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Ethnic Differences in Blood Pressure Response to First and Second-Line Antihypertensive Therapies in Patients Randomized in the ASCOT Trial

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BACKGROUND
Some studies suggest that blood pressure (BP)–lowering effects of commonly used antihypertensive drugs differ among ethnic groups. However, differences in the response to second-line therapy have not been studied extensively.

METHODS
In the BP-lowering arm of the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT-BPLA), BP levels of European ($n = 4,368$), African (203), and South-Asian- (132) origin patients on unchanged monotherapy (atenolol or amlodipine) and/or on second-line therapy (added thiazide or perindopril) were compared. Interaction between ethnicity and BP responses (defined as end BP minus start of therapy BP) to both first- and second-line therapies were assessed in regression models after accounting for age, sex, and several other potential confounders.

RESULTS
BP response to atenolol and amlodipine monotherapy differed among the three ethnic groups (interaction test $P = 0.05$). Among those allocated atenolol monotherapy, black patients were significantly less responsive (mean systolic BP (SBP) difference +1.7 (95% confidence interval: −1.1 to 4.6) mm Hg) compared to white patients (referent). In contrast, BP response to amlodipine monotherapy did not differ significantly by ethnic group. BP responses to the addition of second-line therapy also differed significantly by ethnic group (interaction test $P = 0.004$). On adding a diuretic to atenolol, BP lowering was similar among blacks and South-Asians as compared to whites (referent). However, on addition of perindopril to amlodipine, BP responses differed significantly: compared to whites (SBP difference −1.7 (−2.8 to −0.7) mm Hg), black patients had a lesser response (SBP difference 0.8 (−2.5 to 4.2) mm Hg) and South-Asians had a greater response (SBP difference −6.2 (−10.2 to −2.2) mm Hg).

CONCLUSIONS
We found important differences in BP responses among ethnic groups to both first- and second-line antihypertensive therapies.

Keywords: *antihypertensive agents; blood pressure; ethnicity; hypertension; race; treatment*

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Commonly used antihypertensive drugs vary in their blood pressure (BP)–lowering effect in different ethnic populations. Patients of African origin are generally less responsive to β-blockers, angiotensin-converting enzyme (ACE) inhibitors, and angiotensin-receptor blockers as monotherapy, and are more responsive to calcium channel blockers and diuretics.[1–9] These reported differences in response are likely to result in differential cardiovascular outcomes by ethnic group. For example, in the ALLHAT (Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial),[10,11] ACE inhibitors were found to be less effective than the diuretic chlorthalidone in preventing stroke in African-American patients, consistent with the difference in in-trial BP associated with the two treatments. A systematic review of antihypertensive drug therapy showed differential BP-lowering responses to antihypertensive agents between blacks and whites, but found no compelling evidence of a difference in effect on morbidity or mortality between ethnic groups once BP control was taken into account.[12]

Most hypertension guidelines except those published by the British Hypertension Society and the UK National Institute for Health and Clinical Excellence[13] do not recommend taking ethnicity into account when choosing first-line drugs. In part, this is because there are few reliable comparisons across ethnic groups, with the possible exception of patients of European (white) or African (black) origin. We do not know whether South-Asian populations, originating from the Indian subcontinent, or Oriental populations differ in their response to antihypertensive drugs compared with whites or blacks. Nor do we know whether there are differences among any ethnic

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groups in response to antihypertensive drugs used as second-line therapy. The latter is particularly important because most people with hypertension will require two or more drugs for adequate control of their BP,[13] and choice of second-line agent may be equally important in achieving adequate BP control.

In this article, arising from a prespecified substudy[14] of the BP-lowering arm of the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT-BPLA),[15] we report the BP response to first- and second-line drugs in white, black, and South-Asian patients among UK participants in this parallel-group randomized controlled trial.

METHODS

Study population. In the UK centers participating in the ASCOT Trial, 8,399 patients with hypertension belonging to one of three broad ethnic groups—people of European origin (whites), people of African origin (blacks), and people originating from the Indian subcontinent (South-Asians)—were randomized to receive one of two study medications—atenolol or amlodipine—instead of whatever antihypertensive medication (if any) they were taking. The prespecified second-line agents were added to those not achieving BP targets on allocated monotherapies, specifically perindopril was added to those allocated amlodipine and bendroflumethiazide was added to those allocated atenolol.[15]

Ethnicity was assigned on the basis of self-report in a questionnaire administered by nurses at a screening visit when consent for trial participation was obtained. Systolic (SBP) and diastolic BP (DBP) was recorded at screening, randomization, and every subsequent visit using standard methods.[15] For the purpose of this analysis, BP differences for both mono- and second-line therapies were calculated by subtracting the BP at the start of therapy from that at the end of therapy. We defined the end of both mono- and second-line therapy BP as the reading on the day (or, if not available, the closest reading prior to but within 6 weeks) of uptitration to any further therapy. In a few patients where there was no change in therapy, BP at the exit from the study was taken as the end of therapy BP.

Sample for monotherapy analysis. We included participants in the monotherapy analysis who had taken atenolol or amlodipine as randomized monotherapy at the start of the trial unchanged until the end of monotherapy, and who had BP readings at baseline and at the end of the monotherapy period (per-protocol analysis). A secondary (intention-to-treat) analysis included participants who switched to another monotherapy.

Sample for second-line therapy analysis. We included participants in the second-line therapy analyses who received bendroflumethiazide or perindopril unchanged, as second-line drugs, additional to atenolol or amlodipine monotherapy, respectively, and who had BP readings at the start and end of the second-line therapy period (per-protocol analysis). A secondary (intention-to-treat) analysis included those who switched to other second-line therapy drug regimens after their initially allocated treatments during the monotherapy and second-line therapy periods.

Statistical analysis. The objective of these analyses was to compare SBP and DBP responses to both first-line (atenolol and amlodipine) and second-line drugs (bendroflumethiazide and perindopril) in white, black, and South-Asian participants.

We used two linear regression models with BP difference as the dependent variable, allocated treatment, ethnic groups, and their interaction as independent variables to analyze BP levels by ethnicity separately for both monotherapy and second-line therapy. In model 1, we adjusted for the prespecified covariate (SBP or DBP at the start of mono- or second-line therapy) and *a priori* confounders: age, sex, body mass index, and years of education. We further identified other potential confounders among baseline variables by examining their effect on model 1 when introduced separately one at a time. If found to be statistically significant, these covariates were then added to model 1, thereby developing another comprehensive multivariable linear regression model: model 2. For each of these analyses, the presence of an overall interaction of treatment and ethnicity was assessed using the likelihood ratio test (LRT). However, where occasionally required for clarity, the Wald test results of an individual interaction parameter was also reported. In the intention-to-treat analysis, we ran the two models again, using data from all 5,425 and 3,459 participants started on mono- or second-line therapy, respectively. All models were assessed for any violations of normality and linearity assumptions.

RESULTS

Of 19,257 hypertensive patients in ASCOT-BPLA, 8,399 (43.6%) from the three broad ethnic groups were UK residents at the time of randomization. 5,425 (5,021) white, 250 (4.7%) black, and 154 (2.7%) South-Asian origin) patients were randomized to and initially began on either atenolol (2,580) or amlodipine (2,845) as monotherapy. Although 742 of these 5,425 participants subsequently switched to other monotherapy drugs, 4,683 (86.3%) remained on randomized monotherapy and were the basis of the per-protocol analysis of response to monotherapy (see **Figure 1**).

Among the 5,425 participants initiated on first-line agents, 3,459 went on to receive bendroflumethiazide (added to atenolol) or perindopril (added to amlodipine) as second-line therapy, of whom the majority (3,385, 96.9%) were still receiving their initially allocated first-line monotherapy. Although 591 participants subsequently shifted to other two-drug therapy combinations, the majority (2,794, 82.5%) continued with the allocated two drugs, and these participants are the basis of the per-protocol analysis of BP response to second-line therapy (see **Figure 1**).

Baseline characteristics

The average age (± s.d.) of the 5,425 participants initially randomized to monotherapy was 64 (± 8) years and average body mass index was 28.7 (± 4.5) kg/m^2. Ninety percent of these participants had been taking antihypertensive medication prior to trial entry.

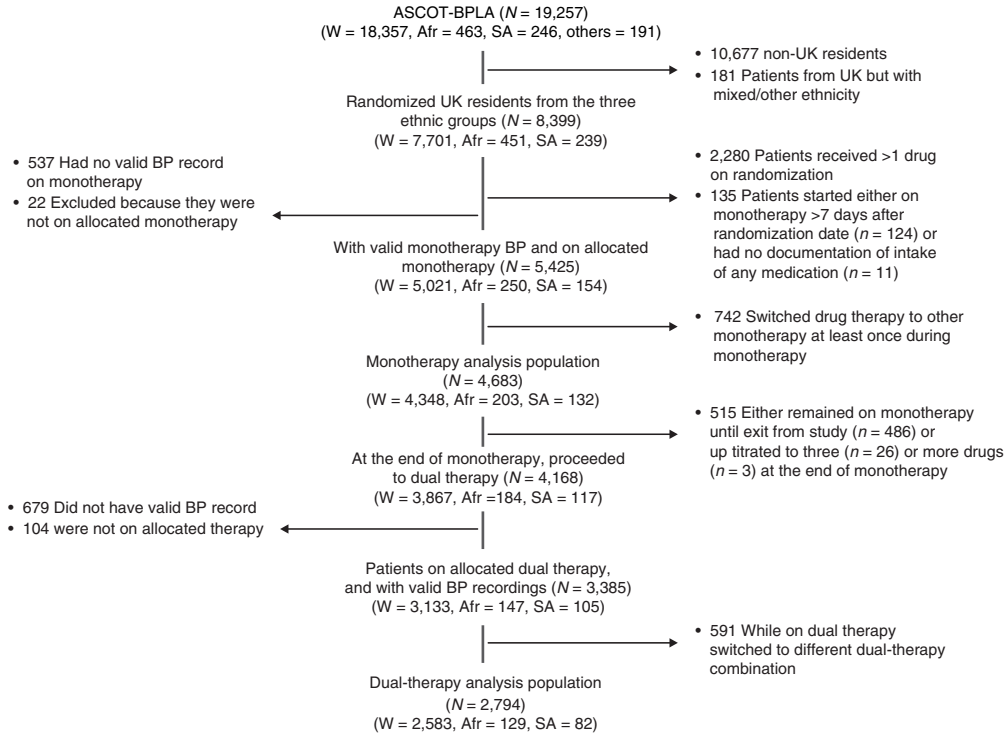

Figure 1 | ASCOT Trial profile: monotherapy and dual-therapy study population (per-protocol). Afr, blacks of African-origin; ASCOT, Anglo-Scandinavian Cardiac Outcomes Trial; SA, South-Asians; W, whites.

Baseline characteristics of those randomized to atenolol monotherapy did not differ from those on amlodipine monotherapy, except the former had lower baseline SBP and DBP and were less likely to be on previous antihypertensive treatment or to have left ventricular hypertrophy on electrocardiography (**Table 1**).

BP response to monotherapy

The median duration of monotherapy use was about 3 months (interquartile range: 47–372 days) with 618 patients (11.4%) remaining on monotherapy until the end of the study (608) or death (10).

Unadjusted BP response to atenolol and amlodipine monotherapy by ethnic groups

Amlodipine caused similar BP lowering in all three ethnic groups, but significant differences were observed in responses to atenolol monotherapy: black participants responded less well compared to the other two groups, with an increase in SBP of 4.5 mm Hg and no change in DBP as compared to reductions in SBPs/DBPs of 1.6/3.6 and 3.5/4.6 mm Hg among whites and South-Asians, respectively (data not shown).

Adjusted BP response to atenolol and amlodipine monotherapy by ethnic groups: per-protocol analyses

SBP. In model 1, a significant interaction between ethnicity and allocated treatment on SBP was found (LRT for overall interaction of ethnicity and allocated treatment, $P = 0.004$), with black participants responding significantly less well than the two other groups to atenolol, and no difference in BP-lowering response on amlodipine monotherapy among the three ethnic groups (**Table 2**). In model 2, differential BP lowering according to the allocated treatment group was also apparent among the three ethnic groups (LRT for overall interaction of ethnicity and allocated treatment; $P = 0.05$), with ethnic groups responding similarly to amlodipine monotherapy, but differing in their response to atenolol monotherapy. Compared with white participants, blacks responded less well to atenolol with an increase in SBP of 1.7 (95% confidence interval: −1.1 to 4.6) mm Hg (Wald test for interaction of treatment × black ethnicity: $P = 0.02$), whereas in the South-Asian group, SBP fell by 3.3 (−7.1 to 0.5) mm Hg (Wald test for interaction of treatment × South-Asian ethnicity: $P = 0.35$) (**Table 2**).

DBP. In model 1, there was a differential DBP response to atenolol and amlodipine monotherapy among the three ethnic groups (LRT for overall interaction, $P = 0.04$), with blacks responding significantly less well than the other two ethnic groups on atenolol, and no difference in BP-lowering response to amlodipine among the three ethnic groups. On adjusting for other confounders (model 2), the DBP response was similar among the three ethnic groups for each treatment group (LRT for overall interaction $P = 0.2$).

BP response to second-line therapy

The median duration of second-line therapy was 412 days (interquartile range: 132–1,457), with about one third of patients remaining on second-line therapy until exit from the study (1,042) or death (6).

Table 1 | Baseline characteristics distribution by ethnic group, for each treatment drug ($n = 5,425$)

Baseline characteristics	Atenolol monotherapy ($n = 2,580$)				Amlodipine monotherapy ($n = 2,845$)			
	Total	Whites	African-origin blacks	South-Asians	Total	Whites	African-origin blacks	South-Asians
	$n = 2,580$	$n = 2,389$	$n = 122$	$n = 69$	$n = 2,845$	$n = 2,632$	$n = 128$	$n = 85$
	Mean (s.d.)/%	Mean (s.d.)/%	Mean (s.d.)/%	Mean (s.d.)/%	Mean (s.d.)/%	Mean (s.d.)/%	Mean (s.d.)/%	Mean (s.d.)/%
Mean age (years)	64.1 (8.2)	64.4 (8.1)	61.9 (7.9)	57.5 (8.3)	64.0 (7.9)	64.3 (7.8)	61.6 (8.6)	58.6 (8.1)
Male (%)	82.0	81.8	80.3	91.3	82.4	82.2	83.6	84.7
Age at leaving education								
12–14 Years (%)	28.7	29.8	20.5	5.8	28.2	29.1	18.0	16.5
15–16 Years (%)	49.5	51.2	36.9	11.6	50.8	52.1	37.5	29.4
17–18 Years (%)	11.9	11.2	14.7	30.4	11.1	10.7	14.8	18.8
≥19 Years (%)	9.9	7.8	27.9	52.2	9.9	8.1	29.7	35.3
BMI (kg/m^2)	28.6 (4.4)	28.7 (4.4)	28.2 (4.8)	28.0 (4.3)	28.8 (4.7)	28.8 (4.7)	29.4 (4.6)	27.7 (4.2)
Current smoker or ex-smoker since 1 year (%)	69.2	71.1	50.0	37.7	68.7	69.9	56.2	50.6
Alcohol intake (units/week)	11.3 (14.1)	11.8 (14.3)	4.5 (7.8)	6.2 (9.3)	11.7 (14.5)	12.1 (14.7)	6.4 (10.5)	6.1 (9.5)
History of previous vascular event (%)	18.4	19.0	10.7	8.7	16.9	17.4	12.5	9.4
History of presence of diabetes (%)	26.2	25.0	41.8	42.0	25.8	24.4	35.2	54.1
LVHE (%)	18.3	17.4	36.9	15.9	20.5	19.9	37.5	13.0
Fasting glucose at baseline (mmol/l)[a]	6.2 (2.2)	6.2 (2.2)	6.6 (2.5)	6.5 (1.6)	6.2 (2.1)	6.1 (2.1)	6.6 (2.6)	7.0 (2.4)
Serum triglyceride (mmol/l)[a]	1.8 (1.0)	1.9 (1.0)	1.4 (1.0)	1.8 (0.9)	1.8 (1.0)	1.9 (1.0)	1.3 (0.6)	1.7 (0.8)
Total cholesterol (mmol/l)	6.0 (1.1)	6.0 (1.1)	5.4 (1.2)	5.6 (1.0)	6.0 (1.1)	6.0 (1.1)	5.6 (1.1)	5.4 (1.1)
HDL-cholesterol (mmol/l)	1.3 (0.3)	1.3 (0.3)	1.4 (0.4)	1.3 (0.3)	1.3 (0.4)	1.3 (0.4)	1.4 (0.4)	1.2 (0.3)
TC/HDL ≥6 (%)	25.2	26.1	9.8	21.8	27.1	27.8	12.5	25.9
Number of CV risk factors at the baseline								
3 Risk factors (%)	50.6	51.1	41.0	50.7	50.0	50.3	43.7	53.0
4 Risk factors (%)	32.9	32.5	41.0	31.9	32.2	32.4	28.9	31.8
>4 Risk factors (%)	16.5	16.4	18.0	17.4	17.7	17.4	27.3	15.3
Number of previous antihypertensive drugs								
No previous treatment (%)	11.2	11.5	9.0	4.4	9.8	10.3	3.9	4.7
One drug (%)	61.8	61.9	54.9	72.5	58.7	58.2	62.5	68.2
≥2 Drugs (%)	27.0	26.6	36.1	23.2	31.4	31.5	33.6	27.1
SBP (mm Hg)	160.2 (15.9)	160.6 (15.9)	155.4 (14.8)	153.8 (14.6)	161.1 (17.1)	161.6 (17.2)	157.3 (15.9)	153.5 (13.3)
DBP (mm Hg)	91.8 (9.5)	91.8 (9.6)	90.3 (8.5)	92.9 (7.5)	92.3 (9.7)	92.4 (9.7)	93.1 (10.0)	90.7 (8.8)
Heart rate (beats/min)	71.2 (12.2)	71.0 (12.1)	73.0 (12.1)	73.6 (15.5)	71.1 (12.5)	70.9 (12.4)	74.1 (13.6)	74.4 (11.8)

BMI, body mass index; CV, cardiovascular; DBP, diastolic blood pressure; HDL, high-density lipoprotein; LVHE, ECG-based left ventricular hypertrophy; SBP, systolic blood pressure; TC, total cholesterol.
[a]After excluding nonfasting values: 2,461 and 2,468 of possible 2,580 in atenolol treatment group, and 2,736 and 2,739 of possible 2,845 in amlodipine treatment contribute to the mean and standard deviation of fasting glucose and serum triglyceride, respectively.

Unadjusted BP differences on addition of bendroflumethiazide and perindopril to atenolol and amlodipine, respectively, among the three ethnic groups

Table 3 shows SBP and DBP lowering, overall and in each treatment group, by the addition of bendroflumethiazide and perindopril to those on atenolol and amlodipine monotherapy, respectively.

SBP. Among per-protocol participants, the addition of thiazide to atenolol (n = 1,424) resulted in similar mean SBP lowering

Table 2 | SBP differences among ethnic groups on atenolol and amlodipine monotherapy in the two regression models: per-protocol analyses

SBP difference[a] (95% CI)	Whites	African-origin blacks	South-Asians	Interaction of treatment and ethnicity
Monotherapy (*n* = 4,683)	***n* = 4,348**	***n* = 203**	***n* = 132**	***P* value[b]**
Model 1[c]				
Atenolol (*n* = 2,257)	Referent	+4.1 (0.9 to 7.3)	−3.0 (−7.3 to 1.3)	0.004
Amlodipine (*n* = 2,426)	−10.2 (−11.1 to −9.2)	−13.5 (−16.8 to −10.3)	−11.8 (−15.5 to −8.0)	
Model 2[d]				
Atenolol (*n* = 2,257)	Referent	+1.7 (−1.1 to 4.6)	−3.3 (−7.1 to 0.5)	0.05
Amlodipine (*n* = 2,426)	−8.9 (−9.7 to −8.0)	−11.7 (−14.6 to −8.8)	−9.8 (−13.2 to −6.5)	

CI, confidence interval; *n*, number; SBP, systolic blood pressure.
[a]Blood pressure (BP) difference between the BP at the end and start of allocated monotherapy. [b]Likelihood ratio test for interaction between ethnicity and treatment received. [c]Adjusting for the SBP at the start of monotherapy and *a priori* confounders: BMI, age, sex, and years of education (model 1). [d]Adjusting for model 1 plus other important determinants of BP response: duration of monotherapy, number of cardiovascular risk factors, previous antihypertensive drugs, presence of diabetes, left ventricular hypertrophy, and alcohol intake (units/week).

Table 3 | Observed unadjusted systolic and diastolic blood pressure differences, overall and in each of the ethnic group, by treatment drug for intention to treat (*n* = 3,459) and per-protocol dual-therapy populations (*n* = 2,794)

	Total dual-therapy population (*n* = 3,459)			Per-protocol population (*n* = 2,794)		
	Total	SBP Diff	DBP Diff	Total	SBP Diff	DBP Diff
Ethnicity	***n***	**Mean (s.d.)**	**Mean (s.d.)**	***n***	**Mean (s.d.)**	**Mean (s.d.)**
Adding thiazide to atenolol						
Overall	1,708	−10.7 (17.4)	−4.02 (9.2)	1,424	−10.5 (16.8)	−3.8 (8.9)
Whites	1,573	−10.8 (17.3)	−4.2 (9.2)	1,309	−10.6 (16.7)	−3.9 (8.9)
African-origin blacks	86	−11.5 (17.3)	−3.3 (9.2)	73	−12 (17.5)	−3.3 (9.3)
South-Asians	49	−4 (17.4)	−0.6 (8.4)	42	−5.1 (17.7)	−1.3 (8.7)
Adding perindopril to amlodipine						
Overall	1,751	−9.2 (15.1)	−5.2 (8.8)	1,370	−9.9 (14.4)	−5.5 (8.5)
Whites	1,622	−9.5 (15)	−5.3 (8.7)	1,274	−10.2 (14.4)	−5.6 (8.4)
African-origin blacks	70	−3.1 (14.9)	−2.9 (9.2)	56	−3.2 (14.2)	−2.5 (9.1)
South-Asians	59	−8.1 (16.4)	−4.6 (8.4)	40	−11.2 (14.4)	−4.8 (7.6)

DBP, diastolic blood pressure; Diff, difference between the blood pressure at the end and start of dual therapy; *n*, number of patients; SBP, systolic blood pressure.

in all ethnic groups. By contrast, the addition of perindopril to amlodipine (n = 1,370) resulted in a differential BP lowering (F test; P = 0.002), with lowering of SBP on average by just 3.2 mm Hg in blacks, as compared to average SBP reductions of 10.2 and 11.2 mm Hg in whites and South-Asians, respectively.

DBP. Among per-protocol participants, addition of thiazide to atenolol therapy was associated with similar DBP lowering in all ethnic groups. By contrast, among those on amlodipine monotherapy, addition of perindopril reduced the average DBP 5.6, 2.5, and 4.8 mm Hg in whites, blacks, and South-Asians, respectively (Table 3).

Adjusted BP difference on addition of bendroflumethiazide and perindopril to atenolol and amlodipine, respectively, among the three ethnic groups: per-protocol analyses only

SBP. The BP-lowering response on addition of thiazide or perindopril differed significantly among the three ethnic groups in model 1 (LRT for overall interaction, P = 0.005) (Table 4). In model 2, the effect of ethnic group on BP response also remained significant (LRT for overall interaction of ethnicity and treatment, P = 0.004). Compared to whites on atenolol and bendroflumethiazide (referent group), when the diuretic was added, the BP difference was 1.7 (−4.7 to +1.2) mm Hg lower in blacks and 2.8 (−1.1 to +6.8) mm Hg higher in South-Asians, but none of these differences were statistically different. However, compared to the referent group, when perindopril was added to amlodipine, the BP differences in the three ethnic groups were statistically different, with whites responding with a further 1.7 (−2.7 to −0.7) mm Hg reduction, whereas the SBP increased in blacks by 0.8 (−2.5 to +4.2) mm Hg and decreased by 6.2 (−10.2 to −2.2) mm Hg in South-Asians (Table 4).

DBP. On linear regression, using model 1, the DBP-lowering effect of adding thiazide or perindopril was not significantly modified by ethnicity (interaction test P = 0.08). These

Table 4 | Systolic blood pressure difference, among the ethnic groups, on adding thiazide or perindopril, as a second-line agent to respective monotherapy (atenolol and amlodipine) in the three regression models: per-protocol analyses

SBP difference[a] (95% CI)	Whites	African-origin blacks	South-Asians	Interaction of treatment and ethnicity
Dual therapy[b] (*n* = 2,794)	***n* = 2,583**	***n* = 129**	***n* = 82**	***P* value[c]**
Model 1[d]				
Addition of diuretic on atenolol therapy (*n* = 1,424)	Referent	−1.5 (−4.8 to 1.9)	+2.9 (−1.6 to 7.4)	0.005
Addition of perindopril on amlodipine therapy (*n* = 1,370)	−3.4 (−4.6 to −2.3)	+1.4 (−2.3 to +5.3)	−6.7 (−11.3 to −2.2)	
Model 2[e]				
Addition of diuretic on atenolol therapy (*n* = 1,424)	Referent	−1.7 (−4.7 to 1.2)	+2.8 (−1.1 to 6.8)	0.004
Addition of perindopril on amlodipine therapy (*n* = 1,370)	−1.7 (−2.8 to −0.7)	+0.8 (−2.5 to 4.2)	−6.2 (−10.2 to −2.2)	

CI, confidence interval; *n*, number of patients; SBP, systolic blood pressure.
[a]Blood pressure (BP) difference between the BP at the end and start of allocated second-line agents. [b]Although 3,385 (A = 147, SA = 105) of 4,683 had valid BP and received allocated dual therapy, but only 82.5% (2,794) of them continued unchanged and uninterrupted on allocated dual therapy. [c]Likelihood ratio test for interaction between ethnicity and treatment received, overall in the model. [d]Adjusting for the SBP at the start of dual therapy plus *a priori* confounders: BMI, age, sex, and years of education (model 1). [e]Adjusting for model 1 plus other independent predictors: duration of dual therapy, previous antihypertensive treatment, presence of diabetes, and diastolic BP at the start of dual therapy.

results are consistent with those arising from the model 2 in which DBP-lowering responses among the three ethnic groups for each regimen were similar (test for interaction, $P = 0.14$). However, even in this model, the point estimates of the DBP response in South-Asians differed from whites, with an increase of 1.6 (−0.6 to 3.8) mm Hg on addition of thiazide and a reduction of 3.7 (−5.9 to −1.4) mm Hg on addition of perindopril as compared to the referent group of whites on atenolol and thiazide therapy (Wald test for interaction of treatment × South-Asian ethnicity, $P = 0.07$) (data not shown).

DISCUSSION

We have found that amlodipine was an equally effective BP-lowering agent when used as monotherapy in three broad ethnic groups, whereas atenolol was less effective in black compared to white participants, consistent with previous studies.[1,3,6,12] The true absolute effect of the first-line agents may have been obscured by the fact that about 90% of those included in analyses were switched directly from other antihypertensive medication taken prior to randomization to this trial.[14,15] However, the relative (and significant) differences observed among the three ethnic groups may well remain valid, as the median number of antihypertensive drugs used before the trial was similar for each ethnic group on the two randomized in-trial regimens, as were the proportions of the different classes of previous antihypertensive medications. Furthermore, we have also performed a sensitivity analysis by limiting these analyses to those on one or no previous antihypertensive therapy and found similar results.

Analyses relating to the impact of second-line agents were not affected by pretrial treatment. Our findings on the impact of ethnicity on the BP-lowering effects of a thiazide diuretic, (bendroflumethiazide) and an ACE inhibitor (perindopril) as second-line agents are new. Although the effect of adding the diuretic was not significantly different across the three ethnic groups, there was a tendency for a smaller response among South-Asians and a greater response in black participants compared with whites. The impact of adding perindopril on SBP differed significantly, being smaller among black and greater among South-Asian, compared with white participants. Similar but nonsignificant patterns were observed for DBPs.

Our finding of a poor BP-lowering response to an ACE inhibitor used as a second-line agent in blacks is new, and extends previous findings that these drugs are not effective as first-line agents in black patients.[11,12] These results in blacks are consistent with lower mean renin levels and increased salt sensitivity previously reported.[4,7,8] However, a pathophysiological mechanism for enhanced efficacy of ACE inhibitors (and to a lesser extent β-blockers) among South-Asians is less clear. Increased sympathetic and renin–angiotensin–aldosterone system activation, as evidenced by considerably greater prevalence of associated visceral adiposity and insulin resistance,[16,17] may possibly contribute toward the increased efficacy of ACE inhibitors in this ethnic group.

These differential effects also raise the possibility that current British guidance[13] for optimal two-drug combinations of antihypertensive therapy may not be applicable to South-Asian and black patients. Currently, the two recommended combinations are an ACE inhibitor or angiotensin-receptor blocker ("A" drug) plus a diuretic ("D" drug) or an A drug plus a calcium channel blocker (C drug).[13] It may be that for black patients "C + D" would be a more effective combination, whereas for South-Asians "A" rather than "D" drugs should be preferentially combined with "C" drugs. This latter combination has been shown to be more effective than A + D in a recently published trial reporting on high-risk hypertensive patients.[18]

Our analyses have some clear limitations. The relatively small number of black and South-Asian participants means that comparisons among ethnic groups are prone to type II

errors (depending upon effect size), reflected in nonsignificant interaction results pertaining to DBP differences. However, the SBP differences, seen in both first- and second-line therapy analyses, were large enough to have an adequate power for detection of a significant interaction (for example, 6 mm Hg BP difference between smallest ethnic group: South-Asians on perindopril (n = 40) and respective referent group: whites on thiazide (n = 1,309) is detectable with >80% power). These relatively small numbers of patients from ethnic minorities are comparable to those in previous similar analysis.[1–3,8] Nonetheless, under-recruitment of ethnic minorities to trials is a problem that has been recognized for over a decade.[19,20] Our prespecified protocol for these analyses[14] had to be substantially revised because of this lower-than-expected recruitment of patients from ethnic minorities. Another possible limitation of the findings is that the broad ethnic categorizations (based on self-reporting) used here may introduce inaccuracies or obscure differences within the three ethnic groups.[21]

Despite these limitations, we have shown significant interactions between ethnicity and both first- and second-line treatments in terms of BP-lowering effect. Our results of intention-to-treat analyses for both mono- and second-line therapy are similar to, and further corroborate, our findings on per-protocol populations (data not shown). Regarding first-line agents, the impact of atenolol on SBP was less in blacks compared with whites and enhanced among South-Asians. Further studies are required to test these new findings among South-Asians. Paradoxically, given the adverse metabolic effects of β-blockers on glucose, high-density lipoprotein-cholesterol, and triglycerides,[22] and the propensity of the South-Asian population to insulin resistance,[16,17,23] any extra BP-lowering effect of β-blockers in this population may potentially be offset in terms of benefits on overall cardiovascular risk.

Regarding the BP-lowering effect of the second-line drugs, the most striking finding is among the South-Asian population in whom there was a poor response to the thiazide diuretic when added to atenolol and also an apparently enhanced effect of perindopril when added to amlodipine. Along with the tendency for black participants to respond well to the addition of a thiazide and less well to the ACE inhibitor, we found a highly significant interaction between ethnicity and second-line therapies on SBP (**Table 4**) with similar nonsignificant trends for DBP.

In summary, differential BP-lowering responses to both first- and second-line antihypertensive agents were apparent among all three ethnic groups studied in these analyses. Black patients were less responsive to the ACE inhibitor (perindopril) and more responsive to a diuretic when used as second-line agents. In contrast, South-Asian patients were more responsive to the ACE inhibitor (perindopril) than white and black patients when used as a second-line agent. These novel and hypothesis-generating findings suggest that optimal combinations of antihypertensive medications (at least in terms of BP-lowering efficacy) may differ among ethnic groups. However, these findings are in relatively small groups of patients, and need cautious interpretation. Most importantly, these findings raise the important question of whether tailored combinations of antihypertensive agents for ethnic groups would provide differential BP control and therefore cardiovascular outcomes. In view of the potential importance of such effects, particularly regarding second-line therapy, further definitive studies are needed.

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