Baseline predictors of resistant hypertension in the Anglo-Scandinavian Cardiac Outcome Trial (ASCOT): a risk score to identify those at high-risk

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Background **Resistant hypertension is a well recognized clinical entity, which has been inadequately researched to date.**

Methods **A multivariable Cox model was developed to identify baseline predictors of developing resistant hypertension among 3666 previously untreated Anglo-Scandinavian Cardiac Outcome Trial (ASCOT) patients and construct a risk score to identify those at high risk. Secondary analyses included evaluations among all 19 257 randomized patients.**

Results **One-third (1258) of previously untreated, and one-half (9333) of all randomized patients (incidence rates 75.2 and 129.7 per 1000 person-years, respectively) developed resistant hypertension during a median follow-up of 5.3 and 4.8 years, respectively. Increasing strata of baseline SBP (151–160, 161–170, 171–180, and >180 mmHg) were associated with increased risk of developing resistant hypertension [hazard ratio 1.24 (95% confidence interval, CI 0.81–1.88), 1.50 (1.03–2.20), 2.15 (1.47–3.16), and 4.43 (3.04–6.45), respectively]. Diabetes, left ventricular hypertrophy, male sex, and raised BMI, fasting glucose, and alcohol intake were other significant determinants of resistant hypertension. Randomization to amlodipine ± perindopril vs. atenolol ± thiazide [0.57 (0.50–0.60)], previous use of aspirin [0.78 (0.62–0.98)], and randomization to atorvastatin vs. placebo [0.87 (0.76–1.00)] significantly reduced the risk of resistant hypertension. Secondary analysis results were similar. The risk score developed allows accurate risk allocation (Harrell's C-statistic 0.71), with excellent calibration (Hosmer–Lemeshow χ^2 statistics, $P = 0.99$). A 12-fold (8.4–17.4) increased risk among those in the highest vs. lowest risk deciles was apparent.**

Conclusion **Baseline SBP and choice of subsequent antihypertensive therapy were the two most important determinants of resistant hypertension in the ASCOT population. Individuals at high risk of developing resistant hypertension can be easily identified using an integer-based risk score.** *J Hypertens* **29:2004–2013 © 2011 Wolters Kluwer Health | Lippincott Williams & Wilkins.**

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Abbreviations: ASCOT, Anglo-Scandinavian Cardiac Outcome Trial; BP, blood pressure; FPG, fasting plasma glucose; LVH, left ventricular hypertrophy

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Introduction

Resistant hypertension is a well recognized clinical entity, which has been poorly researched to date [1,2]. Resistant hypertension is variably defined as a failure to achieve blood pressure (BP) targets in spite of concurrent use of three antihypertensive agents of different classes [1], with a commonly used definition requiring the use of diuretics as one of the three drug classes [3]. Reliable estimates of the determinants, prevalence, and incidence rates of resistant hypertension are currently not available [1,2]. However, estimates based on clinical trial and observational data suggest that 20–30% of all treated hypertensive patients may have resistant hypertension [2–6]. Patients with resistant hypertension are at a higher risk of cardiovascular morbidity and mortality compared with those who have more easily controlled hypertension [1,2,7]. This increased cardiovascular risk among patients with resistant hypertension is likely to be related to high BP levels [8] and the presence of concomitant co-morbidities such as diabetes, sleep apnea, renal diseases, and obesity [2,3,7,9]. However, the possibility remains that resistant hypertension may independently induce increased cardiovascular risk, which needs further investigations [1].

A paucity of data on the development of resistant hypertension exists in part because of the difficulties associated with conducting suitable studies [9]. For example, any study evaluating the incidence and determinants of resistant hypertension would need a strict per-protocol

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driven uptitration of BP-lowering therapy, associated with strict monitoring of drug adherence and accurate BP recordings [2,9]. In addition, patients with other causes of pseudo-resistance such as white-coat hypertension would have to be identified and excluded [1,2].

The database of the BP-lowering arm of the Anglo-Scandinavian Cardiac Outcome Trial (ASCOT-BPLA) [10,11] provides an excellent opportunity to study the baseline determinants of resistant hypertension among hypertensive patients and to develop a risk score to identify those at high risk of developing resistant hypertension.

Materials and methods

Details of the ASCOT-BPLA trial have been described previously [10,11]. However, a brief summary of some relevant aspects of the trial is given below.

Participants

Patients with either untreated hypertension (SBP $\geq$160 mmHg or a DBP $\geq$100 mmHg) or previously treated hypertension (SBP $\geq$140 mmHg or DBP $\geq$90 mmHg), aged 40–79 years, with at least three other prespecified cardiovascular risk factors were eligible for randomization, if there was no current or past history of coronary heart disease or presence of a cerebrovascular event within the previous 3 months. Patients with known secondary causes of hypertension were among those excluded by study design [10,11].

Procedures

Patients were randomized using a 2×2 factorial design to receive one of two antihypertensive regimens: atenolol adding a thiazide as required to achieve BP targets (defined as <140/90 mmHg for patients without diabetes and <130/80 mmHg for those with diabetes at baseline), or amlodipine adding perindopril as required. A subsample of 10 305 patients was further randomized in the lipid-lowering arm of the ASCOT trial to receive either atorvastatin or placebo (ASCOT-LLA).

At the screening and randomization visits, and at each follow-up visit (6 weeks, 3 months, 6 months, and subsequently 6 monthly until death or exit from the study), BP was measured three times using a validated semi-automated device (Omron HEM 705CP; Omron Healthcare, Henfield, Sussex, UK). BPs were also measured, and antihypertensive medications reviewed, during any other nonscheduled visit. Per-protocol, the antihypertensive therapy of every patient was uptitrated at every follow-up visit according to a predefined BP-management algorithm, if BP targets had not been reached (Table 1). Nonadherence (interruptions or discontinuations) with prescribed therapy was documented at each visit.

Definition

Serial data on BP measurements and antihypertensive medications, collected at each follow-up visit were used to identify the development of resistant hypertension. For the purpose of this analysis, resistant hypertension was defined as the presence of uncontrolled BP ($\geq$140/90 mmHg) using three antihypertensive medications of different drug classes at maximum (or maximum tolerated) dose unchanged and uninterrupted for at least 1 month, or intake of more than three different drug classes (unchanged and uninterrupted for $\geq$1 month) regardless of BP control.

Statistical analysis

STATA 10 statistical software was used for all analyses. Primary analysis was done using data from previously untreated hypertensive patients at randomization ('untreated' population; $n = 3666$). Secondary analysis was done using data from all randomized patients ('total' population; $n = 19\,257$), the majority ($n = 15\,591$, 81%) of whom were previously treated.

Baseline characteristics of those who developed resistant hypertension (resistant hypertension group) were compared with those who did not (nonresistant hypertension group). Incidence rates [per 1000 person-years (pyrs)] of developing resistant hypertension were estimated for the untreated and total populations.

Multivariable Cox models were developed (separately for each analysis population) to identify the baseline determinants of (and individual risk scores for) the development of resistant hypertension, using backward

Table 1 Blood pressure treatment algorithm of the Anglo-Scandinavian Cardiac Outcome Trial

ASCOT trial	Antihypertensive treatment algorithm	
Titration step	Amlodipine-based regimen	Atenolol-based regimen
Step 1 (initiate)	Amlodipine 5 mg OD	Atenolol 50 mg OD
Step 2 (uptitrate)	Amlodipine 10 mg OD	Atenolol 100 mg OD
Step 3 (add)	Perindopril 4 mg OD	Bendroflumethiazide/K^+ 1.25 mg OD
Step 4 (uptitrate)	Perindopril 8 mg OD	Bendroflumethiazide/K^+ 2.5 mg OD
Step 5 (add)*	Doxazosin gastrointestinal therapeutic system (GITS) 4 mg	
Step 6 (uptitrate)*	Doxazosin GITS 8 mg OD	
Step 7 (add)*	Another (nonstudy) antihypertensive agent at investigator's discretion (ideally from list of suggested drugs including spironolactone, moxonidine)	

K^+, with potassium supplement; OD, once daily; * common steps for the two treatment regimens.

stepwise selection. All baseline variables were considered for inclusion in the multivariate model; however, age, sex, ethnicity, presence of diabetes, years of full-time education (reflecting socio-economic status), and baseline SBP were forced into the model as prespecified covariates, if not identified by stepwise selection. The proportional hazards assumption was assessed both graphically and by using Schoenfeld residuals. All continuous variables were tested for linearity and were categorized if found to have a nonlinear effect in the model; hence, both alcohol intake (per week) and SBP were categorized. Weekly alcohol intake was categorized using standard sex-based cut-offs; however, in both Cox models, weekly alcohol intake categories were used as a continuous variable as they had a linear relationship with developing resistant hypertension. Competing risk analysis [12], correcting for increased risk of mortality associated with uncontrolled (or poorly controlled) BP before resistant hypertension diagnosis, was performed for each of these analyses, as a sensitivity analysis.

The risk score for each patient was determined from the final Cox model by summing the products of the coefficients derived from the Cox model, and the actual baseline values ($\times 10$) of the variables in the model. The distribution of risk scores was then divided into deciles of increasing risk. Calibration of the model was evaluated by comparison of the plots of the actual (observed) and predicted (expected) 5-year outcomes and using the Hosmer–Lemeshow χ^2 statistics test [13]. Model discrimination was assessed using Harrell's C-statistics. Finally, these risk scores were converted into 'user-friendly' integer scores for 5-year risks of developing resistant hypertension by rounding the exact β-coefficient from Cox models. The estimated probability of resistant hypertension within 5 years is 1 – 0.98927 exp(0.1 * risk score). The validity of this risk score (developed from the untreated population) was also assessed in the total population by comparing the numbers of patients estimated to develop resistant hypertension with the numbers observed to develop resistant hypertension. In addition, the calibration of the risk score developed from the total population was evaluated by comparing the estimated and observed numbers of patients developing resistant hypertension in the same population.

Results

About one-third (1258) of previously untreated patients and about one-half (9333) of the total population (incidence rates 75.2 per 1000 pyrs and 129.7 per 1000 pyrs, respectively) developed resistant hypertension during a median follow-up of 5.3 and 4.8 years, respectively (Fig. 1 and online Fig. 1, http://links.lww.com/HJH/A115).

Baseline characteristics

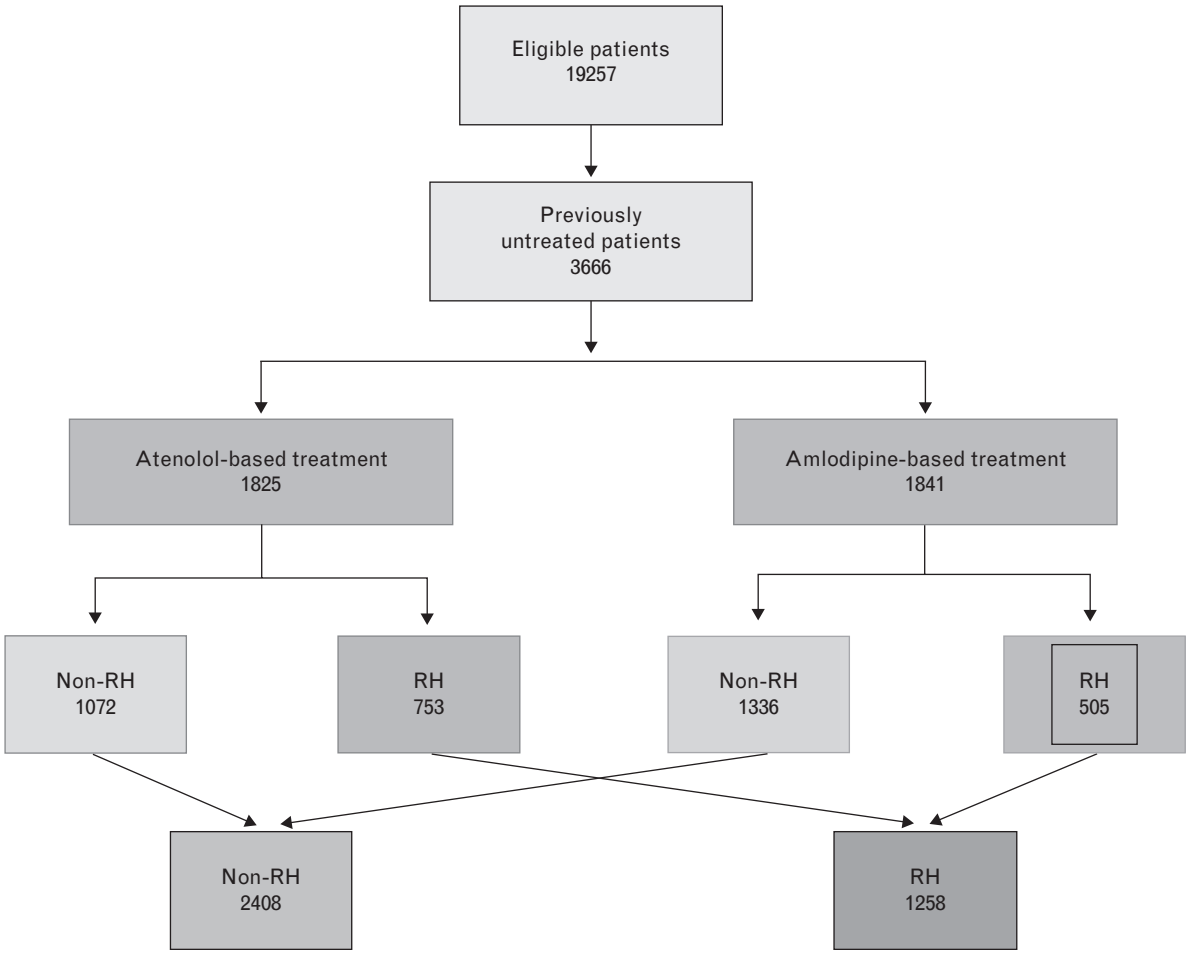
Among 3666 previously untreated patients, those who developed resistant hypertension, compared with those who did not, were more likely to be men and to have a higher baseline SBP, DBP, BMI, fasting plasma glucose (FPG), alanine transaminase, serum triglyceride, serum creatinine, and less years of full-time education. The participants in resistant hypertension group were also more likely at randomization to have diabetes, metabolic syndrome, left ventricular hypertrophy (LVH), microalbuminuria, and a higher average weekly alcohol intake, and were less likely to be allocated to either amlodipine-based treatment or atorvastatin therapy (Table 2). Similar observations were made when evaluating data from the total population, except those who developed resistant hypertension, as compared with those who did not, were also more likely to be older, of non-European descent, current smokers, and to have a history of previous use of aspirin and/or lipid-lowering therapy. In addition, those in the resistant hypertension group from the total population were more likely to have received a greater number of antihypertensive medications compared with those in nonresistant hypertension group (online appendix Table 1, http://links.lww.com/HJH/A115).

Predictors of resistant hypertension

Figure 2 shows that among the untreated population, there was a progressive increase in unadjusted incidence rates of developing resistant hypertension with an increase in the baseline SBP category. Similar trends were seen among the total population.

On multivariable Cox regression, among the untreated population (Table 3), increasing strata of baseline SBP (151–160, 161–170, 171–180, and >180 mmHg) were significantly associated with an increased risk of developing resistant hypertension [hazard ratio 1.24 (95% confidence interval, CI) 0.81–1.88, 1.50 (1.03–2.20), 2.15 (1.47–3.16), and 4.43 (3.04–6.45), respectively]. The presence of diabetes [1.69 (1.40–2.04)], LVH [1.27 (1.11–1.46)], male sex [1.56 (1.33–1.83)], raised BMI [1.04 (1.02–1.05) per kg/m^2] and fasting glucose [1.05 (1.01–1.09) per mmol/l], and higher alcohol intake category [1.14 (1.07–1.23)] were other significant putative risk factors. By contrast, randomization to the amlodipine-based treatment strategy compared with the atenolol-based strategy [0.57 (0.50–0.60), $P < 0.001$], previous use of aspirin [0.78 (0.62–0.98), $P = 0.04$], randomization to atorvastatin compared with placebo [0.87 (0.76–1.00), $P = 0.04$], and at least 19 years of full-time education were significant protective factors (Table 3). Results of multivariable Cox regression, using the total population, were similar except that the previous use of BP medications and African race [1.29 (1.13–1.47)] were significant risk factors, and increasing age was marginally protective [1.00 (0.99–1.00), $P = 0.01$] against

Fig. 1



Development of resistant hypertension among the untreated population in the Anglo-Scandinavian Cardiac Outcome Trial. ASCOT, Anglo-Scandinavian Cardiac Outcome Trial; RH, resistant hypertension.

developing resistant hypertension. Compared with previously untreated patients, a history of prior use of one or more antihypertensive agents was associated with 1.7-fold and 3.9-fold increased risk, respectively, of developing resistant hypertension (online appendix Table 2, http://links.lww.com/HJH/A115).

Competing risk analyses

In both the untreated and the total populations, the majority of all deaths occurring within 2 years after randomization occurred in those in the nonresistant hypertension group (58 of 62, and 272 of 338 deaths, respectively). As an early death would preclude identification (or alter the probability) of the development of resistant hypertension, we used the development of resistant hypertension or death as two competing outcomes in a competing risk analysis. On stratified Cox regression (competing risk analysis) among the untreated group (online appendix Table 3, http://links.lww.com/HJH/A115), the findings were similar (but with slightly attenuated effect sizes) to those shown in Table 3, and resistant hypertension was significantly associated with age in this setting. There was a 1% [(1.00–1.02), $P = 0.02$] increase in the risk of developing resistant hypertension with every year increase in age (from 40 years onward). Similar results were seen using data from the total population (data not shown).

Risk score

The β-coefficients and Z-scores – denoting strength of the association – of the predictors of resistant hypertension among previously untreated patients are shown in Table 3. The risk score developed using this population (model-A) allows for accurate risk allocation (Harrell's C-statistic 0.71), with the risk of developing resistant hypertension increasing steadily with the increase in risk score (online appendix Fig. 2, http://links.lww.com/HJH/A115). This model has an excellent calibration, with no significant differences between the numbers of patients expected to develop resistant hypertension based on

Table 2 Baseline characteristics among those who develop resistant hypertension during follow-up, and who do not, among 3666 previously untreated patients from the Anglo-Scandinavian Cardiac Outcome Trial

Baseline characteristics among previously untreated (numbers)	Total; mean (SD) or [%] (3666)	Nonresistant hypertension group; mean (SD) or [%] (2408)	Resistant hypertension group; mean (SD) or [%] (1258)	*P* value*
Demographics				
Age (years)	61.8 (8.9)	61.7 (8.7)	62.0 (9.1)	0.333
Sex (male [%])	77.0	75.0	80.8	<0.001
Whites (%)	98.6	98.8	98.2	0.129
BMI (kg/m^2)	28.1 (4.4)	27.7 (4.3)	28.8 (4.4)	<0.001
Age at leaving full-time education (%)				
12–14 (years)	31.2	30.2	33.2	0.023
15–16 (years)	30.7	31.1	30.0	
17–18 (years)	14.6	14.5	14.7	
≥19 (years)	23.5	24.2	22.1	
Alcohol intake (per week) (%)[a]				
None	25.4	26.4	23.4	0.029
Mild	42.0	42.5	40.9	
Moderate	24.4	23.5	26.2	
Severe	8.3	7.6	9.5	
Current smokers/ex-within 1 year (%)	29.1	28.7	29.9	0.450
Diagnostic measurements				
SBP (mmHg)	172.5 (15.2)	169.7 (13.5)	177.9 (16.8)	<0.001
SBP classification (%)				
≤150 (mmHg)	5.0	6.1	2.7	<0.001
151–160 (mmHg)	11.1	13.1	7.2	
161–170 (mmHg)	33.9	38.2	25.8	
171–180 (mmHg)	24.6	24.5	24.7	
>180 (mmHg)	25.4	18.0	39.6	
DBP (mmHg)	100.0 (10.2)	99.5 (9.5)	100.8 (11.3)	0.001
Heart rate (beats/min)	74.6 (12.2)	74.4 (12.1)	74.8 (12.5)	0.437
Presence of LVH (%)	24.0	22.4	27.0	0.002
Serum sodium (mmol/dl)	140.3 (2.3)	140.4 (2.3)	140.1 (2.3)	<0.001
Serum potassium (mmol/dl)	4.2 (0.4)	4.2 (0.4)	4.2 (0.4)	0.308
Alanine transaminase (mg/dl)	32.9 (20.8)	31.9 (20.7)	34.8 (21.0)	<0.001
Fasting glucose (mmol/l)[b]	6.0 (1.9)	5.8 (1.6)	6.5 (2.2)	<0.001
Total cholesterol (mmol/l)	6.0 (1.1)	6.0 (1.1)	6.0 (1.1)	0.017**
HDL (mmol/l)	1.3 (0.4)	1.4 (0.4)	1.3 (0.4)	0.100
Triglycerides (mmol/l)[b]	1.8 (1.0)	1.7 (0.9)	1.8 (1.0)	0.001
Presence of microalbuminuria (%)	61.3	59.9	63.8	0.021
Creatinine (mmol/l)	96.2 (14.5)	95.8 (14.3)	96.9 (14.9)	0.046
Medical and treatment history				
Diabetes (%)	21.0	15.8	30.8	<0.001
Previous lipid-lowering treatment (%)	5.8	5.4	6.4	0.257
Previous aspirin intake (%)	9.7	10.6	7.9	0.009
Study treatment[c]				
Randomized to amlodipine-based treatment group (%)	50.2	55.5	40.1	<0.001
Randomized to atorvastatin treatment group (%)	27.4	28.4	25.5	0.066

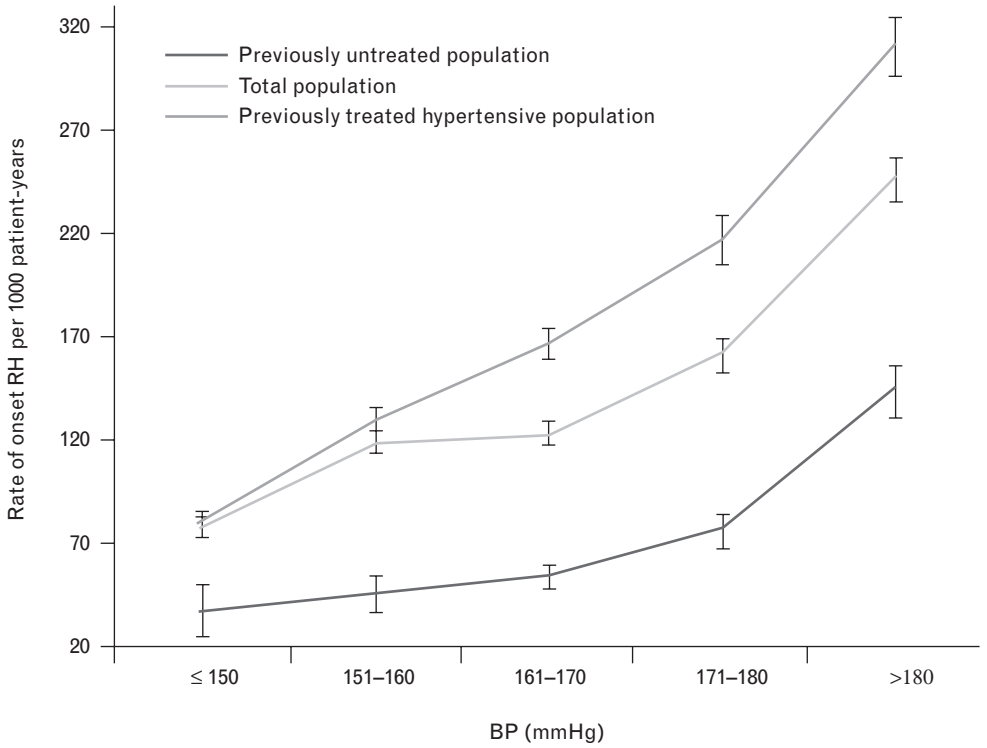
BP, blood pressure; LVH, left ventricular hypertrophy; RH, resistant hypertension. [a] Alcohol categories based on units intake per week for both sexes (male/female) were described as following: none, 0.0 units/week; mild, 0.1–7.0/0.1–3.0 units/week; moderate, 8.0–21.0/4.0–14.0 units/week; severe, >21.0/14.0 units/week. [b] Only fasting values of either triglycerides or glucose were considered [c] Intention to treat. * χ^2 or *t*-test, whichever was applicable. ** Total cholesterol in RH (5.95 mmol/l) and non-RH (6.04 mmol/l) group appears similar because of rounding-off error, combined with small SD.

their risk scores and the numbers of those who actually developed resistant hypertension during 5 years of follow-up (Hosmer–Lemeshow χ^2 statistics, $P = 0.99$; Fig. 3a). There was more than a 12-fold (8.4–17.4) increased risk among those in the highest vs. lowest deciles of risk. When model-A was applied to the total population, it performed similarly to the model developed using the total population (model-B; online appendix Fig. 3, http://links.lww.com/HJH/A115). However, some differences were apparent: model-A underpredicted the risk among those in the lowest risk score decile and overpredicted the risk among those at the highest risk decile. Figure 3b shows the Kaplan–Meier estimates of developing resistant hypertension, among previously untreated patients, stratified by risk score quartiles (re-estimated after excluding the treatment effect) and treatment allocation. It shows that regardless of baseline risk category, there was a similar reduction in the risk of developing resistant hypertension among those allocated to amlodipine-based therapy compared with those allocated to atenolol-based therapy. An easy-to-use integer-based risk table, to estimate the 5-year risk of developing resistant hypertension among previously untreated patients, was developed using the output from Table 3 (online appendix Table 4a and b, http://links.lww.com/HJH/A115).

Discussion

These analyses show that in the ASCOT population, baseline SBP and subsequent choice of antihypertensive

Fig. 2



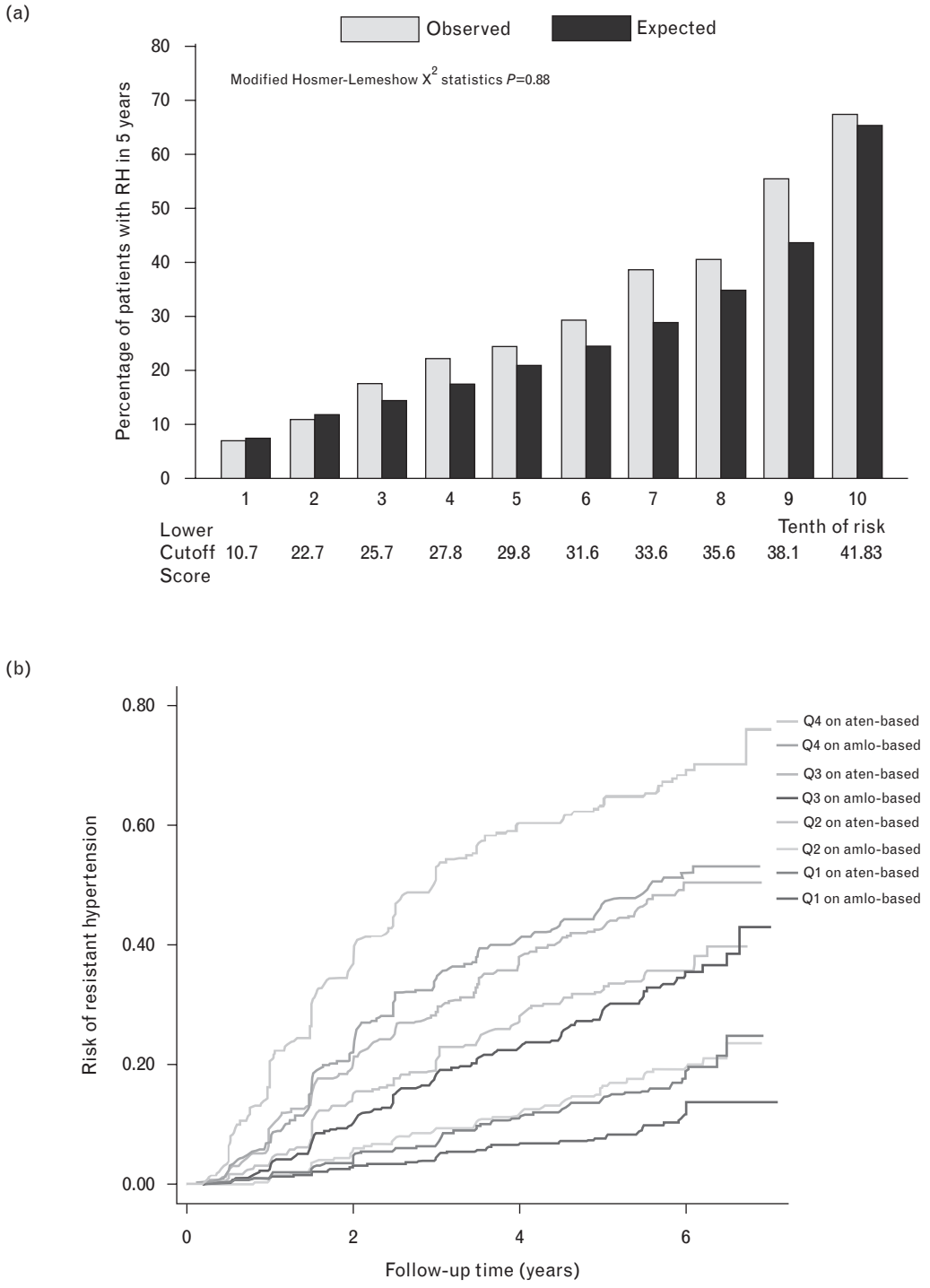
Baseline SBP and incidence rates of developing resistant hypertension among the untreated and total population. BP, blood pressure; RH, resistant hypertension.

Table 3 Cox regression model showing predictors of development of resistant hypertension among 3666 previously untreated (or newly diagnosed) hypertensive patients

Baseline characteristics	Hazard ratio (95% CI)	β-Coefficient	Z-score[a]	P value
Randomization to amlodipine-based treatment group[b]	0.57 (0.50–0.64)	−0.57	−9.15	<0.001
SBP (mmHg, per category)[c]				
151–160	1.24 (0.81–1.88)	0.21	0.99	0.322
161–170	1.50 (1.03–2.20)	0.41	2.11	0.035
171–180	2.15 (1.47–3.16)	0.77	3.93	<0.001
>180	4.43 (3.04–6.45)	1.49	7.74	<0.001
Diabetes (yes/no)	1.69 (1.40–2.04)	0.53	5.52	<0.001
BMI (per kg/m^2)	1.04 (1.02–1.05)	0.04	5.45	<0.001
Male sex	1.56 (1.33–1.83)	0.44	5.42	<0.001
Alcohol consumption (per category)[d]	1.14 (1.07–1.23)	0.13	3.81	<0.001
Presence of LVH (yes/no)	1.27 (1.11–1.46)	0.24	3.41	0.001
Age leaving full-time education[e]				
15–16 (years)	0.83 (0.71–0.97)	−0.18	−2.34	0.019
17–18 (years)	0.88 (0.72–1.06)	−0.13	−1.34	0.181
≥19 (years)	0.80 (0.67–0.95)	−0.23	−2.58	0.010
Fasting glucose (per mmol/l)	1.05 (1.01–1.09)	0.05	2.48	0.013
Previous use of aspirin (yes/no)	0.78 (0.62–0.98)	−0.24	−2.10	0.036
Randomization to atorvastatin treatment group (yes/no)	0.87 (0.76–1.00)	−0.14	−2.02	0.043
Ethnicity[f]				
African	0.92 (0.48–1.79)	0.08	0.16	0.815
South Asian	1.51 (0.56–4.07)	0.41	1.07	0.414
Others	2.21 (1.04–4.69)	0.79	1.91	0.039
Age (per year)	1.00 (0.99–1.01)	0.00	−0.24	0.813

Apriori variables included in the model were SBP, age, sex, diabetes, race, and age at leaving full-time education. All variables as described in Table 2 (baseline characteristics) were considered for inclusion in the model. CI, confidence interval; LVH, left ventricular hypertrophy. [a] Irrespective of sign, it indicates strength of association and relative influence. [b] Atenolol-based treatment group was considered as reference group. [c] SBP ≤150 mmHg was considered as reference category. [d] Alcohol categories based on units intake per week for both sexes (male/female; see footnote of Table 2). Alcohol categories were included as a continuous variable in the model. [e] 12–14 years were considered as reference category. [f] Whites were considered as reference category.

Fig. 3



Risk score model. (a) Expected and observed probabilities of developing resistant hypertension in 5 years, stratified by tenths (deciles) of the risk score among the untreated population. (b) Kaplan–Meier estimates for developing resistant hypertension, stratified by the risk score quartiles and the treatment allocation. RH, resistant hypertension.

medications were the two most important determinants of resistant hypertension among hypertensive patients. The presence of diabetes, LVH, male sex, randomization to atorvastatin therapy, and raised FPG and BMI were other significant predictors in both the untreated and total populations. In addition, the number of previous antihypertensive medications, African origin, and age were significant predictors only among those in

the total group, whereas previous history of receiving aspirin therapy and numbers of years in full-time education were significant determinants only among those in the untreated group. The risk score developed to predict resistant hypertension among untreated hypertensive adults is robust with an excellent internal validity and is able to assign correctly the risk of resistant hypertension among all patients randomized in the ASCOT trial, irrespective of previous antihypertensive treatment. The integer-based simpler version of this risk score could potentially guide physicians to identify and, therefore, manage patients at high risk of developing resistant hypertension more assertively.

Our findings of a significantly increasing risk of resistant hypertension with each increasing stratum of baseline SBP (Table 3) support more assertive approach to BP-lowering made in recent guidelines [1,14], whereby a combination of drugs is recommended as initial therapy for people with higher BP levels (SBP $\geq$160 mmHg). The association between higher baseline SBP (>160 mmHg) and risk of developing resistant hypertension is not surprising [15] and may be mediated by arterial stiffness, which either by cause or effect is associated with the raised SBP observed with aging [2,16]. Our finding of prevalences of resistant hypertension at the time of exit from the study of approximately 35 and 50% among the untreated and total groups, respectively, is in keeping with previous reports of the prevalence of uncontrolled BPs from the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) [4] and the International Verapamil-Trandolapril Study (INVEST) [6,17]. However, unlike previous reports [4,6,15,17], this study has documented the prevalence of resistant hypertension using the standard definition [2].

On multivariable Cox regression, age had no significant effect on the incidence of resistant hypertension. However, on competing risk analysis, increasing age was significantly associated with an increase in the risk of resistant hypertension [5,16]. This suggests that the true relationship between resistant hypertension and age was masked due to early deaths, particularly among those who were prone to develop resistant hypertension. Regardless of the complex relationship between age and incident resistant hypertension, the prevalence of resistant hypertension, as reported in other studies [2,5,16,18], increased with increasing age. For example, among the untreated group, 46% of those aged more than 75 years had resistant hypertension at study exit compared with 34% of younger patients. The increase in risk of resistant hypertension, associated with the presence of diabetes [2,17,19] and with increased BMI [4,9,18], is consistent with previous findings and may be explained on the basis of the presence of insulin resistance, impaired sodium secretion, and activation of sympathetic nervous activity in both diabetes and obesity [2,3]. Of note, we have used the same definition of BP control (<140/90 mmHg) for patients with and without diabetes. This reduces the likelihood of an apparent disparity in the numbers of medications required to achieve BP targets between the patients with diabetes and those without, and allows an evaluation of the independent effect of diabetes on the development of resistant hypertension. The observed increased risk of resistant hypertension among men, and those with LVH or a higher alcohol intake has been previously reported among patients with uncontrolled BPs [2–5]. Our analysis shows that those who spent more than 19 years at full-time education are at lower risk of developing resistant hypertension, compared with those who spent less time in education. This finding is consistent with the presence of an inverse relationship between SBP levels and socio-economic status as previously reported [5,20]. Among the untreated group, the lack of association between ethnicity and development of resistant hypertension may reflect a lack of power as suggested by the results in the total group, when African origin or mixed race origin was associated with significantly increased risk of resistant hypertension, and results of earlier publications [4,5,18].

The relative importance of each of these determinants of resistant hypertension is implied by the size of the *Z*-scores (regardless of the positive or negative sign; see Table 3). Accordingly, randomization to amlodipine-based treatment was the most protective variable against the risk of developing resistant hypertension. Potential mechanisms for this protection include a greater reduction in brachial BP [10], central aortic BP [21], BP variability [22], and possibly arterial stiffness, compared with the atenolol-based treatment strategy. Similarly, the protection afforded by statin therapy may be due to beneficial effects on arterial stiffness [23,24]. The risk score developed among the untreated group is able to assign accurately the risk of developing resistant hypertension among those in the total group. This implies that this risk score could potentially be used among all hypertensive patients, regardless of previous treatment. The integer-based version allows an easy estimation of the risk of developing resistant hypertension in a routine clinical setting. It illustrates the benefits of one antihypertensive treatment strategy over another, with (or without) the addition of a statin. Figure 3b (and online appendix Fig. 4, http://links.lww.com/HJH/A115) shows that the benefits associated with amlodipine-based therapy compared with atenolol-based therapy were similar regardless of baseline risk. This finding suggests that the optimal selection of combinations of antihypertensive agents can reduce the risk of developing resistant hypertension among all patients regardless of associated co-morbidities or baseline risk.

The use of the ASCOT database for these analyses may be criticized because the predominance of whites and the required co-existence of three other cardiovascular

Table 4 Mean SBP and DBP difference from the baseline, and the antihypertensive medications used, at the time of resistant hypertension diagnosis and at the time of exit from the study, among resistant hypertension patients in the two populations

	Untreated population $n=3666$ [mean (SD)/%]		Total population $n=19\,257$ [mean (SD)/%]	
Characteristics at diagnosis of RH or study exit (either due to censoring or death)	RH group ($n=1258$) at time of RH diagnosis	RH group ($n=1258$) at the study exit	RH group ($n=9333$) at time of RH diagnosis	RH group ($n=9333$) at the study exit
Blood pressure measurements				
SBP diff (mmHg)[a]	−26.5 (18.4)	−36.9 (22.7)	−14.4 (20.4)	−27.9 (23.8)
DBP diff (mmHg)[a]	−16.6 (10.8)	−22.4 (12.2)	−9.7 (11.1)	−17.0 (12.1)
Antihypertensive medications				
Total number of drugs	3.0 (0.2)	3.0 (1.0)	3.1 (0.2)	3.2 (1.0)
ACEIs or ARBs (%)	44.2	46.2	44.8	51.4
CCBs (%)	37.7	36.9	40.0	44.1
Diuretics (%)	65.4	63.5	63.9	62.9
β-Blockers (%)	60.0	53.3	58.7	53.5
α-Blockers (%)	85.8	73.2	85.9	72.7
Aldosterone antagonists (%)	3.7	10.2	2.1	11.0
Antiadrenergic centrally acting agents (%)	7.4	17.6	9.1	24.3
Other antihypertensive agents(%)	0.1	0.2	0.1	0.7

diff, difference between SBP at RH diagnosis or the study exit and SBP at baseline [SBP (RH diagnosis/exit) minus SBP randomization]; RH, resistant hypertension. [a] From randomization.

risk factors at randomization resulted in an atypical population. However, the majority of patients randomized in ASCOT were recruited from, and were fairly typical of, patients commonly seen in general practice. For example, the two most common cardiovascular risk factors for inclusion in the ASCOT trial were the presence of male sex and age more than 55 years. Nevertheless, there is a possibility that these data may overestimate the prevalence and incidence of resistant hypertension among the minority of hypertensive patients, aged less than 55 years, with no other cardiovascular risk factors. The use of diuretics in defining resistant hypertension was not essential in our definition (based on an expert consensus [1]). This could be interpreted by some as a possible limitation of these analyses. It could also be argued that the prevalence and incidence of resistant hypertension would have been less if more patients had been on a diuretic prior to the diagnosis. However, (despite the supposition) about two-thirds of resistant hypertension patients at the time of diagnosis were on diuretics (Table 4) in both the untreated and total groups. Furthermore, 41% of patients randomized to the atenolol and thiazide (diuretic) regimen developed resistant hypertension compared with only 27% of those randomized to the amlodipine and perindopril regimen (of whom, 87 and 20%, respectively, were on diuretics at the time of resistant hypertension diagnosis). Interestingly, although BP control improved after the diagnosis of resistant hypertension, the proportional use of diuretics remained the same (Table 4). It is also plausible that higher BPs experienced throughout the trial by those randomized to the atenolol-based regimen caused the higher rates of resistant hypertension, rather than the drug regimen *per se*. However, given almost identical baseline BPs, and similar follow-ups, it seems inherently more likely that the differential BP levels observed were function of the two treatment regimens used, as was the subsequent propensity to develop resistant hypertension. Perhaps, a more important limitation of our analyses was the use by trial design of only two drug combinations (atenolol and thiazide or amlodipine and perindopril). However, this limitation does not detract from the results relating to the other determinants of resistant hypertension or the risk score thus developed. Furthermore, the study design did allow a robust comparison of two commonly used drug combinations. Another important limitation of this analysis is a lack of external validation of the risk score developed. Despite these limitations, the ASCOT database efficiently documents resistant hypertension incidence, by incorporating serial records of accurately measured BPs and antihypertensive medications, with a study design promoting uptitration of antihypertensive medications until BP control was achieved.

These analyses on determinants of resistant hypertension add substantially to the available literature, which currently has several gaps and inconsistencies. We have documented the incidence rates of resistant hypertension in a large database of hypertensive patients. Our findings suggest that the treatment strategy used is important in preventing the development of resistant hypertension among newly diagnosed hypertensive patients. Our findings on prevalence rates provide further support to a recent expert consensus statement on resistant hypertension [2]. The easy-to-use integer-based risk score to identify those at high risk of developing resistant hypertension confirms the critical role of other predictors such as BMI, alcohol intake, diabetes, and LVH, in developing resistant hypertension. Our results are the most comprehensive evaluations of the determinants of resistant hypertension (using the standard definition) to date. Nevertheless, they need confirmation in other populations to ensure generalizability. Meanwhile, we believe these results could be used to provide guidance for physicians in day-to-day clinical practice to improve understanding of the associations and determinants of resistant hypertension.

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Conflicts of interests

C.C. and E.N. have no conflicts of interest to declare. A.G. has received travel assistance to attend conferences from Pfizer and Servier. N.P., P.S., and B.D. have received honoraria and served as consultants to several pharmaceutical companies producing blood pressure-lowering and lipid-lowering agents, including Pfizer and Servier.

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