Effect of Doxazosin Gastrointestinal Therapeutic System as Third-Line Antihypertensive Therapy on Blood Pressure and Lipids in the Anglo-Scandinavian Cardiac Outcomes Trial

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Background—The role of doxazosin in treatment of hypertension remains controversial.

Methods and Results—We evaluated the effects on blood pressure (BP) and biochemical parameters of doxazosin GITS (gastrointestinal therapeutic system) as a third-line antihypertensive agent among 10 069 participants in the Anglo-Scandinavian Cardiac Outcomes Trial–Blood Pressure Lowering Arm (ASCOT-BPLA) whose BP remained above 140/90 mm Hg (130/80 mm Hg in those with diabetes mellitus). Among those who received doxazosin, mean age was 63 years (SD 9 years), 79% were male, and 32% had diabetes. Doxazosin was initiated a median of 8 months (interquartile range 3 to 24 months) after randomization and was added to a mean of 2.0 (SD 0.3) other antihypertensive drugs; the mean starting and final doses were 4.1 (SD 0.6) and 7.0 (SD 3.1) mg, respectively. During a median of 12 months (interquartile range 4 to 31 months) of uninterrupted doxazosin treatment, during which other antihypertensive treatments remained unchanged, mean BP fell 11.7/6.9 mm Hg (SD 18.8/9.6 mm Hg, $P<0.0001$) from 158.7/89.2 mm Hg (SD 18.3/10.6 mm Hg). After the addition of doxazosin, 29.7% of participants achieved target BP. There was no apparent excess of heart failure among doxazosin users. There were associated modest favorable effects on plasma lipid profiles, but a small rise in fasting plasma glucose was observed. Doxazosin was generally well tolerated, with 7.5% of participants discontinuing the drug because of adverse events, most frequently dizziness, fatigue, headache, and edema.

Conclusions—α-Blockers are no longer recommended as add-on therapy in some hypertension guidelines. However, although they are nonrandomized and were not placebo-controlled, the present findings suggest that doxazosin is a safe and effective third-line antihypertensive agent. **(*Circulation*. 2008;118:42-48.)**

Key Words: blood pressure ■ drugs ■ hypertension

The α-adrenergic blocking drug doxazosin lowers blood pressure (BP) effectively[1,2] and is reported to improve plasma lipid profiles, insulin sensitivity, and glucose metabolism.[3–5] However, its use as a first-line antihypertensive drug has declined[6] since publication of the results of the prematurely terminated doxazosin limb of the Antihypertensive and Lipid-Lowering treatment to prevent Heart Attack Trial (ALLHAT). In a randomized comparison with chlorthalidone, those randomized to doxazosin had higher rates of stroke (a secondary end point) and particularly congestive heart failure (a component of a secondary composite cardiovascular disease end point)[7,8]; subsequent interpretation of these findings has varied considerably, however.[9–11] Although there are some limited data from randomized trials evaluating doxazosin as add-on therapy,[12,13] α-blockers are no longer recommended in some guidelines,[14] although they are still indicated in others as add-on therapy or for the compelling indication of hypertension in men with benign prostatic hypertrophy.[15–17] In view of continued uncertainty regarding doxazosin use, we conducted an observational analysis of its efficacy and safety in the Anglo-Scandinavian Cardiac Outcomes Trial–Blood Pressure Lowering Arm (ASCOT-BPLA), a large-scale, randomized, controlled study of BP-lowering therapy in which participants received doxazosin GITS (gastrointestinal therapeutic system) as third-line therapy when previous study medication had failed to control BP.

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Methods

Study Population and Treatment

ASCOT-BPLA was a multicenter, international, randomized trial that compared 2 open-label antihypertensive regimens in hyperten-

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Table 1. ASCOT Antihypertensive Treatment Algorithm

	Amlodipine-Based Regimen	Atenolol-Based Regimen
Steps 1–2	Amlodipine 5–10 mg	Atenolol 50–100 mg
Steps 3–4	Perindopril 4–8 mg	Bendroflumethiazide+K^+ 1.25–2.5 mg
Steps 5–6	Doxazosin GITS 4–8 mg	
Step 7	Other drugs added at discretion of investigators	

GITS indicates gastrointestinal therapeutic system.

sive patients with additional cardiovascular risk factors but no history of coronary heart disease. The study conformed to Good Clinical Practice guidelines and was conducted in accordance with the Declaration of Helsinki. The protocol was approved by ethics review boards in the United Kingdom and by ethics and statutory bodies in Ireland and the Nordic countries. Participating subjects gave written informed consent.

The study methods and main results have been published previously.[18,19] Briefly, participants were randomly assigned an antihypertensive regimen based on either amlodipine or atenolol instead of existing antihypertensive medication. Therapy was titrated to achieve target BP <140/90 mm Hg (<130/80 mm Hg in those with diabetes mellitus). Perindopril or bendroflumethiazide was added to amlodipine or atenolol, respectively, as a second-line agent, and doxazosin GITS (Pfizer, New York, NY) was added as a common third-line antihypertensive (Table 1).

Follow-Up and BP Measurement

After randomization, routine follow-up visits took place after 6 weeks, 3 months, and 6 months and every 6 months thereafter, with additional visits if necessary. At each visit, BP was measured by standard protocols and validated semiautomatic devices (Omron HEM705CP, Omron Healthcare, Inc, Bannockburn, Ill).[20] Three seated measurements were made after at least 5 minutes' rest, and the mean of the final 2 measurements was used in analyses.

The present BP analyses included all participants who were prescribed doxazosin and who had valid BP measurements both before commencing and during doxazosin treatment. Pre-doxazosin BP was defined as that recorded on the day doxazosin was prescribed or the nearest prior measurement; on-treatment BP was defined as that recorded at the final study visit, the date that doxazosin was discontinued (permanently or for ≥3 days) if this preceded study end, or the date of any change to other antihypertensive treatments (drugs or dosages) if this preceded either of the other events. If no measurement was available on these dates, then the most recent on-treatment measurement was used. Where doxazosin was prescribed for >1 period, (eg, if discontinued for ≥3 days for any reason), only the first continuous period of use was included in analyses.

Biochemical Measurements and Analyses

Blood samples (ideally fasting) were taken at study entry, 6 months later, and annually thereafter for the measurement of sodium, potassium, creatinine, glucose, and lipid profiles at 1 of 2 central laboratories. The analyses reported here were limited to participants with available biochemical data both before and during doxazosin treatment.

Lipid analyses were limited to subjects in whom both samples were taken while they were fasting, as well as to the period of continuous treatment during which there were no changes in other antihypertensive treatments and no use of lipid-lowering therapy. However, analyses did include not only participants who took no lipid-lowering therapy during ASCOT but also those who started such therapy at some point after a fasting on-doxazosin blood sample had been taken. Fasting glucose analyses were limited to those without diabetes before they began taking doxazosin and to the period of continuous treatment during which there were no changes in antihypertensive treatments or use of hypoglycemic drugs. Duration of doxazosin treatment for biochemical analyses was measured from the start of therapy until the last valid blood test before the study end, discontinuation of doxazosin (if prior to this), or before any change in other treatments as described above. For those who developed new-onset diabetes mellitus, the duration of treatment for glucose analyses was until the last valid blood test before this diagnosis.

Adverse Events

Information was routinely recorded about adverse events (AEs) at each study visit, and investigators were asked to record their opinion on causality (study drug, other drug, or concurrent condition or illness). Because investigators were not required to distinguish between doxazosin and other study drugs as the cause of AEs, the present analyses are limited to those that resulted in discontinuation of doxazosin. However, the analyses do include AEs that occurred at any point during doxazosin use (not just during the BP evaluation period).

Heart failure was a prespecified secondary end point in ASCOT (rather than an AE) and was analyzed separately. It was defined and evaluated rigorously according to strict criteria. For a diagnosis of heart failure to be made, investigators had to confirm the following: (1) presence of ≥2 new symptoms (eg, dyspnea at rest or on exertion or orthopnea) and/or signs (eg, pulmonary rales, third heart sound, peripheral edema, raised jugular venous pressure) and/or response to treatment (diuresis and symptomatic relief) with loop diuretic; (2) ≥1 investigation abnormality (eg, typical abnormalities on chest radiograph or evidence of impaired left ventricular function on echocardiography, multigated acquisition scan, or coronary angiography); and (3) a statement of a diagnosis of heart failure by the attending physician. There was no requirement that the patient be hospitalized. Details of all suspected cases were reviewed independently by 2 members of the trial End Point Committee, who were provided with all available information, including narrative statements, clinical notes, results of investigations, and death certificates and autopsy reports where appropriate. If these members failed to agree on classification of suspected cases, they were reviewed by the complete 4-member committee, and a decision was reached by consensus. The present analyses refer to all validated diagnoses of heart failure and are not limited to those that resulted in discontinuation of doxazosin.

Statistical Analysis

Within-subject changes in BP and biochemical parameters were evaluated with 2-tailed paired Student's *t* tests. Changes in subgroups of participants ≤60 years and >60 years of age at study entry, men and women, randomized group (atenolol- or amlodipine-based therapy), those with and without diabetes, and those with and without metabolic syndrome were compared with ANCOVA adjusted for pre-doxazosin BP. Adjustments for additional potential confounders (age, sex, and body mass index) were also performed. Heart failure analyses compared crude rates of heart failure that occurred at any time during the study among those who did and did not receive doxazosin and rates per 1000 person-years during doxazosin treatment with rates among those who never received doxazosin. In addition, to minimize bias associated with nonrandom censoring caused by participants discontinuing doxazosin because of prodromal symptoms of heart failure (eg, edema), rates per 1000 patient-years were compared between doxazosin users from the time of initiation until the development of heart failure or trial end and those who never received doxazosin. Assumptions of statistical tests and models were assessed.

The authors had full access to the data and take full responsibility for its integrity. All authors have read and agree to the manuscript as written.

Results

Study Participants

Of 19 257 participants in ASCOT, 11 768 received doxazosin during the study (Figure 1). Of these, 1699 had no recorded

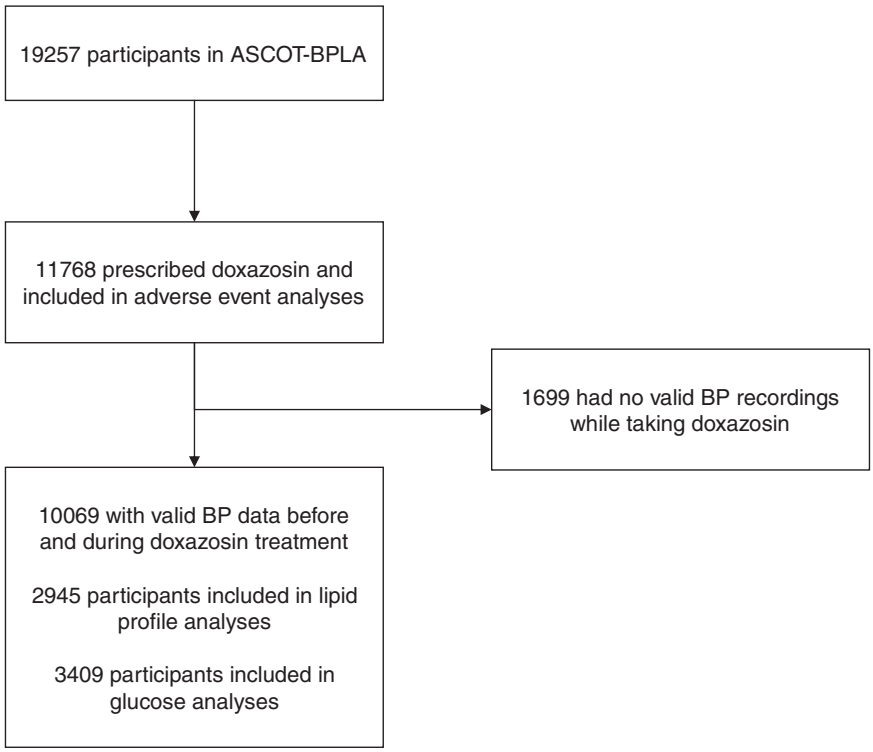

Figure. Flow diagram of ASCOT participants taking doxazosin and included in the present analyses.

BP measurements while taking doxazosin; BP analyses reported here refer to the remaining 10 069 individuals with data both before and during treatment.

Characteristics at study entry of participants who did and did not receive doxazosin are shown in Table 2. Those who received doxazosin had higher mean systolic BP (SBP) and fasting plasma glucose levels and were more likely to have left ventricular hypertrophy and diabetes mellitus and to have been randomized to atenolol-based therapy. They were less likely to smoke. Lipid and other biochemical parameters were similar in both groups.

Table 2. Characteristics at Study Entry of Participants Who Did and Did Not Receive Doxazosin

Characteristics at Study Entry	Doxazosin Patients (n=11 768)	Nondoxazosin Patients (n=7489)
Age, y (SD)	62.7 (8.5)	62.2 (8.5)
Male	9254 (78.6%)	5488 (73.3%)
White/European	11 167 (94.9%)	7190 (96.0%)
Systolic BP, mm Hg (SD)	166.7 (18.5)	159.7 (19.25)
Diastolic BP, mm Hg (SD)	94.9 (10.7)	94.25 (9.9)
Heart rate, bpm (SD)	71.6 (12.9)	72.3 (12.3)
Left ventricular hypertrophy*	2752 (23.4%)	1415 (18.9%)
Diabetic	3791 (32.2%)	1346 (18.0%)
Current smoker	3431 (29.2%)	2846 (38.0%)
Body mass index, kg/m^2	29.08 (4.62)	28.15 (4.45)
Allocated amlodipine	5011 (42.6%)	4628 (61.8%)
Total cholesterol, mmol/L (SD)	5.87 (1.07)	5.97 (1.08)
LDL cholesterol, mmol/L (SD)	3.74 (0.96)	3.85 (0.98)
HDL cholesterol, mmol/L (SD)	1.29 (0.36)	1.32 (0.37)
Triglycerides, mmol/L (SD)	1.88 (1.01)	1.79 (0.98)
Glucose mmol/L (SD)	6.44 (2.24)	5.91 (1.84)

*ECG or echocardiographic left ventricular hypertrophy identified by study investigators.

Compared with doxazosin users excluded because of inadequate BP data, participants included in the present BP analyses were slightly younger (mean age 63.0 [SD 8.4] versus 64.0 [SD 8.7] years, $P<0.0001$), were more likely to be male (79.7% versus 72.4%, $P<0.0001$), and had slightly lower SBP (166.6 [SD 18.4] versus 167.8 [SD 19.1] mm Hg, $P=0.01$). Other baseline characteristics were similar.

Effects of Doxazosin on BP

Doxazosin was initially prescribed a median of 8 months (interquartile range [IQR] 3 to 24 months) after randomization and was added to a mean of 2.0 other antihypertensive drugs (SD 0.3); by design, this remained constant during the observation period. The median duration of uninterrupted treatment with no changes in other antihypertensive treatments was 12 months (IQR 4 to 31 months). Mean initial and final doses of doxazosin were 4.1 (SD 0.6) and 7.0 (SD 3.1) mg, respectively.

After addition of doxazosin, mean BP fell from 158.7/89.2 mm Hg (SD 18.3/10.6 mm Hg) to 147.0/82.3 mm Hg (SD 20.4/11.5 mm Hg). The mean within-individual reduction was 11.7 mm Hg (SD 18.8 mm Hg, $P<0.0001$) in SBP and 6.9 mm Hg (SD 9.6, $P<0.0001$) in diastolic BP (DBP). After addition of doxazosin, 29.7% of subjects achieved target BP. Heart rate increased slightly from 66.5 to 67.1 bpm (mean within-individual change 0.6 bpm [SD 10.1], $P<0.0001$).

Highly significant reductions in SBP and DBP were observed in all subgroups (Table 3; $P<0.0001$ for each subgroup); however, some differences were apparent within pairs of subgroups. For example, SBP reduction was signif-

Table 3. Changes in SBP and DBP During Doxazosin Treatment in Subgroups

	Systolic BP, mm Hg				Diastolic BP, mm Hg			
Category	Before Doxazosin	After Doxazosin	Unadjusted Mean Within-Subject Change	Adjusted Mean Difference (SE)*	Before Doxazosin	After Doxazosin	Unadjusted Mean Within-Subject Change	Adjusted Mean Difference (SE)*
All (n=10 069)	158.7 (18.3)	147.0 (20.4)	−11.7 (18.8)		89.1 (10.6)	82.3 (11.5)	−6.9 (9.6)	
Age ≤60 y (n=3678)	154.9 (16.4)	145.4 (18.9)	−9.5 (17.1)		92.8 (9.5)	86.2 (10.7)	−6.5 (9.3)	
Age >60 y (n=6391)	160.8 (19.1)	147.9 (21.2)	−12.9 (19.6)	−1.0 (0.4), P=0.006	87.1 (10.7)	80.0 (11.3)	−7.0 (9.8)	−2.5 (0.2), P<0.0001
Male (n=8024)	157.9 (17.8)	146.7 (19.8)	−11.2 (18.0)		89.7 (10.5)	83.0 (11.4)	−6.8 (9.5)	
Female (n=2045)	161.6 (20.2)	148.1 (22.6)	−13.5 (21.6)	−0.8 (0.4), P=0.06	86.8 (10.8)	79.6 (11.4)	−7.2 (10.3)	−1.4 (0.2), P<0.0001
Atenolol (n=5787)	162.0 (20.0)	148.6 (21.8)	−13.4 (19.9)		91.0 (10.6)	83.9 (11.5)	−7.1 (10.0)	
Amlodipine (n=4282)	154.2 (14.8)	144.8 (18.2)	−9.4 (17.0)	0.9 (0.4), P=0.02	86.6 (10.1)	80.2 (11.1)	−6.5 (9.1)	−0.8 (0.2), P<0.0001
Without diabetes (n=6840)	159.1 (17.8)	146.7 (20.2)	−12.3 (19.2)		90.3 (10.4)	83.2 (11.5)	−7.1 (9.8)	
With diabetes (n=3229)	157.8 (19.4)	147.5 (20.9)	−10.3 (17.9)	1.6 (0.4), P<0.0001	86.6 (10.6)	80.3 (11.1)	−6.3 (9.1)	−0.5 (0.2), P=0.01
Without metabolic syndrome (n=5487)	159.3 (18.3)	147.1 (20.6)	−12.2 (19.1)		89.4 (10.6)	82.4 (11.6)	−7.0 (9.6)	
With metabolic syndrome (n=4582)	157.9 (18.4)	146.8 (20.2)	−11.1 (18.5)	0.6 (0.3), P=0.11	88.8 (10.6)	82.1 (11.4)	−6.7 (9.6)	0.1 (0.2), P=0.55

*Second listed compared with first listed; ANCOVA difference in postdoxazosin BP adjusted for pre-doxazosin BP.

icantly greater in older subjects, those randomized to atenolol, and those without diabetes. DBP reductions were significantly greater in older subjects, females, those randomized to amlodipine, and those with diabetes. Adjustment for additional potential confounding factors made no material difference to these findings.

The relationship between BP reduction and continuous variables was examined. For each year older, SBP and DBP reductions were greater by 0.04 mm Hg (P=0.05) and 0.17 mm Hg (P<0.0001), respectively. For each 1-kg greater baseline weight, SBP and DBP reductions were both 0.05 mm Hg less (both P<0.0001). For each 1-kg/m^2 greater baseline body mass index, SBP and DBP reductions were 0.15 and 0.11 mm Hg less, respectively (both P<0.0001).

Biochemical Analyses

Among those who received doxazosin, 5916 either took no lipid-lowering therapy during ASCOT or initiated such treatment after starting doxazosin. Of these, 2945 had valid fasting blood samples both before and during doxazosin treatment but before starting lipid-lowering therapy and are included in these analyses. Baseline characteristics of these subjects were similar to all those who received doxazosin, apart from a lower prevalence of diabetes (27.7% versus 32.2%, respectively) and lower fasting plasma glucose (6.30 [SD 2.16] versus 6.44 [2.24] mmol/L). Lipid profiles were similar. Median duration of uninterrupted treatment for these analyses was 9 months (IQR 4 to 21 months). Total cholesterol decreased by 0.28 mmol/L (SD 0.73 mmol/L, P<0.0001; Table 4) from 5.91 mmol/L (SD 1.04 mmol/L). LDL cholesterol decreased by 0.21 mmol/L (SD 0.66 mmol/L, P<0.0001) from 3.82 mmol/L (SD 0.93 mmol/L). HDL cholesterol did not change. Triglycerides decreased by 0.17 mmol/L (SD 0.88 mmol/L, P<0.0001) from 1.86 mmol/L (SD 1.07 mmol/L). Significant reductions in total cholesterol, LDL cholesterol, and triglycerides were observed in all subgroups.

Glucose analyses included data on 3409 participants without diabetes before doxazosin treatment began, among whom median duration of uninterrupted doxazosin treatment was 19 months (IQR 7 to 38 months). Baseline characteristics of these subjects were similar to all those who received doxazo-

Table 4. Changes in Biochemical Parameters During Doxazosin Treatment

	No. of Participants Included in Analyses	Before Doxazosin	After Doxazosin	Mean Within-Individual Difference (SD)	Paired t Test P Value
Total cholesterol, mmol/L	2945*	5.91 (1.04)	5.64 (1.02)	−0.28 (0.73)	<0.0001
LDL cholesterol, mmol/L	2853*	3.82 (0.93)	3.61 (0.91)	−0.21 (0.66)	<0.0001
HDL cholesterol, mmol/L	2934*	1.28 (0.36)	1.28 (0.37)	0.00 (0.22)	0.97
Triglycerides, mmol/L	2936*	1.86 (1.07)	1.69 (0.92)	−0.17 (0.88)	<0.0001
Glucose, mmol/L	3409†	5.48 (0.68)	5.59 (0.82)	0.11 (0.80)	<0.0001
Sodium, mmol/L	7790	140.3 (2.8)	140.2 (2.9)	−0.1 (2.9)	0.004
Potassium, mmol/L	7739	4.25 (0.48)	4.22 (0.48)	−0.03 (0.52)	<0.0001
Creatinine, μmol/L	7816	98.3 (18.3)	98.9 (19.9)	0.6 (11.6)	<0.0001

*Subjects who received no lipid-lowering agent or received lipid-lowering therapy after starting doxazosin.
†Those without diabetes at baseline.

sin, apart from the absence of subjects with diabetes (by definition) and a lower fasting glucose (5.35 [SD 0.62] versus 6.44 [2.24] mmol/L). There was a small significant increase in fasting glucose of 0.11 mmol/L (SD 0.80 mmol/L, $P<0.0001$) while subjects were taking doxazosin, from 5.48 mmol/L (SD 0.68), which was equivalent to a 3.5% (SD 34.6%) mean within-subject change (Table 4). Significant increases occurred in all subgroups. Among a subgroup of 1925 participants with body weights recorded before and during doxazosin treatment, weight increased by 1.38 kg (SD 5.32 kg, $P<0.0001$). Small changes in plasma sodium, potassium, and creatinine levels were apparent but not clinically significant (Table 4).

Adverse Events

In ASCOT, 11 768 participants took doxazosin at some time and accumulated 39 996 years' exposure to the drug, all of which were included in AE analyses; this compares with 16 656 years' exposure included in the BP analyses. Overall, 1055 AEs in 877 participants (7.5%) resulted in temporary or permanent discontinuation of doxazosin. The most common AEs that necessitated discontinuation were dizziness (28.8% of AEs), fatigue (13.4%), headache (8.8%), vertigo (8.6%), and edema (8.3%). Urinary incontinence led to discontinuation in 42 participants (0.4% of those who took doxazosin), of whom most (36 of 42) were female.

During the entire ASCOT follow-up period (median 5.5 years), crude heart failure rates were 1.51% (178 of 11 768 participants) among those who received doxazosin at any point and 1.54% (115 of 7489) among those who never received doxazosin. Heart failure occurred in 118 participants while actually taking doxazosin, a rate of 2.97 per 1000 person-years; this compares with 2.85 per 1000 person-years among those who never received doxazosin (rate ratio 1.04 [95% CI 0.80 to 1.36], $P=0.76$). Heart failure occurred in 168 participants during or after discontinuation of doxazosin treatment, a rate of 3.34 per 1000 person-years (rate ratio 1.17 [95% CI 0.92 to 1.49], $P=0.20$ compared with those who never received doxazosin).

Discussion

These analyses of observational data from a substantial subpopulation of participants in ASCOT show that modified-release doxazosin, used as third-line antihypertensive therapy, lowered BP by approximately 12/7 mm Hg. During treatment, plasma lipid profiles improved slightly, but there was a small increase in fasting glucose levels. Doxazosin was generally well tolerated and, on the basis of these data, was not associated with increased risk of heart failure.

The observed mean BP reductions were substantial, particularly given that doxazosin was used as third-line therapy in subjects with BP uncontrolled despite the use of 2 other drugs, and they are consistent with those observed with other drugs used as initial or add-on therapy.[21–24] By design, the analyses were restricted to periods during which other antihypertensive treatments remained unaltered, thus minimizing obvious influences on BP. However, a major limitation of these data are that they are uncontrolled, and as such, we cannot exclude the possibility that some of the observed BP reduction was due to acclimatization or regression to the mean, although the former is unlikely given that doxazosin was first administered a median of 8 months after randomization (when participants would, on average, have undergone at least 5 sets of BP readings). In addition, 1699 subjects who received doxazosin were excluded from analyses because of lack of valid on-treatment BP measurements. Although baseline characteristics of these subjects were broadly similar to those included in the analyses, we cannot exclude the possibility that they may have differed systematically in their response to doxazosin. For example, had they been nonresponders, this may have resulted in overestimation of the true effect of doxazosin on BP; conversely, in some, doxazosin may have been discontinued because of events (such as dizziness) associated with excessive BP falls, potentially leading to underestimation of the effect.

Although doxazosin appeared to lower BP effectively, we cannot be certain that this would result in reductions in cardiovascular outcomes. Although most evidence suggests that magnitude of BP reduction rather than choice of antihypertensive is the most important factor influencing the risk of most major cardiovascular events,[24] doxazosin lacks robust supportive data from randomized morbidity and mortality trials. Indeed, the best evidence available, from ALLHAT, suggests that doxazosin as first-line therapy is less effective than chlorthalidone at lowering BP and preventing some events. Although there was no difference in the primary end point (fatal coronary heart disease or nonfatal myocardial infarction) during the mean 3.2 years of follow-up, those randomized to doxazosin had higher rates of stroke and particularly congestive heart failure.[7,8] Consequently, the trial was discontinued early (which itself may have exaggerated any true differences),[25] and the results have since provoked divergent interpretation.[9–11] Opinions differ as to what extent the observed differences in SBP during the study (average 2 to 3 mm Hg higher among those randomized to doxazosin) could account for the differences in stroke and heart failure rates and how valid the latter diagnosis was.[11,26–28]

In ASCOT, heart failure was a rigorously standardized and validated secondary end point,[18] which occurred infrequently (overall 1.5%) in contrast to ALLHAT (4.6% among those randomized to chlorthalidone or doxazosin).[8] Although the present data are nonrandomized, there appeared to be no excess of heart failure during almost 40 000 patient-years of exposure to doxazosin, despite the fact that participants who received doxazosin had more severe hypertensive disease (higher SBP and prevalence of left ventricular hypertrophy at study entry). These findings were similar for both crude rates of heart failure (occurring at any point in the study) and when heart failure rates associated with doxazosin treatment (during or after use) were compared with rates among those who never received doxazosin. Whether the differences between ASCOT and ALLHAT reflect the inadequacies of observational data (including various possible sources of bias), use of different formulations of doxazosin (modified versus immediate release), differences between use of doxazosin as third- or first-line therapy, the presence in ASCOT of a drug systematically used in heart failure (ACE inhibitor or thiazide diuretic) in each randomized arm, or differences in the

validity of heart failure diagnosis remains unclear. However, although doxazosin may be less effective than chlorthalidone at reducing BP and preventing stroke, the present data do not suggest that it increases heart failure risk.

Doxazosin was associated with modest favorable changes in fasting plasma lipid profiles, with modest reductions in total and LDL cholesterol and triglycerides. These are observational data from a subpopulation of all those who received doxazosin and are therefore theoretically subject to bias; however, evidence for selection bias was not apparent in baseline characteristics, and the findings are consistent with previous observations.[3–5]

A small rise in fasting plasma glucose levels was observed during doxazosin treatment. Doxazosin favorably affects insulin sensitivity, and some, but not all, studies also report favorable effects on glucose levels.[3,4] In ALLHAT, fasting glucose levels fell by 0.3 mmol/L (from 6.8 to 6.5 mmol/L) among those in the doxazosin limb, which contrasted with a small increase (from 6.8 to 6.9 mmol/L) among those randomized to chlorthalidone,[8] a diuretic with known adverse metabolic effects; however, 36% of ALLHAT participants had diabetes, and the observed changes are likely to be confounded by use of hypoglycemic and other medications. In contrast, in the present ASCOT analyses, those with diabetes were excluded from glucose analyses, which were also limited to periods with no changes in drugs anticipated to influence glucose levels. The observed glucose rise may reflect in part the modest weight gain observed with doxazosin (although this is presumably due at least in part to fluid retention); more importantly, however, those who received doxazosin had higher SBP and fasting plasma glucose at study entry and were more likely to have been randomized to atenolol-based therapy, all of which predicted new-onset diabetes among the whole ASCOT cohort.[29] The observed rise may therefore simply reflect the natural increase in glucose levels to be expected in such an elderly population.

Doxazosin was generally well tolerated. AEs led to discontinuation in only 7.5% of those who received it. However, ASCOT was not designed to identify AEs specific to doxazosin, and therefore, we were only able to identify with certainty those of sufficient severity to require discontinuation of doxazosin. The true frequency of any doxazosin-related AEs would therefore almost certainly have been substantially higher than demonstrated from the present analyses.

It must be stressed that these are observational data, albeit of a large data set that included a total of almost 40 000 patient-years of doxazosin exposure; as such, cautious interpretation of the findings is required. However, this is the only sizeable data set available to allow evaluation of the BP-lowering efficacy and safety of α-blockers used as third-line antihypertensive therapy, and the data provide reassurance on both counts.

Conclusions

These data suggest that doxazosin is an effective third-line antihypertensive agent. In addition, treatment was associated with modest improvements in plasma lipid profiles, was well tolerated, and was not obviously associated with an excess of heart failure. Although we recognize the limitations of these uncontrolled observational data, the data support the continued use of doxazosin as add-on antihypertensive therapy.

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CLINICAL PERSPECTIVE

The use of doxazosin in the management of hypertension has declined after publication of the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) because of concerns about its safety, particularly with regard to heart failure. In view of this, investigators from the Anglo-Scandinavian Cardiac Outcomes Study–Blood Pressure Lowering Arm (ASCOT-BPLA) conducted an observational analysis of the blood pressure–lowering efficacy and safety of modified-release doxazosin used as a common third-line agent in study participants whose blood pressure was uncontrolled despite their other randomized study drugs (either amlodipine and perindopril or atenolol and bendroflumethiazide). Among 10 069 participants who received doxazosin for a median of 12 months of uninterrupted treatment, blood pressure fell by an average of almost 12/7 mm Hg. This was associated with modest reductions in total and LDL cholesterol but a small rise in fasting plasma glucose concentrations. Doxazosin was generally well tolerated; 7.5% of recipients discontinued the drug because of adverse events, most commonly dizziness, fatigue, headache, and edema. There was no apparent excess of heart failure (a rigorously defined and validated secondary end point in ASCOT) among those who received doxazosin, despite the fact that they had more severe hypertensive disease (higher systolic blood pressure and more left ventricular hypertrophy at baseline) than those who did not receive the drug. The authors acknowledge the limitations of the uncontrolled, observational data while concluding that they provide evidence to support the efficacy and safety of modified-release doxazosin used as third-line therapy in the treatment of hypertension.