Efficacy and safety of atorvastatin in South Asian patients with dyslipidemia: an open label noncomparative pilot study

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Background: Rates of coronary heart disease (CHD) mortality are 40% higher amongst South Asian men and women living in the UK compared with the general UK population. Despite an established excess CHD risk, little is known of the efficacy and safety of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors (statins) amongst South Asian migrants.

Methods and results: Hyperlipidemic South Asian patients (raised or uncontrolled low-density lipoprotein cholesterol [LDL-C]) were recruited from two UK centers (n = 33). After a five-week period, which included dietary advice, patients received atorvastatin 10 mg/d for five weeks to achieve a target LDL-C goal of <3.0 mmol/L, titrated to 20 mg, 40 mg, or 80 mg for a further 12 weeks as required. Significant reductions in LDL-C levels from baseline were observed after 4 weeks' and 17 weeks' treatment with atorvastatin ($\geq$33.6%; 26.0, 41.2). Overall, 81% (95% confidence interval [CI]: 62.5, 92.6%) achieved the target LDL-C after 4 weeks' treatment with 10 mg atorvastatin. Titration to a dose of more than 20 mg was required in only one patient (40 mg) at any point during the study. Nineteen patients reported at least one adverse event during the study; the majority were mild in severity and considered unrelated to atorvastatin.

Conclusions: Atorvastatin was effective in achieving target lipid levels and was well tolerated. Statin therapy for high-risk South Asian individuals is likely to benefit CHD outcomes, although further and larger prospective trials are required.

Keywords: hyperlipidemia, lipids, cholesterol, dyslipidemia, statins, coronary heart disease, South Asians

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Introduction

Coronary heart disease (CHD) is indiscriminately common to the global diaspora of people who originate from the Indian subcontinent (South Asia). Despite varied geographical origins, preserved customs, and adopted lifestyles in host countries (Shaunak et al 1986), CHD mortality is consistently reported as exceptionally high amongst South Asian migrants compared with indigenous populations (Derry et al 1987; Miller et al 1989; McKeigue et al 1989; Chadha et al 1993; Balarajan 1995). Migrants living in the UK consistently show markedly higher CHD mortality rates compared with the general UK population (Gill et al 2002).

Cross-sectional studies from the UK suggest that serum cholesterol is not particularly high among South Asians compared with the general population (Whitty et al 1999). However, preferred studies of prospective design confirm that established CHD risk factors such as serum cholesterol do operate among South Asian populations (Miller 1989; Chadha et al 1993; Lee et al 2001). Moreover, the risk from serum

cholesterol has been shown to increase with migration to the UK among migrants from the Punjab (Bhatnagar et al 1995) and Gujarat, India (Patel et al 2005).

Overwhelming evidence from primary and secondary prevention trials have demonstrated that lipid-lowering intervention can lower the incidence of CHD. Pharmacological intervention trials using 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors (statins) have established that lowering low-density lipoprotein cholesterol (LDL-C) levels will lead to a substantial reduction in the risk of CHD events (Scandinavian Simvastatin Survival Group 1994; Heart Protection Study Collaborative Group 2002; Sever et al 2003).

Atorvastatin is a well established member of the statin class that has demonstrated tolerability, efficacy, and safety in the treatment of hypercholesterolemia in preclinical and clinical studies (Black et al 1998; Jones et al 1998). However, the uptake of statin therapy in South Asian patients is reportedly lower than in other populations (Patel et al 2002), and information relating to the efficacy of statin use is scarce. This open label, noncomparative, two center pilot study provides a basis for further studies in this high-risk patient population. The primary objective was to achieve target lipid-lowering goals as defined by the Joint British Guidelines (JBG) on prevention of CHD in clinical practice (British Cardiac Society et al 2000). A secondary objective of the study was to assess the feasibility of conducting a multicenter study among this undertreated group of patients by testing ideas that will help to recruit and retain patients in clinical studies.

Methods
Study design
Patients were recruited over a one-year period from two sites in the UK and underwent a 5-week dietary period of study (dietary counseling and withdrawal of existing lipid-lowering therapy). Baseline total cholesterol and LDL-C levels were determined at week 4 of the dietary period, and those with LDL-C ≥3.0 mmol/L received atorvastatin 10 mg/day for 5 weeks. The lipid profile was reassessed after 4 weeks to determine whether the dose of atorvastatin needed to be titrated to 20 mg/d, 40 mg/d, or 80 mg/d. The treatment period continued for a further 12 weeks. Recruitment continued until 30 evaluable patients were enrolled. A local research ethics committee at both investigational sites reviewed the study protocol and its amendments. All patients

gave written informed consent prior to enrollment. A patient information sheet written in English, Hindi, and Urdu, was provided to all patients before signed consent was given.

To be eligible for inclusion, patients had to be of South Asian ethnic origin (defined as both parents originating from the Indian subcontinent), male or female aged 18–80 years, have hyperlipidemia, and fulfil at least one of the following criteria:

- Currently receiving lipid-lowering therapy that did not adequately control their dyslipidemia (total cholesterol ≥5.0 mmol/L [190 mg/dL], LDL-C ≥3.0 mmol/L).
- Currently receiving or had previously received lipid-lowering therapy that either they or their physician considered unacceptable.
- Were not receiving lipid-lowering therapy, but had elevated serum cholesterol and LDL-C levels that met the criteria for lipid-lowering therapy.

Major exclusion criteria included the following: uncontrolled hypertension; unsatisfactory glycemic control defined by hemoglobin A1c >9%; hepatic dysfunction; creatine phosphokinase levels >3 times the upper limit of normal; use of any drugs known to affect lipid levels (eg, systemic steroids), immunosuppressive agents, or drugs associated with rhabdomyolysis in combination with statins (eg, cyclosporin, erythromycin).

Evaluation of efficacy
The primary analysis of efficacy was the change in LDL-C from baseline to 4 weeks' and 17 weeks' treatment, and the proportion of patients who achieved the target LDL-C level of <3.0 mmol/L after 4 weeks' and 17 weeks. Secondary efficacy measures were the changes from baseline in high-density lipoprotein cholesterol (HDL-C), total cholesterol, total cholesterol/HDL-C ratio, triglycerides, apolipoprotein AI (Apo-AI), and apolipoprotein B (Apo-B) after 4 weeks' and 17 weeks' treatment.

Evaluation of safety
Adverse events were defined as any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporarily associated with the use of a medicinal product, whether or not related to the product. The relationship of an adverse event to atorvastatin and the intensity of an adverse event were assessed by the investigator.

Treatment-emergent adverse events were defined as those not reported during screening, or at baseline, or not

Table 1 Treatment-emergent AEs by body system in patients treated with atorvastatin (n = 33)

| Body system | Patients with at least one event (%) | Causality (number of events) | |
		Related	Not related
Body as a whole	11	2	13
Cardiovascular	1	0	1
Digestive	3	1	3
Hemic and lymphatic	1	0	1
Metabolic and nutritional	4	1	3
Musculoskeletal	4	2	3
Nervous	4	0	4
Respiratory	1	0	1
Skin and appendages	2	0	2

Abbreviations: AEs, adverse events.

recorded as continuing on medical history, or any event that had worsened relative to screening, baseline, or medical history.

Serious adverse events were defined as: those that were fatal; life threatening; required hospitalization (new or long-term); resulted in persistent or significant disability; or resulted in a congenital anomaly/birth defect. Jaundice and myopathy were considered serious adverse events for the purposes of this study. Clinical laboratory determinations, including aspartate aminotransferase, alanine amino-transferase, and creatine phosphokinase, were performed at each clinic visit.

Compliance

Treatment compliance was assessed according to the number of tablets returned after 5 weeks' and 17 weeks' treatment. Patients were considered to be protocol violators if they had taken less than 70% of the study medication.

Statistical methods

We hypothesised that a significant proportion of hyperlipidemic patients would achieve target LDL cholesterol with 4 weeks' and 17 weeks' atorvastatin therapy. Based on measures from a Caucasian population (März et al 1999), we calculated a total of 33 patients would be sufficient to observe a comparable proportion (67%) of South Asian patients achieving target LDL-C using a two-sided test with a power of 80%, $\alpha < 0.05$. We aimed to screen dyslipidemic South Asian patients in excess (double) of this number to allow for poor recruitment into the study. The intent-to-treat (ITT) population was used for safety evaluations and was defined as all patients who received at

least one dose of atorvastatin. Changes from baseline in lipid measures were determined using a last observation carried forward (LOCF) analysis where there were missing values. Data are reported as mean absolute change and mean percent change from baseline, together with 95% confidence intervals (CI). All lipid outcomes were assessed using a paired t-test, with the exception of serum triglycerides, for which a Wilcoxon signed rank test was performed due to a skew from the normal distribution in the dataset.

Results
Patient population and baseline characteristics

Fifty-six patients were screened, of whom 33 received atorvastatin (10 mg/d), and were subsequently included in the safety analysis. Twenty-two patients (67%) had primary risk factors for CHD, of whom 16 had no established CHD or peripheral vascular disease. Thirty-one patients were included in the modified ITT population. Ten patients discontinued from the study prematurely (four due to adverse events, three due to noncompliance with atorvastatin, and three lost to follow-up). Mean age (standard deviation [± SD]) of patients was 52.2 (± 10.0) years for men (n = 24) and 60.9 (± 7.4) years for women (n = 9). The mean duration of dyslipidemia since initial diagnosis was 1.6 (± 2.3) years. Twenty-nine patients reported at least one concomitant disease at time of entry into the study, the most common of which were hypertension (39%) and diabetes (30%).
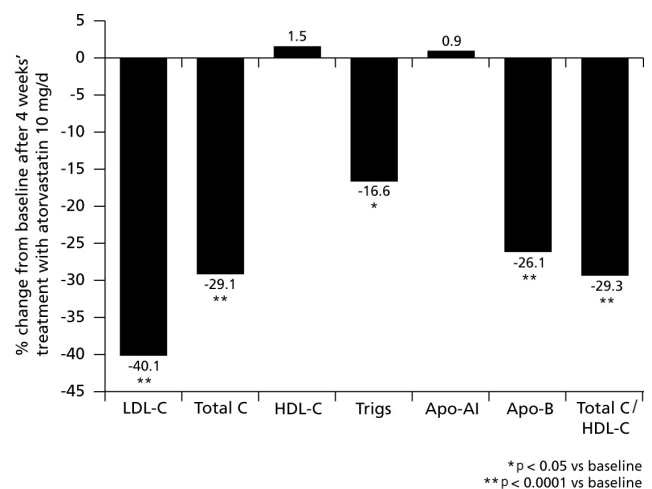

*p < 0.05 vs baseline
**p < 0.0001 vs baseline

Figure 1 Mean percent change from baseline in lipid measures after 4 weeks' treatment with atorvastatin 10 mg/d (n = 31 for all measures).
Abbreviations: LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; Apo, apolipoprotein.
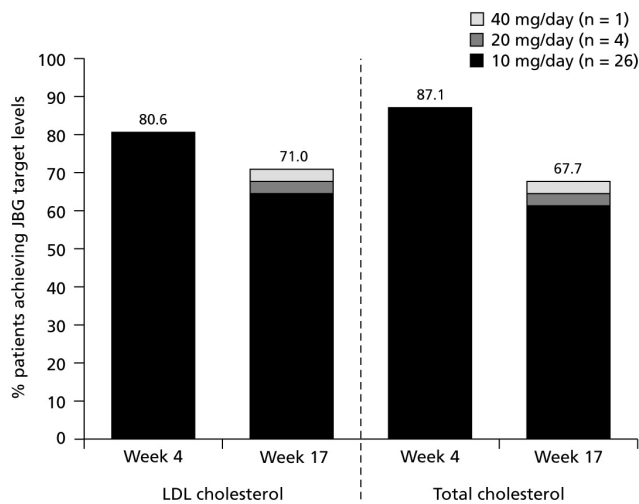
Figure 2 Percent of patients achieving Joint British Guidelines (JBG) target LDL-C and total cholesterol levels after 4 weeks' treatment with 10 mg/d and 17 weeks' treatment with 10–40 mg/d atorvastatin.

Efficacy

After 4 weeks' treatment with atorvastatin 10 mg/d, a significant reduction in LDL-C levels from baseline was observed (–1.6 mmol/L; 95% CI –1.9 to –1.4; p<0.0001). This represented a mean reduction of 40.1% (95% CI 45.2–35.0) from baseline (Figure 1). Eighty-one percent (95% CI 62.5–92.6) of patients achieved the target LDL-C level (<3.0 mmol/L) after 4 weeks' treatment with atorvastatin 10 mg/d (Figure 2).

After 17 weeks' treatment with atorvastatin 10 mg/d–40 mg/d, a significant reduction in LDL-C levels from baseline was observed (–1.4 mmol/L; 95% CI –1.7 to –1.0; p<0.0001); a mean reduction of 33.6% (95% CI –41.2 to –26.0) (Figure 3). Titration from 10 mg/d to 40 mg/d

*p ≤ 0.001 vs baseline
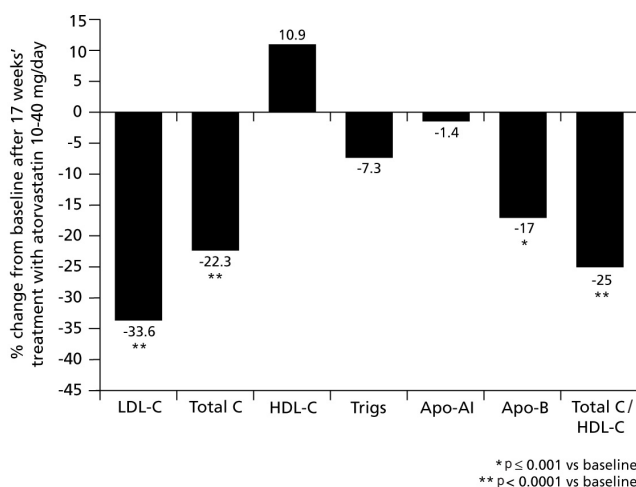** p< 0.0001 vs baseline

Figure 3 Mean percent change from baseline in lipid measures after 17 weeks' treatment with atorvastatin 10 mg/d–40 mg/d (n = 31 for all measures).

atorvastatin enabled 71% (95% CI 52.0–86.8) of patients to achieve target LDL-C level after 17 weeks' treatment (Figure 2). Titration to a dose of more than 20 mg/d was required in only one patient (40 mg/d) at any point during the study. For the secondary analyses of efficacy, significant reductions from baseline were observed after 4 weeks' and 17 weeks' treatment with atorvastatin for total cholesterol, total cholesterol/HDLC ratio, Apo-B, and triglycerides. HDL-C and Apo-AI levels increased from baseline over the same time period, but did not reach statistical significance (Figures 1 and 3). Between study entry and baseline (week 4 of the dietary run-in period) there was an increase in mean ± SD LDL-C levels from 3.73 (±0.94) mmol/L – 4.07 (±0.73) mmol/L. However, at week 5 of the dietary period, mean LDL-C had returned to the screening levels (3.76 [0.76] mmol/L). When week 5 of the dietary period was used as the baseline assessment, similar significant reductions were still observed after 4 weeks and 17 weeks of treatment.

Recruitment

Recruitment was poor at both centres; the majority of patients (18) were enrolled at the Sandwell Healthcare NHS Trust. Both centres employed staff of Asian origin to aid recruitment. The response rate was 33% from a target population of 283 referrals.

Safety

Of a total of 33 patients, five patients required a dose of atorvastatin >10 mg/d (four patients received 20 mg/d and one patient 40 mg/d). The theoretical duration of treatment was 119 days (17 weeks). Almost 90% of patients (29/33) received atorvastatin for at least 91 days. Nineteen patients (58%) reported at least one treatment-emergent adverse event. The majority of treatment-emergent adverse events were mild in severity and considered unrelated to atorvastatin treatment; the most common being headache (7 patients), myalgia (4 patients), and back pain (3 patients). There were no deaths or serious adverse events reported, and no laboratory results were considered to be clinically significant. Five patients reported adverse events that resulted in discontinuation of atorvastatin therapy and four of these patients withdrew from the study.

Discussion

Atorvastatin was an effective and well tolerated treatment for lowering total cholesterol, LDL-C, triglycerides, and Apo-B in this cohort of South Asian patients with

dyslipidemia, while causing no significant changes in HDL-C and Apo-A. The majority of patients (81%) achieved JBG target levels of LDL-C within the initial 4 weeks of atorvastatin treatment. Titration between 10 mg/d and 40 mg/d of atorvastatin resulted in 71% of patients achieving JBG target levels after 17 weeks' treatment; however, all patients achieved target levels at some point during the study. Furthermore, for most patients, it was not necessary to increase the dose of atorvastatin in order to achieve these target levels. The percentage reduction in LDL-C in this study is consistent with previous reports (Black et al 1998) following treatment with doses of atorvastatin up to 80 mg/d.

Recruitment of these South Asian origin patients was challenging and a period of one year was required to recruit the 33 patients for the study. The difficulty in CHD risk assessment in South Asians is likely due to different attitudes and knowledge of risk factors for CHD compared with the general UK population, combined with language barriers (Gill et al 2002). In Sandwell, South Asian-origin community healthcare staff were enlisted to educate and promote initial interest amongst a close-knit Indian Gujarati group. This culturally sensitive approach was the most successful for patient participation in this study: one-third of all patients were generated from the same Gujarati neighborhood. Similarly, a community link worker of Asian background at Whipps Cross helped to facilitate recruitment, but almost all patients enrolled were from the cardiac clinic.

Whole communities were targeted using an approach that included presentations on CHD within community centres. This allowed the concept of volunteering for clinical research to be debated within a broad forum, and employment of a nurse from the same community was likely to have benefited compliance with the study. One-on-one interaction between the study nurse and patient meant that sensitive cultural issues were aired freely with a good understanding between both parties. Interpreter services may not have instilled the same confidence amongst patients. The broad range of dialects and customs from the Indian subcontinent limits the value of Indian-origin healthcare staff to particular migrant populations. While the inclusion of culture-specific cohorts restricts epidemiological extrapolation, it avoids the danger of generalization. Inference from this particular study is limited as the South Asian cohort combines different religions, cultures, diets, and geographical origins. This preliminary work has nonetheless highlighted issues that need to be addressed by a more ambitious investigation.

Cross-sectional analysis against the general UK population suggests that serum cholesterol is not an obvious risk amongst people of South Asian origin (McKeigue et al 1989). Nonetheless, serum cholesterol has been shown to have a causal relationship with incident CHD amongst Indian migrants and residents in India (Miller et al 1989; Chadha et al 1993; Lee et al 2001). Therefore, while patients do not have elevated LDL-C, the target threshold may not be appropriate for this population, who commonly manifest with high CHD risk. In this study, 30% of all patients were diabetic and 39% were hypertensive. There was a reduction in serum triglycerides after 4 weeks' statin intervention (~17%) as well as Apo B (~26%). Although these reductions in triglycerides and apolipoproteins appear quite marked, it would be difficult to compare these data with those from larger trials. Reductions in these risk factors may prove an important intervention for CHD amongst South Asians. It is important to follow up the Apo B and triglyceride lowering effects of atorvastatin with quantitative data on LDL density in a South Indian migrant population.

Conclusion

Atorvastatin therapy was effective and well tolerated in treating this population of South Asian patients with hyperlipidemia to LDL-C goals. Considering that these patients are at a relatively higher risk of CHD than their age- and sex-matched European counterparts, it is all the more important that modifiable CHD risk factors, such as hypercholesterolemia, are effectively and aggressively treated, and atorvastatin appears to be both safe and effective in this regard. However, the difficulties reported in recruiting patients for this pilot study highlight the challenges to overcome so that patients can be recruited for any future large multicenter trial in the South Asian population.

Acknowledgments

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