ETHNIC VARIATIONS IN LIPID-LOWERING IN RESPONSE TO A STATIN (EVIREST): A SUBSTUDY OF THE ANGLO-SCANDINAVIAN CARDIOVASCULAR OUTCOMES TRIAL (ASCOT)

Background: Statins improve lipid profiles and reduce cardiovascular morbidity and mortality but there are few data on their relative effects in different ethnic groups.

Methods: We used data from the randomised, placebo-controlled Anglo-Scandinavian Cardiac Outcomes Trial-Lipid Lowering Arm (ASCOT-LLA) to conduct a prespecified comparison of the lipid-lowering efficacy of statin therapy among hypertensive participants from different ethnic groups in the UK and Ireland. The effects of atorvastatin (10mg daily) and placebo on fasting plasma lipid profiles were compared in matched groups of Whites and Blacks (of African-Caribbean or African origin) and Whites and South Asians (from the Indian subcontinent), adjusting for placebo effect.

Results: In the active treatment group, 156 Blacks and 72 South Asians were compared with 419 and 198 Whites, respectively. In multivariable analyses adjusted for baseline lipid levels and other potential confounders, atorvastatin reduced total cholesterol, low-density lipoprotein (LDL)-cholesterol and triglycerides from baseline in all ethnic groups. There were no clinically or statistically significant differences in the effect between Whites and Blacks or between Whites and South Asians after adjusting for placebo effect; similar proportions in each group achieved lipid targets. There was no significant effect of atorvastatin on high-density lipoprotein (HDL)-cholesterol in any group.

Conclusions: A standard dose of atorvastatin improved lipid profiles to a similar extent in Whites, Blacks and South Asians. Given the proven benefits of statins, these results suggest that, when used in standard doses, they are likely to be similarly effective for cardiovascular disease prevention in all ethnic groups. (Ethn Dis. 2011;21(2):150–157)

Key Words: Statins, Lipid Levels, Cholesterol, Ethnic Groups

INTRODUCTION

Statins (3-hydroxy-3-methylglutaryl coenzyme A [HMGCoA] reductase inhibitors) lower low-density lipoprotein (LDL) cholesterol and have been shown to cause important reductions in coronary and other cardiovascular events as well as all-cause mortality. Although the lipid-lowering effects of statins have been demonstrated in a variety of non-White populations, there is some evidence from observational studies suggesting that different ethnic groups may differ in their responsiveness. The existence of any such differences may have important implications for cardiovascular disease prevention. However, few data published so far have directly compared the lipid-lowering efficacy of statins in different ethnic groups within (or between) randomised trials.

We therefore used data from the Anglo-Scandinavian Cardiac Outcomes Trial-Lipid Lowering Arm (ASCOT-LLA) to conduct a prespecified comparison of the lipid-lowering efficacy of atorvastatin among different ethnic groups in the United Kingdom and Ireland. Here we present the findings of the Ethnic Variations in Response to a Statin (EVIREST) Study, a substudy of ASCOT-LLA, which aimed to compare the impact of atorvastatin among White participants compared with Blacks (of African-Caribbean and African origin), and those of South Asian origin (from the Indian subcontinent).

METHODS

ASCOT was a multicenter, international, randomised trial, which compared two antihypertensive strategies for the prevention of coronary heart disease (CHD) and vascular events in patients with hypertension and at least three additional cardiovascular risk factors but no history of CHD. In addition, by means of a two-by-two factorial design, ASCOT included a double-blind randomised comparison of the effects of atorvastatin with placebo among those participants with total cholesterol ≤6.5 mmol/L. The trial conformed to good clinical practice guidelines and was conducted in accord with the Declaration of Helsinki. The protocol was reviewed and ratified by central and regional ethics review boards or by national ethics and statutory bodies as appropriate in each country.

The methods and main results of ASCOT-LLA have been described previously. Briefly, participants eligible for inclusion in the blood pressure-lowering arm were randomised to a...
blood pressure-lowering regimen based on either amlodipine (with perindopril added as required to achieve blood pressure targets) or atenolol (with bendroflumethiazide added as required). Those with total cholesterol levels ≤6.5 mmol/L and who were not taking a statin or fibrate at study entry were also eligible for inclusion in ASCOT-LLA and were randomised to receive either atorvastatin 10mg daily or matching placebo. Participants could be included if they were taking lipid-lowering therapy other than statins and fibrates. Subsequently, during the trial, open-label lipid-lowering therapy (including additional nonstudy statins) could be added to randomised treatment at the discretion of investigators if considered clinically indicated. The primary outcome was nonfatal myocardial infarction or fatal CHD. Plasma lipid profiles (total cholesterol, LDL cholesterol, high-density lipoprotein [HDL] cholesterol and triglycerides) were measured on fasting samples (by a single laboratory for the United Kingdom and Ireland) at study selection, randomisation, 6 months, and then annually until the end of follow-up. The study was terminated after a median follow-up of 3.3 years when an interim safety analysis demonstrated clear benefits of atorvastatin treatment.18

**EVIREST Study Population**

At ASCOT registration, participants were asked to identify their ethnic origin as being either White/Europid, or of African, Oriental, South Asian or mixed/other origin). For the purpose of the current analyses, all participants in the United Kingdom and Ireland who identified themselves as any ethnicity other than White were identified from the ASCOT-LLA database. For each Black (of African-Caribbean or African origin) and South Asian (from the Indian subcontinent; India, Pakistan, Bangladesh and Sri Lanka) individual, up to 3 White participants were randomly selected from the database matched for age (±1 year), sex, diabetes status, study investigator, randomised group (atorvastatin or placebo) and study visit at which on-treatment lipid data were available. Where possible, on-treatment lipid profiles measured at 6 months were used; if these were not available then the next nearest available matched data were used. Other ethnic groups (eg. Oriental of East Asian origin, mixed or other) made up only about 1% of the ASCOT-LLA study population, thus precluding meaningful analysis.

**Statistical Methods**

Baseline characteristics of participants were compared between ethnic groups using t tests for continuous variables, χ² tests for categorical variables and Mann-Whitney tests for skewed data. Assumptions of normality of lipid parameters were examined prior to fitting statistical models; as triglycerides were not normally distributed, log-transformed data were used.

General linear models were used to perform two separate analyses of changes in lipids from baseline: 1) analysis of covariance (ANCOVA) with baseline lipids as a covariate; and 2) multivariable analyses adjusted for a priori confounders (baseline smoking status, alcohol consumption, body mass index [BMI], educational level [as a measure of socio-economic status], and family history of CHD), baseline lipids and randomised study blood pressure-lowering regimen (amlodipine- or atenolol-based therapy) as covariates. For both actively-treated and placebo groups, absolute changes from baseline in each lipid parameter (and percentage changes in normally-distributed parameters) in each ethnic group were estimated using least squares mean, hereafter referred to as adjusted mean, and standard error (SE). For each ethnic group placebo-corrected adjusted mean changes from baseline were calculated. P-values were based on differences in the placebo-corrected adjusted mean change between ethnic groups (White vs Black or White vs South Asian). Sensitivity analyses were performed after excluding placebo-treated participants whose follow-up lipid profiles were measured while taking open-label lipid-lowering treatment. Statistical tests were considered significant at the .05 (2-sided) level.

The proportions of actively-treated participants achieving the audit standards for lipid-lowering proposed in the 2005 UK Joint British Societies’ (JBS2) guidelines (total cholesterol <5 mmol/L and LDL-cholesterol <3 mmol/L) were also compared between the different ethnic groups.19

**RESULTS**

In total, 4853 individuals (2445 assigned atorvastatin and 2408 assigned placebo) participated in ASCOT-LLA in the United Kingdom and Ireland and were potentially eligible for inclusion in the current analyses (Figure 1). After matching and the exclusion of participants without baseline and on-treatment lipid profiles, 156 Black participants were matched to 419 Whites in the active treatment limb, and 147 Blacks were matched to 385 Whites in the placebo limb. Likewise, 72 South Asian participants were matched to 198 Whites in the active treatment limb, and 80 South Asians were matched to 210 Whites in the placebo limb. Lipid profiles measured at 6 months post-randomisation were available for 94% of participants.

Baseline characteristics of actively-treated participants for each comparison set (White vs. Black and White vs. South Asian) are shown in Table 1. Compared with Whites, Blacks had significantly lower total cholesterol, LDL-cholesterol and triglyceride levels, lower BMI, higher HDL-cholesterol and creatinine, greater numbers of cardiovascular risk factors and were
more likely to have left full-time education aged >16 years; they were less likely to drink alcohol or smoke and less likely to have a family history of CHD. Compared with Whites, South Asians had significantly lower systolic BP, lower BMI and lower total cholesterol levels; they were less likely to drink alcohol but were more likely to have left full-time education aged >16 years. Similar patterns of differences between ethnic groups were seen among placebo-treated participants (data not shown).

Placebo-corrected mean changes in lipids in White and Black participants are shown in Table 2. Among both groups, atorvastatin produced significant placebo-corrected reductions in total cholesterol, LDL-cholesterol and triglycerides but had little effect on...
HDL-cholesterol. There were no statistically significant differences between the effects of atorvastatin in Whites and Blacks for any of the parameters tested. There was no difference in the proportion of actively treated participants achieving target lipid levels (86% and 83% of Whites and South Asians, respectively; \( P=.37 \)).

Placebo-corrected mean changes in lipids in Whites and South Asians are shown in Table 3. In both groups atorvastatin produced significant placebo-corrected reductions in total and LDL-cholesterol. Placebo-corrected reductions in triglycerides were observed in both groups although this was only of borderline significance in South Asians. No effect was observed on HDL-cholesterol. The effects of atorvastatin did not differ between Whites and South Asians for any of the parameters tested. There was no difference in the proportion of actively treated participants achieving target lipid levels (86% and 83% of Whites and South Asians, respectively; \( P=.53 \)).

Discontinuation rates differed significantly between the different ethnic groups; among those assigned active therapy, 5% of Whites permanently discontinued statin therapy prior to measurement of their on-treatment lipid levels compared with 10% of Blacks and 13% of South Asians (\( P=.02 \)). Sensitivity (on-treatment) analyses after exclusion of these subjects did not materially alter the results (data not shown).

Only 11 placebo-treated participants (from all ethnic groups) were receiving open-label lipid-lowering therapy at the time of their on-treatment blood test. Repeating analyses after the exclusion of these participants did not materially alter the results.

**DISCUSSION**

These analyses compared the effects of atorvastatin in people of different ethnic groups in the UK and Ireland who participated in the ASCOT-LLA study. The results revealed no clinically or statistically significant differences...
Table 2. Placebo-corrected changes in lipids from baseline during atorvastatin treatment in Whites and Blacks

<table>
<thead>
<tr>
<th></th>
<th>White ANCOVA*</th>
<th>White Fully adjusted†</th>
<th>Black ANCOVA*</th>
<th>Black Fully adjusted†</th>
<th>White vs Black</th>
<th>Mean difference†</th>
<th>P</th>
<th>% difference P</th>
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<td></td>
<td>Mean change</td>
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<tr>
<td>Total cholesterol, mmol/L</td>
<td>-1.26</td>
<td>-23.4</td>
<td>-1.26</td>
<td>-23.1</td>
<td>-1.08</td>
<td>-19.7</td>
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<tr>
<td>LDL-cholesterol, mmol/L</td>
<td>-1.14</td>
<td>-34.1</td>
<td>-1.12</td>
<td>-32.8</td>
<td>-1.05</td>
<td>-30.0</td>
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<tr>
<td>HDL-cholesterol, mmol/L</td>
<td>-0.01</td>
<td>0.7</td>
<td>-0.03</td>
<td>1.2</td>
<td>-0.01</td>
<td>1.1</td>
<td></td>
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<tr>
<td>log triglycerides, mmol/L</td>
<td>-0.20</td>
<td>-27.0</td>
<td>-0.27</td>
<td>-27.0</td>
<td>-0.15</td>
<td>-22.0</td>
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<tr>
<td></td>
<td>(-0.25, -0.14)</td>
<td>(-0.36, -0.19)</td>
<td>(-0.36, -0.19)</td>
<td>(-0.36, -0.19)</td>
<td>(-0.23, -0.06)</td>
<td>(-0.33, -0.10)</td>
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Data are mean or % (95% confidence intervals).
* Adjusted for baseline lipid value
† Adjusted for baseline lipid value, smoking status, alcohol consumption, BMI, educational level, family history of CHD and randomised study blood pressure lowering regimen (amlodipine- or atenolol-based therapy)

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<table>
<thead>
<tr>
<th></th>
<th>White</th>
<th>South Asian</th>
<th>Mean difference†</th>
<th>P</th>
<th>% difference</th>
<th>P</th>
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<tbody>
<tr>
<td></td>
<td>ANCOVA*</td>
<td>Fully adjusted†</td>
<td>ANCOVA*</td>
<td>Fully adjusted†</td>
<td></td>
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<tr>
<td>Total cholesterol, mmol/L</td>
<td>-1.20 (−1.33, −1.07)</td>
<td>-1.12 (−1.24, −.99)</td>
<td>-1.24 (−1.45, −1.03)</td>
<td>-1.13 (−1.41, −.86)</td>
<td>-0.01 (−.36, .34)</td>
<td>.96 (−6.7, 6.0)</td>
</tr>
<tr>
<td>LDL-cholesterol, mmol/L</td>
<td>-1.14 (−1.36, −.93)</td>
<td>-1.10 (−1.31, −.89)</td>
<td>-1.13 (−1.41, −.86)</td>
<td>-1.09 (−2.61, −1.16)</td>
<td>-0.01 (−3.36, .34)</td>
<td>.3 (−6.7, 6.0)</td>
</tr>
<tr>
<td>HDL-cholesterol, mmol/L</td>
<td>-21.4 (−25.3, −17.5)</td>
<td>-33.8 (−40.1, −27.4)</td>
<td>-21.1 (−26.1, −16.1)</td>
<td>-33.3 (−41.0, −25.5)</td>
<td>.01 (−7.7, 6.9)</td>
<td>.91 (−10.5, 9.5)</td>
</tr>
<tr>
<td>log triglycerides, mmol/L</td>
<td>-.17 (−.04, −.05)</td>
<td>-.02 (−.16, 1.2)</td>
<td>-.02 (−.10, −.6)</td>
<td>.002 (−.13, .09)</td>
<td>.07 (−7.7, 6.9)</td>
<td>.91 (−10.5, 9.5)</td>
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Data are mean or % (95% confidence intervals).

* Adjusted for baseline lipid value
† Adjusted for baseline lipid value, smoking status, alcohol consumption, BMI, educational level, family history of CHD and randomised study blood pressure lowering regimen (amlodipine- or atenolol-based therapy).

There are relatively few published data directly comparing the efficacy of statins in different ethnic groups; this minimises confounding groups; this minimises confounding effects and increases the statistical power of studies. There are relatively few published studies of cardiovascular outcomes in different ethnic groups; this minimises confounding between White, Black and Japanese patients. There are relatively few published data directly comparing the efficacy of statins in different ethnic groups; this minimises confounding.
the analyses. Although the sample sizes were limited, particularly for South Asians, they still represent the largest published sample that we are aware of to have compared the effects of statins in Whites and South Asians. The comparison of the effects in Whites and Blacks is larger than previously published data comparing Whites and Blacks (eg, the EXCEL study)\(^{11}\).

However, we acknowledge that the current analyses are based on small numbers and hence provide limited power to detect small differences between ethnic groups. Other weaknesses include the lack of data on other ethnic groups (particularly East Asians, among whom plasma levels may differ from Whites)\(^{2,5,11}\) and uncertainty as to whether our findings are generalizable to other ethnic groups or other countries. It is also possible that participants in the current study may not be representative of the UK population; for example, these analyses are limited to participants with total cholesterol \(\geq 6.5\) mmol/L at study entry and the observed differences in the proportions of participants leaving full-time education \(>16\) years may not be nationally representative. It is uncertain whether these findings are generalizable to other statins since heterogeneity between statins might explain inconsistencies between previous studies. The current analyses did not distinguish between Blacks of African and those of Caribbean origin and there may be significant genetic differences between these groups that may affect statin responsiveness. Finally, although we found no differences in the efficacy of statins in the groups studied, data are insufficient as yet to confirm that proportionally similar reductions in lipids would reduce cardiovascular events to the same extent in different ethnic groups. However, the relative effects of statins appear to be broadly consistent in different study populations\(^{3,1}\) and existing evidence, albeit limited, shows a beneficial effect of statins on cardiovascular morbidity and mortality in non-White populations\(^{20}\).

Discontinuation rates differed significantly between the different ethnic groups with higher rates of permanent discontinuation among non-Whites. However, ASCOT was not designed to identify adverse effects associated with individual drugs and reasons for differences in tolerability or discontinuation cannot be reliably determined. Repeating the analysis after exclusion of those patients who discontinued active statin therapy prior to measurement of on-treatment lipid levels made no material difference to the results or conclusions.

In conclusion, in the EVIREST study, we found no clinically meaningful or statistically significant differences in the lipid-lowering efficacy of atorvastatin between Whites and Blacks and Whites and South Asians. Given the clear benefits of statins on cardiovascular events and mortality in many previous trials, the current results suggest that such therapy given in standard doses to White, Black and South Asian patients for the primary and secondary prevention of cardiovascular disease is likely to be equally effective regardless of their ethnic origin.

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REFERENCES


AUTHOR CONTRIBUTIONS

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Statistical expertise: Chang
Administrative: Chapman, Chang
Supervision: Chapman, Caulfield, Dahlo¨f, Sever, Poulter