one requires a higher starting dose in order to successfully achieve target. In contrast to NASDAC, high-risk statin-free subjects in ACTFAST showed better results on 10 and 20 mg doses, because baseline LDL-C was taken into account.

A dosing regimen that allows for a larger number of subjects to reach LDL-C target is expected to significantly improve cardiovascular outcomes, as illustrated by recent studies comparing aggressive treatment with atorvastatin to usual care-based regimens [8,40]. Thus, shortening the delay between treatment initiation and achievement of LDL-C target is attractive and potentially beneficial. The recommendations from NCEP-III support the use of a higher initial dose in subjects requiring a large LDL-C reduction to reach target [2]. Recently, several regulatory agencies around the world (for example: USA, Canada, Italy) have approved the use of atorvastatin at starting doses ranging from 10 to 40 mg. If required, the dose can then be titrated upward to a maximum of 80 mg in order to achieve LDL-C target. Subjects with CHD or CHD-equivalent have the lowest LDL-C target and may require higher doses. Thus, given the lack of safety concern in the initiation phase, it is logical to initiate therapy using a dose of atorvastatin that is appropriate for the required LDL-C reduction.

The results of the statin-treated group must be considered separately from the statin-free subjects. Based on their lower baseline blood pressure, fasting plasma glucose, TC and LDL-C, one can assume that these subjects had already received therapy for their heightened cardiovascular risk

level. These subjects are more difficult to treat and exhibit a certain level of treatment resistance as they failed to achieve LDL-C target with their initial therapy. The results of ACTFAST show that the dosing assignment table also worked for the subjects who did not reach target while on another statin. It must be remembered, however, that this study specifically excluded patients on atorvastatin at baseline and therefore the results may only be applicable to switching from another statin to atorvastatin. In these statin-treated subjects, significant additional reductions of 21–41% in LDL-C were achieved with doses of 20–80 mg of atorvastatin. This is important considering recent evidence from head-to-head trials which showed that more aggressive LDL-C lowering with atorvastatin 80 mg improved outcomes in subjects with acute coronary syndromes and stopped atherosclerotic progression in subjects with stable CHD or familial hypercholesterolemia [34–37].

The ratio of TC/HDL-C is a more sensitive and specific index of cardiovascular risk than total cholesterol. For that reason, it is used in some countries as a secondary target of treatment [1,12]. The dose assignment scheme tested in ACTFAST allowed for a large majority of both statin-free and statin-treated subjects to achieve a target ratio of <4.0. Given the large contribution of LDL-C and TG reductions to achievement of the TC/HDL-C ratio and the modest HDL-C elevation provided by atorvastatin, it is not surprising that slightly more statin-free subjects reached the TC/HDL-C target compared to the LDL-C target. The same is true for the statin-treated subjects, although the contribution of the change in HDL-C to achievement of the TC/HDL-C target was small.

No significant safety issues were observed when initiating atorvastatin at higher doses. In a recent review of pooled results from 44 trials involving 9416 subjects on atorvastatin, there was no dose–response relationship for adverse events and laboratory abnormalities across the dose range [46]. In NASDAC, the proportion of subjects with treatment-related adverse events was 10.9%, 11.8%, 11.3% and 16.5% with the 10, 20, 40 and 80 mg doses, respectively, which is comparable to our results [15]. In ATGOAL, 18.4% of high-risk subjects experienced treatment-related adverse events [48]. The proportion of subjects discontinuing treatment due to treatment-related adverse events in ACTFAST (3.3%) is similar or slightly lower than what was observed in NASDAC (3.2%) and ATGOAL (4% overall and 6% in high-risk subjects). In NASDAC, two subjects out of 919 exhibited a CK rise >10 times the upper limit of normal and in ATGOAL, there were no case out of 1295, while only one case in 2150 subjects occurred in ACTFAST. When considering any rise >3 times the upper limit of normal in AST or ALT, there were six cases (0.7%) in NASDAC, two to six cases (0.3–0.9%) in high-risk subjects in ATGOAL and 26 (1.2%) in ACTFAST [15,48]. In a pooled analysis of the atorvastatin clinical trials database, an incidence of 0.96% was reported across the dose range, which is consistent with our results [46]. As demonstrated by other studies, the results from ACTFAST further confirm the safety of the 80 mg dose of atorvastatin and confirm that it can be safely used as a starting dose in subjects at high risk for CHD and with a baseline LDL-C between 4.5 and 5.7 mmol/L [34,35,47].

5. Conclusion

Subjects with CHD or CHD-equivalent have the lowest LDL-C target (<2.6 mmol/L) and are likely to require higher doses of statins in order to achieve goal. Given that the undertreatment of elevated LDL-C in high-risk subjects is still a significant health care issue, identifying ways to improve the achievement of lipid targets in this population is critical. Tailoring the starting dose of atorvastatin according to the required level of LDL-C reduction and status of statin use at baseline provides a solution to achieve this objective. Using such a regimen, the ACTFAST study demonstrated that a large majority of high-risk subjects were able to achieve their LDL-C target safely within 12 weeks, with the initial dose or with just a single titration step. These results provide clinicians with a simple strategy to manage dyslipidemia and help decrease CHD risk faster and more effectively in high-risk subjects.

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Appendix A

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