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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.