Ethnic Variations in Lipid-lowering in Response to a Statin (EVIREST): a Substudy of the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT)

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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

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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.[1] Although the lipid-lowering effects of statins have been demonstrated in a variety of non-White populations,[2–10] there is some evidence from observational studies suggesting that different ethnic groups may differ in their responsiveness.[5,11,12] 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.[13–15]

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).[16]

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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.[17] 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.[17,18] 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, χ^2 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

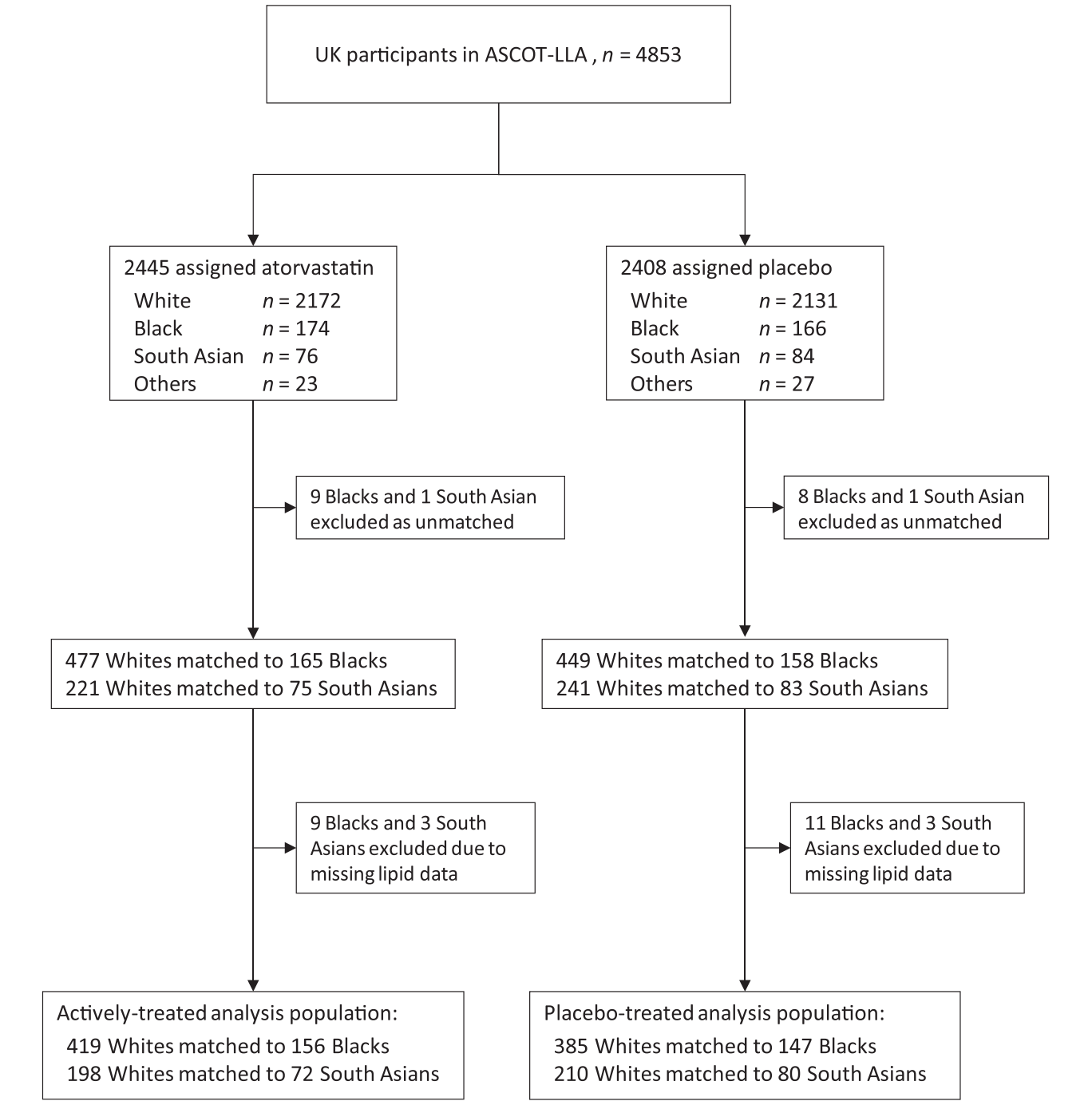

Fig 1. Flow chart of UK participants in ASCOT-LLA included in EVIREST analyses

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

Table 1. Characteristics at study entry of actively-treated patients in EVIREST by ethnic group

	White (*n*=419)	Black (*n*=156)	*P*	White (*n*=198)	South Asian (*n*=72)	*P*
Male	341 (81.4%)	124 (79.5%)	.61	187 (94.4%)	68 (94.4%)	1.00
Age (Years)	62.7 (7.3)	62.5 (7.7)	.74	58.8 (7.3)	58.5 (7.5)	.70
Randomised to amlodipine-based therapy	201 (48.0%)	72 (46.2%)	.70	116 (58.6%)	38 (52.8%)	.39
Current smoker	121 (28.9%)	31 (19.9%)	.03	58 (29.3%)	19 (26.4%)	.64
Alcohol drinker	325 (77.6%)	91 (58.3%)	<.0001	158 (79.8%)	40 (55.6%)	.0001
Age >16 years leaving full-time education	91 (21.7%)	64 (41.0%)	<.0001	46 (23.2%)	54 (75.0%)	<.0001
SBP, mm Hg	159.1 (16.1)	157.7 (16.6)	.37	159.0 (16.3)	153.6 (12.4)	.01
DBP, mm Hg	91.3 (9.2)	91.8 (9.4)	.59	92.9 (9.6)	91.0 (7.9)	.14
Heart rate, bpm	71.5 (12.8)	71.7 (14.2)	.83	72.1 (12.9)	75.2 (13.3)	.08
BMI, kg/m^2	29.6 (5.2)	28.6 (4.3)	.04	30.1 (5.0)	27.3 (3.6)	<.0001
Total Cholesterol, mmol/L	5.51 (.82)	5.26 (.84)	.002	5.52 (.80)	5.23 (.92)	.01
LDL-cholesterol, mmol/L*	3.45 (.73)	3.27 (.77)	.01	3.42 (.74)	3.25 (.80)	.11
HDL-cholesterol, mmol/L	1.27 (.33)	1.47 (.38)	<.0001	1.28 (.41)	1.25 (.30)	.59
Triglyceride, median (IQR), mmol/L*†	1.5 (1.1, 2.1)	1.0 (.7, 1.4)	<.0001	1.7 (1.2, 2.3)	1.5 (1.2, 2.0)	.11
Fasting glucose, mmol/L	6.6 (2.6)	6.4 (2.3)	.38	6.9 (2.7)	6.9 (1.9)	.88
Creatinine, µmol/L*	97.5 (15.1)	109.5 (19.1)	<.0001	96.4 (14.5)	98.7 (14.4)	.26
Prior stroke/TIA	34 (8.1%)	12 (7.7%)	.87	14 (7.1%)	3 (4.2%)	.38
Diabetes	166 (39.6%)	64 (41.0%)	.76	104 (52.5%)	38 (52.8%)	.97
Family history of CHD	72 (17.2%)	14 (9.0%)	.01	50 (25.3%)	11 (15.3%)	.08
Number of vascular risk factors	3.7 (.9)	4.0 (1.0)	.0005	3.9 (1.0)	3.7 (.8)	.14

Data are mean (SD) or *n* (%) unless otherwise stated. Patients were matched for age, sex and diabetes status.

SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index; LDL, low-density lipoprotein; HDL, high-density lipoprotein; TIA, transient ischaemic attack; CHD, coronary heart disease.

* Missing low-density lipoprotein data in 42 White, 11 Black and 4 South Asian; missing triglyceride data in 24 White, 10 Black and 2 South Asian participants; missing creatinine data in 15 White, 3 Black and 2 South Asians.

† Mann-Whitney test.

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 82% of Whites and Blacks, 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

…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.

Table 2. Placebo-corrected changes in lipids from baseline during atorvastatin treatment in Whites and Blacks

	White				Black				White vs Black			
	ANCOVA*		Fully adjusted†		ANCOVA*		Fully adjusted†		Mean difference†	*P*	% difference	*P*
	Mean change	%	Mean change	%	Mean change	%	Mean change	%				
Total cholesterol, mmol/L	−1.26 (−1.35, −1.16)	−23.4 (−25.2, −21.6)	−1.26 (−1.42, −1.10)	−23.1 (−26.1, −20.0)	−1.08 (−1.23, −0.93)	−19.7 (−22.5, −16.8)	−1.07 (−1.28, −.85)	−19.2 (−23.2, −15.1)	−.19 (−.46, .07)	.16	−3.9 (−9.0, 1.2)	.13
LDL-cholesterol, mmol/L	−1.14 (−1.23, −1.05)	−34.1 (−37.1, −31.2)	−1.12 (−1.27, −.96)	−32.8 (−37.8, −27.8)	−1.05 (−1.19, −.91)	−30.0 (−34.6, −25.3)	−1.01 (−1.21, −.82)	−28.4 (−34.9, −21.9)	−.10 (−.35, .15)	.42	−4.4 (−12.6, 3.8)	.30
HDL-cholesterol, mmol/L	.01 (−.02, .04)	.7 (−1.5, 2.9)	.03 (−.02, .07)	1.2 (−2.4, 4.8)	.01 (−.04, .05)	.1 (−3.4, 3.6)	.02 (−.04, .09)	.3 (−4.5, 5.2)	.003 (−.08, .08)	.94	.9 (−5.2, 6.9)	.78
log triglycerides, mmol/L	−.20 (−.25, −.14)	-	−.27 (−.36, −.19)	-	−.15 (−.23, −.06)	-	−.22 (−.33, −.10)	-	−.06 (−.20, .09)	.44	-	-

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)

between Whites and Blacks or between Whites and South Asians in the effect of atorvastatin on any of the lipid parameters tested.

Statins have been shown to safely and effectively reduce LDL-cholesterol in a variety of different ethnic groups including Whites, Blacks, South Asians and several East Asian populations.[2–10] Data from large-scale randomised trials conducted among predominantly White populations have further demonstrated that they also reduce cardiovascular events and all-cause mortality; each 1 mmol/L reduction in LDL-cholesterol is associated with a 21% reduction in major vascular events.[1] However, to date, there is only limited evidence on the effects of statins on cardiovascular morbidity and mortality in non-White ethnic groups.[20]

There is evidence from ethnically diverse populations, particularly in the United States, that lipid levels are less well controlled among non-White groups than among Whites.[21–28] The reasons for this are complex and are likely to include differences in accessing health care, statin prescriptions and treatment concordance. However, there is also some evidence of ethnic and genetic differences in the pharmacokinetics of, and clinical response to, statins. For example, certain gene polymorphisms associated with reduced response to statins are more common in Blacks than Whites,[12] and higher plasma levels of statins have been demonstrated in East and South Asians compared with Whites,[5,11] possibly due to differences in metabolising enzymes and drug transporter activity.[5] Early anecdotal experience among patients attending a lipid clinic in Singapore, suggested that statin effects on HDL-cholesterol might differ between Indian and Chinese and Malaysian populations, although this has not been formally tested due to limited patient numbers.[7] Others, meanwhile, have reported no differences in clinical response to cerivastatin (now with-

Table 3. Placebo-corrected changes in lipids from baseline during atorvastatin treatment in Whites and South Asians

	White				South Asian				White vs South Asian			
	ANCOVA*		Fully adjusted†		ANCOVA*		Fully adjusted†		Mean difference†	*P*	% difference	*P*
	Mean change	%	Mean change	%	Mean change	%	Mean change	%				
Total cholesterol, mmol/L	−1.20 (−1.33, −1.07)	−22.0 (−24.4, −19.6)	−1.14 (−1.36, −.93)	−21.4 (−25.3, −17.5)	−1.24 (−1.45, −1.03)	−22.9 (−26.7, −19.0)	−1.13 (−1.41, −.86)	−21.1 (−26.1, −16.1)	−.01 (−.36, .34)	.96	−.3 (−6.7, 6.0)	.92
LDL-cholesterol , mmol/L	−1.12 (−1.24, −.99)	−32.9 (−36.6, −29.1)	−1.10 (−1.31, −.89)	−33.8 (−40.1, −27.4)	−1.12 (−1.31, −0.93)	−33.4 (−39.1, −27.7)	−1.09 (−1.35, −.84)	−33.3 (−41.0, −25.5)	−.01 (−.34, .32)	.97	−.5 (−10.5, 9.5)	.92
HDL-cholesterol , mmol/L	.01 (−.04, .05)	1.3 (−1.6, 4.2)	−.02 (−.09, .04)	−.6 (−5.1, 3.9)	−.02 (−.10, .05)	−1.7 (−6.4, 3.0)	−.002 (−.09, .09)	−.2 (−5.9, 5.6)	−.02 (−.13, .09)	.68	−.4 (−7.7, 6.9)	.91
log triglycerides, mmol/L	−0.17 (−0.25, −.10)	-	−.10 (−.22, .03)	-	−.17 (−.28, −.05)	-	−.17 (−.31, −.02)	-	.07 (−.12, .26)	.46	-	-

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)

drawn) between White, Black and Japanese patients.[29]

There are relatively few published data directly comparing the efficacy of statins in different ethnic groups within randomised trials.[13–15] In the large (n=8245) placebo-controlled Expanded Clinical Evaluation of Lovastatin (EXCEL) Study,[13] active therapy was associated with 2.9% to 6.3% greater LDL-cholesterol reductions (at different doses of lovastatin) in White patients compared with Blacks. However, these findings were based on small numbers of Black participants (between 75 and 90 for different dose comparisons) and were not statistically robust; after exclusion of outliers differences were reduced (0% to 2.3%) and no longer significant. A report comparing the results of two small uncontrolled open-label studies of similar design,[14] one conducted among East Asians and non-Asians (from Latin America, United States, Europe and South Africa) and the other solely in East Asians, found similar responses to simvastatin (in terms of targets achieved and doses required) in Asian (n=116) and non-Asian (n=155) participants. A recent open-label study of the effects of a single-pill combined antihypertensive-statin therapy (containing atorvastatin)[15] demonstrated that lipid targets were achieved in a high proportion of patients in an ethnically diverse population (27 countries from Latin America, the Middle East, Africa and the Asia-Pacific region) but did not report in detail the effects on lipid profiles in different ethnic groups.

Strengths of our analyses include that they were prespecified in the protocol of a large randomised controlled trial. The presence of a placebo arm should have avoided over-estimation of the effect of active treatment. The relatively large size of ASCOT-LLA allowed matching of each Black and South Asian participant to multiple Whites resulting in closely matched groups; this minimises confounding and increases the statistical power of

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).[13]

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)[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 ≤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[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

1. Baigent C, Keech A, Kearney P, et al. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. *Lancet*. 2005;366:1267–1278.
2. Jacobson T, Chin M, Curry C, et al. Efficacy and safety of pravastatin in African Americans with primary hypercholesterolemia. *Arch Intern Med*. 1995;155:1900–1906.
3. Prisant L, Downton M, Watkins L, et al. Efficacy and tolerability of lovastatin in 459 African-Americans with hypercholesterolemia. *Am J Cardiol*. 1996;78:420–424.
4. Zhu J, Tomlinson B, Ro Y, Sim K, Lee Y, Sriratanasathavorn C. A randomised study comparing the efficacy and safety of rosuvastatin with atorvastatin for achieving lipid goals in clinical practice in Asian patients at high risk of cardiovascular disease (DISCOVERY-Asia study). *Curr Med Res Opin*. 2007; 23:3055–3068.
5. Liao J. Safety and efficacy of statins in Asians. *Am J Cardiol*. 2007;99:410–414.
6. Itoh T, Matsumoto M, Hougaku H, et al. Effects of low-dose simvastatin therapy on serum lipid levels in patients with moderate hypercholesterolemia: a 12-month study. The Simvastatin Study Group. *Clin Ther*. 1997;19: 487–497.
7. Tan C, Loh L, Tai E. Do Singapore patients require lower doses of statins? The SGH Lipid Clinic experience. *Singapore Med J*. 2003;44: 635–638.
8. Patel J, Gupta S, Lie F, Hughes E. Efficacy and safety of atorvastatin in South Asian patients with dyslipidemia: an open label noncomparative pilot study. *Vasc Health Risk Manag*. 2005;1:351–356.
9. Deedwania P, Gupta M, Stein M, Ycas J, Gold A. Comparison of rosuvastatin versus atorvastatin in South-Asian patients at risk of coronary heart disease (from the IRIS Trial). *Am J Cardiol*. 2007;99:1538–1543.
10. Chung N, Cho S, Choi D, et al. STATT: a titrate-to-goal study of simvastatin in Asian patients with coronary heart disease. Simvastatin Treats Asians to Target. *Clin Ther*. 2001;23:858–870.
11. Lee E, Ryan S, Birmingham B, et al. Rosuvastatin pharmacokinetics and pharmacogenetics in White and Asian subjects residing in the same environment. *Clin Pharmacol Ther*. 2005;78:330–341.
12. Krauss R, Mangravite L, Smith J, et al. Variation in the 3-hydroxyl-3-methylglutaryl coenzyme a reductase gene is associated with racial differences in low-density lipoprotein cholesterol response to simvastatin treatment. *Circulation*. 2008;117:1537–1544.
13. Shear C, Franklin F, Stinnett S, et al. Expanded Clinical Evaluation of Lovastatin (EXCEL) study results. Effect of patient characteristics on lovastatin-induced changes in plasma concentrations of lipids and lipoproteins. *Circulation*. 1992;85:1293–1303.
14. Morales D, Chung N, Zhu J, et al. Efficacy and safety of simvastatin in Asian and non-Asian coronary heart disease patients: a comparison of the GOALLS and STATT studies. *Curr Med Res Opin*. 2004;20:1235–1243.
15. Erdine S, Ro Y, Tse H, et al. Single-pill amlodipine/atorvastatin helps patients of diverse ethnicity attain recommended goals for blood pressure and lipids (the Gemini-AALA study). *J Hum Hypertens*. 2009;23:196–210.

16. Poulter N, Caulfield M, Feder G. Ethnic variations in response to a statin (EVIREST). *J Hum Hypertens*. 2001;15(Suppl 1):S87–89.
17. Sever P, Dahlöf B, Poulter N, et al. Rationale, design, methods and baseline demography of participants of the Anglo-Scandinavian Cardiac Outcomes Trial. ASCOT investigators. *J Hypertens*. 2001;19:1139–1147.
18. Sever P, Dahlöf B, Poulter N, 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;361:1149–1158.
19. JBS 2: Joint British Societies' guidelines on prevention of cardiovascular disease in clinical practice. *Heart*. 2005;91(Suppl 5):v1–52.
20. Kushiro T, Mizuno K, Nakaya N, et al. Pravastatin for cardiovascular event primary prevention in patients with mild-to-moderate hypertension in the Management of Elevated Cholesterol in the Primary Prevention Group of Adult Japanese (MEGA) Study. *Hypertension*. 2009;53:135–141.
21. Mann D, Reynolds K, Smith D, Muntner P. Trends in statin use and low-density lipoprotein cholesterol levels among US adults: impact of the 2001 National Cholesterol Education Program guidelines. *Ann Pharmacother*. 2008;42:1208–1215.
22. Ashworth M, Lloyd D, Smith R, Wagner A, Rowlands G. Social deprivation and statin prescribing: a cross-sectional analysis using data from the new UK general practitioner 'Quality and Outcomes Framework'. *J Public Health (Oxf)*. 2007;29:40–47.
23. Wong N, Lopez V, Tang S, Williams G. Prevalence, treatment, and control of combined hypertension and hypercholesterolemia in the United States. *Am J Cardiol*. 2006;98: 204–208.
24. Yood M, McCarthy B, Kempf J, et al. Racial differences in reaching target low-density lipoprotein goal among individuals treated with prescription statin therapy. *Am Heart J*. 2006;152:777–784.
25. Clark L, Maki K, Galant R, Maron D, Pearson T, Davidson M. Ethnic differences in achievement of cholesterol treatment goals. Results from the National Cholesterol Education Program Evaluation Project Utilizing Novel E-Technology II. *J Gen Intern Med*. 2006;21:320–326.
26. Jha A, Varosy P, Kanaya A, et al. Differences in medical care and disease outcomes among Black and White women with heart disease. *Circulation*. 2003;108:1089–1094.
27. Kaplan R, Bhalodkar N, Brown EJ, White J, Brown D. Race, ethnicity, and sociocultural characteristics predict noncompliance with lipid-lowering medications. *Prev Med*. 2004; 39:1249–1255.
28. Williams M, Morris MT, Ahmad U, Yousseff M, Li W, Ertel N. Racial differences in compliance with NCEP-II recommendations for secondary prevention at a Veterans Affairs medical center. *Ethn Dis*. 2002;12:S1-58-62.
29. Mück W, Unger S, Kawano K, Ahr G. Interethnic comparisons of the pharmacokinetics of the HMG-CoA reductase inhibitor cerivastatin. *Br J Clin Pharmacol*. 1998;45:583–590.

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