Impact of amlodipine-based therapy among older and younger patients in the Anglo-Scandinavian Cardiac Outcomes Trial—Blood Pressure Lowering Arm (ASCOT-BPLA)

David J. Collier[a], Neil R. Poulter[b], Björn Dahlöf[c], Peter S. Sever[b], Hans Wedel[d], Jan Buch[e] and Mark J. Caulfield[a], on behalf of the ASCOT Investigators

Objectives **Older patients experience higher rates of cardiovascular disease than younger patients, but studies have suggested that relative risk reductions due to antihypertensive therapy are lower in older than younger patients. The Anglo-Scandinavian Cardiac Outcomes Trial—Blood Pressure Lowering Arm (ASCOT-BPLA) allowed an evaluation of the efficacy and safety of an amlodipine versus an atenolol-based antihypertensive regimen among older (≥65 years) and younger (<65 years) patients.**

Methods **In ASCOT-BPLA 19 257 patients (8137 aged ≥65 years and 11 020 <65 years) were randomly assigned to receive amlodipine or atenolol-based antihypertensive therapy. The primary endpoint (nonfatal myocardial infarction and fatal coronary heart disease) and seven secondary endpoints were consistent with the original trial design.**

Results **All cardiovascular endpoints evaluated favoured the amlodipine-based regimen, significantly so in seven of the 16 age-stratified endpoints. Compared with the atenolol-based regimen, the amlodipine-based regimen reduced the relative risk of cardiovascular events by 17% in older and 15% in younger patients ($P<0.01$). Overall, older patients experienced more cardiovascular events [$n=1625$ (20%)] than younger patients [$n=1339$ (12%)]. Discontinuations due to serious adverse events were low in both age groups and less frequent in the amlodipine-based versus atenolol-based regimen: 0.6 versus 1.1% among older patients and 0.4 versus 0.8% among younger patients.**

Conclusions **The amlodipine-based regimen reduced the relative risk of cardiovascular events more effectively than the atenolol-based regimen in both older and younger patients. However, because event rates were higher among older patients, the absolute benefits were greater for older compared with younger patients.** *J Hypertens* **29:583–591 © 2011 Wolters Kluwer Health | Lippincott Williams & Wilkins.**

Journal of Hypertension 2011, **29**:583–591

Keywords: angiotensin-converting enzyme inhibitors, amlodipine, antihypertensive agents, atenolol, cardiovascular disease prevention, coronary disease mortality, diuretics, elderly, hypertension, randomized controlled trials

Abbreviations: ACE, angiotensin-converting enzyme; ALLHAT, Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial; ARB, angiotensin receptor blocker; ASCOT, Anglo-Scandinavian Cardiac Outcomes Trial; ASCOT-BPLA, Anglo-Scandinavian Cardiac Outcomes Trial–Blood Pressure Lowering Arm; BMI, body mass index; BP, blood pressure; CCB, calcium channel blocker; CHD, coronary heart disease; CI, confidence interval; CVD, cardiovascular disease; DBP, diastolic blood pressure; ECG, electrocardiograph; ECHO, echocardiogram; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; LVH, left-ventricular hypertrophy; MI, myocardial infarction; RR, relative risk; RRR, relative risk reduction; SAE, serious adverse event; SBP, systolic blood pressure; TC, total cholesterol; TIA, transient ischemic attack; β-blocker, beta blocker

[a]Barts and The London, Queen Mary's School of Medicine and Dentistry, [b]Imperial College London, London, UK, [c]Sahlgrenska University Hospital/Östra, [d]Nordiska School of Public Health, Göteborg, Sweden and [e]Pfizer Inc, New York, New York, USA

Correspondence to David J. Collier, PhD, Clinical Pharmacology, William Harvey Research Institute, Barts and The London School of Medicine and Dentistry, Queen Mary University of London, Charterhouse Square, London, EC1M 6BQ, UK
Tel: +44 20 7882 3415; fax: +44 20 7882 3430; e-mail: d.j.collier@qmul.ac.uk

Received 22 March 2010 **Revised** 5 October 2010
Accepted 17 November 2010

See editorial comment on page 440

Introduction

Many guidelines for the prevention of cardiovascular disease (CVD) recommend the use of absolute risk profiles to guide decisions on initiating antihypertensive therapy [1–3]. Age is a major risk factor for CVD and almost half of all patients with established CVD are aged 65 years and older [4]. Thus implementing a risk-based treatment strategy should target treatment at older rather than younger patients. Despite the publication of several trials demonstrating the benefits of antihypertensive therapy in older patients [5–7], population-based surveys from several countries have suggested that older patients with hypertension are often undertreated [8,9]. This observation has become known as the treatment-risk paradox [10]. The reluctance to adequately treat older patients may, in part, stem from the apparently conflicting evidence from recent observational studies and meta-analysis of trials of antihypertensives together with the complexity of handling both absolute and relative measures of cardiovascular risk. For example, both the Prospective Studies Collaboration [11] and the Asia-Pacific Cohort Studies Collaboration [12] reported that

0263-6352 © 2011 Wolters Kluwer Health | Lippincott Williams & Wilkins DOI:10.1097/HJH.0b013e328342c845

the relative reduction in risk attributable to blood pressure (BP) lowering was smaller in older than younger patients, although the absolute reduction in risk observed when comparing high with lower BP was greater among the elderly. In contrast to these findings, the Treatment Trialists' Collaboration meta-analysis of BP reduction among 190 606 patients reported there were no differences in relative risk (RR) with increasing age, although they agreed that older patients experienced greater absolute benefits because of their higher average risk [13].

The differential effects of antihypertensive drug classes among older and younger patients also remains controversial. For example, in 2002 the ALLHAT investigators concluded that diuretics led to fewer adverse cardiovascular outcomes in both older (≥65 years) and younger (<65 years) patients when compared with both angiotensin-converting enzyme (ACE) inhibitors and calcium channel blockers (CCBs) [14], although this interpretation has been disputed [2]. This was closely followed by the results from the Australian Blood Pressure Group who reported that ACE inhibitors were superior to diuretics in their elderly cohort (mean age 71.9 years), although their finding was only statistically significant among male participants [15]. In contrast to these findings, the Treatment Trialist's Collaboration meta-analysis reported no clear differences in major cardiovascular events when different antihypertensive drug regimens were compared among older (≥65 years) and younger (<65 years) patients [13]. Whereas the current evidence remains inconclusive, it is plausible that age does influence the efficacy of some antihypertensive drug classes. For example, drugs that inhibit the renin angiotensin system may be less effective at reducing BP in older patients and hence may prevent fewer cardiovascular events. Indeed, the latest British guidelines recommend initiating antihypertensive therapy with ACE inhibitors/angiotensin receptor blockers (ARBs) in younger patients (<55 years) and either CCBs or thiazide diuretics in older patients (≥55 years) to reflect the differences in BP-lowering with age that may be mediated by renin activity [2].

In view of the aging population and the increasingly challenging therapeutic targets, it is important to establish any differences in cardiovascular event rates when antihypertensive drugs are used in older and younger patients. This post-hoc analysis of the Anglo-Scandinavian Cardiac Outcomes Trial–Blood Pressure Lowering Arm (ASCOT-BPLA) investigated the reduction in cardiovascular events and safety profile of amlodipine-based versus atenolol-based antihypertensive regimens in older (≥65 years) and younger (<65 years) patients.

Methods

ASCOT-BPLA was a multicentre, international randomized trial that compared the cardioavscular effects of two antihypertensive regimens [amlodipine ± perindopril (amlodipine-based) versus atenolol ± thiazide diuretic (atenolol-based)] in 19 257 patients with hypertension and at least three additional cardiovascular risk factors but no history of coronary heart disease (CHD) [16,17]. In a two-by-two factorial design, ASCOT included a double-blind, randomized comparison of the cardiovascular effects of atorvastatin versus placebo among 10 305 patients who had total baseline cholesterol concentrations 251 mg/dl or less (≤6.5 mmol/l) [16]. The impact of atorvastatin among older and younger patients is described in the accompanying study [18].

The study design, trial management, and main results of ASCOT-BPLA have been published previously [16,17]. In brief, participants were men and women with hypertension and aged from 40 to 79 years at randomization. All patients were required to have at least three of the following cardiovascular risk factors: male sex, age at least 55 years, microalbuminuria or proteinuria, smoking, ratio of plasma total cholesterol to high-density lipoprotein (HDL) cholesterol at least 6, premature family history of CHD, left-ventricular hypertrophy, other specified abnormalities on electrocardiogram, peripheral arterial disease, type 2 diabetes, previous stroke, or transient ischemic attack (TIA).

Hypertension was defined as a systolic BP (SBP) of 160 mmHg or more or a diastolic BP (DBP) of 100 mmHg or more, or both, if untreated, or a SBP of 140 mmHg or more or a DBP of 90 mmHg or more, or both, if treated. The BP management algorithm, together with other details on the study design, has been described previously [16]. Furthermore, the antihypertensive treatment algorithm is summarized here in Table 1. At each study visit, antihypertensive therapy was titrated and additional agents were added to achieve a target BP of less than 140/90 mmHg (<130/80 mmHg in those with diabetes). In addition, information about adverse events and study endpoints was recorded at each study visit.

The post-hoc analysis compares the cardiovascular effects of amlodipine-based versus atenolol-based antihypertensive regimens among older (aged ≥65 years) and younger patients (aged <65 years). The evaluated endpoints were consistent with the original trial design and included the primary end point of nonfatal myocardial infarction [MI (including silent MI)] and fatal CHD. The seven secondary endpoints were nonfatal MI (excluding silent MI) and fatal CHD; total coronary endpoints; total cardiovascular events and procedures; all-cause mortality; cardiovascular mortality; fatal and nonfatal stroke; and fatal and nonfatal heart failure.

Statistical methods

Time to first endpoint was compared between amlodipine-based and atenolol-based therapy in both age groups on an intention-to-treat basis. Confidence intervals (CIs) were calculated using the log-rank procedure and a Cox

Table 1 Antihypertensive treatment algorithm in ASCOT-BPLA

Titration step	Amlodipine-based regimen	Atenolol-based regimen
Step 1	Start amlodipine 5 mg	Start atenolol 50 mg
Step 2	Increase amlodipine to 10 mg	Increase atenolol to 100 mg
Step 3	Add perindopril 4 mg	Add bendroflumethiazide/K^+ 1.25 mg
Step 4	Increase perindopril to 8 mg	Increase bendroflumethiazide/K^+ to 2.5 mg
Step 5	Add doxazosin gastrointestinal transport system 4 mg	
Step 6	Increase doxazosin gastrointestinal transport system to 8 mg	
Step 7	Add additional antihypertensive drugs (suggestions included moxonidine and spironolactone) at the investigator's discretion	

proportional hazards model. Cumulative incidence curves were generated by the Kaplan–Meier method for primary and secondary endpoints in both treatment groups. All statistical tests were two-sided.

Results

Among the 19 257 patients in ASCOT-BPLA, 8137 patients (42%) were aged 65 years or older and 11 120 patients (58%) were aged less than 65 years. In both age groups, baseline characteristics were well matched between those randomized to amlodipine-based and atenolol-based antihypertensive regimens (Table 2).

At baseline, the mean age of the older group was 71 years and the younger group was 57 years (Table 2). In both age groups, patients were predominantly white and male. Although both groups had a similar number of additional cardiovascular risk factors (mean: 3.8 ± 0.9 in the older group and 3.7 ± 0.9 in the younger group) they were distributed very differently. For example, at baseline the older group had higher SBP (168.1 ± 18.7 versus 161.1 ± 16.9 mmHg), lower DBP (91.8 ± 10.5 versus 96.8 ± 9.8 mmHg) and hence wider pulse pressures; had higher rates of previous stroke or TIA (15.5 versus 7.7%); and reported taking more prophylactic aspirin (26.0 versus 14.2%), than those younger than 65 years. Younger patients had higher fasting triglyceride levels, heart rates, and body mass index (BMI) than those aged 65 years or older. Patients aged less than 65 years consumed more alcohol and were more likely to be current smokers than those aged 65 years or older (all $P < 0.01$) (Table 2).

ASCOT-BPLA was stopped prematurely after a median follow-up of 5.5 years on the recommendation of the Data Safety Monitoring Board due to a significant mortality benefit of amlodipine-based therapy. Among the older group, complete follow-up information was obtained for

Table 2 Baseline characteristics

	Patients aged ≥65 years		Patients aged <65 years	
	Amlodipine-based regimen $n = 4042$	Atenolol-based regimen $n = 4095$	Amlodipine-based regimen $n = 5597$	Atenolol-based regimen $n = 5523$
Demographic and clinical characteristics				
Men, *n* (%)	2974 (73.6)	3009 (73.5)	4407 (78.7)	4352 (78.8)
Age, years, mean (SD)	71.1 (4.0)	71.1 (4.0)	57.2 (5.6)	57.1 (5.6)
White, *n* (%)	3906 (96.6)	3941 (96.2)	5281 (94.4)	5229 (94.7)
Current smoker, *n* (%)	961 (23.8)	911 (22.2)	2207 (39.4)	2198 (39.8)
Alcohol consumption, mean units/week, (SD)	6.7 (10.3)	6.6 (10.5)	9.0 (12.4)	8.9 (12.3)
SBP, mean mmHg (SD)	168.4 (18.7)	167.8 (18.6)	161.0 (16.9)	161.1 (16.9)
DBP, mean mmHg (SD)	92.0 (10.5)	91.6 (10.5)	96.8 (9.8)	96.7 (9.8)
Heart rate, mean beats/min (SD)	70.1 (12.3)	70.3 (12.6)	73.2 (12.8)	73.0 (12.5)
BMI, mean kg/m^2 (SD)	27.9 (4.2)	28.0 (4.2)	29.3 (4.8)	29.2 (4.7)
TC, mean mg/dl (SD)	227.8 (42.6)	228.5 (42.4)	228.6 (41.1)	227.3 (40.6)
LDL-C, mean mg/dl (SD)	147.0 (38.2)	147.5 (37.7)	145.8 (37.0)	144.4 (36.5)
HDL-C, mean mg/dl (SD)	51.6 (14.3)	51.6 (14.2)	49.5 (13.8)	49.4 (14.0)
Triglycerides, mean mg/dl (SD)	150.6 (74.4)	150.7 (73.8)	171.7 (96.8)	173.5 (97.0)
Glucose, mean mg/dl (SD)	111.7 (36.0)	111.7 (37.8)	113.5 (39.6)	111.7 (37.8)
Creatinine, mean mg/dl (SD)	1.2 (0.2)	1.5 (0.2)	1.1 (0.2)	1.1 (0.2)
Medical history				
Previous stroke or TIA, *n* (%)	640 (15.8)	622 (15.2)	410 (7.3)	441 (8.0)
Diabetes mellitus, *n* (%)	1148 (28.4)	1166 (28.5)	1419 (25.4)	1412 (25.6)
ECG abnormalities (not LVH), *n* (%)	703 (17.4)	719 (17.6)	665 (11.9)	666 (12.1)
LVH (on ECG or ECHO), *n* (%)	921 (22.8)	950 (23.2)	1170 (20.9)	1126 (20.4)
Peripheral vascular disease, *n* (%)	334 (8.3)	333 (8.1)	252 (4.5)	280 (5.1)
Number of risk factors, mean (SD)	3.8 (0.9)	3.8 (0.9)	3.7 (0.9)	3.7 (0.9)
Drug therapy				
No previous antihypertensive use, *n* (%)	681 (16.8)	677 (16.5)	1160 (20.7)	1148 (20.8)
Aspirin use, *n* (%)	1066 (26.4)	1046 (25.5)	785 (14.0)	791 (14.3)

BMI, body mass index; CVD, cardiovascular disease; DBP, diastolic blood pressure; ECG, electrocardiograph; ECHO, echocardiogram; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; LVH, left-ventricular hypertrophy; SBP, systolic blood pressure; TC, total cholesterol; TIA, transient ischemic attack.

all but 117 patients and vital status for all but 17 patients. Among the younger group, complete follow-up information was obtained for all but 175 patients and vital status for all but 32 patients.

Blood pressure

The amlodipine-based regimen was associated with a greater BP reduction than the atenolol-based regimen and this was more marked among older than younger patients. The mean BP among those randomized to the amlodipine-based regimen fell from 168.4/92.0 to 137.3/73.8 mmHg in the older group (mean reduction −31.7/−18.9 mmHg) and from 161.0/96.8 to 135.4/79.7 mmHg in the younger group (mean reduction −25.6/−17.2 mmHg). The mean BP among those randomized to the atenolol-based regimen fell from 167.8/91.6 to 139.7/75.9 mmHg in the older group (mean reduction −28.2/−15.7 mmHg) and from 161.1/96.7 to 136.4/81.4 mmHg in the younger group (mean reduction −24.7/−15.3 mmHg).

The mean BP difference between treatments in favour of the amlodipine-based regimen was 4.2/2.2 mmHg in the older group and 1.7/1.7 mmHg in the younger group (Fig. 1a and 1b). The greatest difference between the treatment arms was seen during the first 2 years of therapy. During the remaining follow-up period the BP difference was reduced but never totally disappeared.

As ASCOT-BPLA progressed, the number of antihypertensive medications used to help patients achieve the BP targets increased. In both age groups, more antihypertensive drugs were prescribed to those randomized to the atenolol-based regimen compared with the amlodipine-based regimen. Among older patients, at the final study visit those randomized to the atenolol-based regimen were prescribed a mean of 2.40 antihypertensive drugs versus 2.23 in the amlodipine-based regimen ($P < 0.01$). In the younger group the equivalent figures were 2.36 and 2.22, respectively ($P < 0.01$) (Fig. 1a and 1b).

Cardiovascular outcomes

The primary endpoint of nonfatal MI (including silent MI) and fatal CHD was not significantly reduced with amlodipine-based versus atenolol-based therapy in the overall cohort of ASCOT-BPLA, and this was also the case in those aged 65 years or older and less than 65 years (Figs 2 and 3). However, all the cardiovascular endpoints evaluated favoured the amlodipine-based regimen and were statistically significant in seven of the 16 age-stratified endpoints. For two of the seven secondary endpoints, significant differences in favour of the amlodipine-based regimen were apparent among both age strata (Figs 2 and 3). Compared with the atenolol-based regimen, the amlodipine-based regimen reduced total cadiovascular events and procedures by 17% in the older group (hazard ratio 0.83; 95% CI 0.75, 0.91; $P < 0.01$) and by 15% in the younger group (hazard ratio 0.85; 95% CI 0.78, 0.95; $P < 0.01$). Compared with the atenolol-based regimen, the amlodipine-based regimen reduced cardiovascular mortality by 23% in the older group (hazard ratio 0.77; 95% CI 0.63, 0.94; $P < 0.01$) and by 24% in the younger group (hazard ratio 0.76; 95% CI 0.58, 1.00; $P = 0.05$).

Compared with the atenolol-based regimen, the amlodipine-based regimen reduced fatal and nonfatal stroke by 30% in the older group (hazard ratio 0.70; 95% CI 0.59, 0.84; $P < 0.01$) and by a nonsignificant 9% in the younger group (hazard ratio 0.91; 95% CI 0.71, 1.15; $P = 0.42$) (Figs 2 and 3). In contrast, compared with the atenolol-based regimen, the amlodipine-based regimen was associated with significant reductions in total coronary endpoints, nonfatal MI (excluding silent MI), and fatal CHD in the younger group but not in the older group (Figs 2 and 3). However, there was no statistically significant heterogeneity between the hazard ratios observed between the older and younger groups (Figs 2 and 3).

As expected, older patients consistently experienced more events across all study endpoints in both the amlodipine-based and atenolol-based therapy groups, putting the older group at higher absolute cardiovascular risk. For example, among the older group 18.3% of those on amlodipine-based and 21.6% of those on atenolol-based therapy reported a cardiovascular event or procedure compared with 11.1 and 13.0%, respectively, in the younger group (Fig. 3).

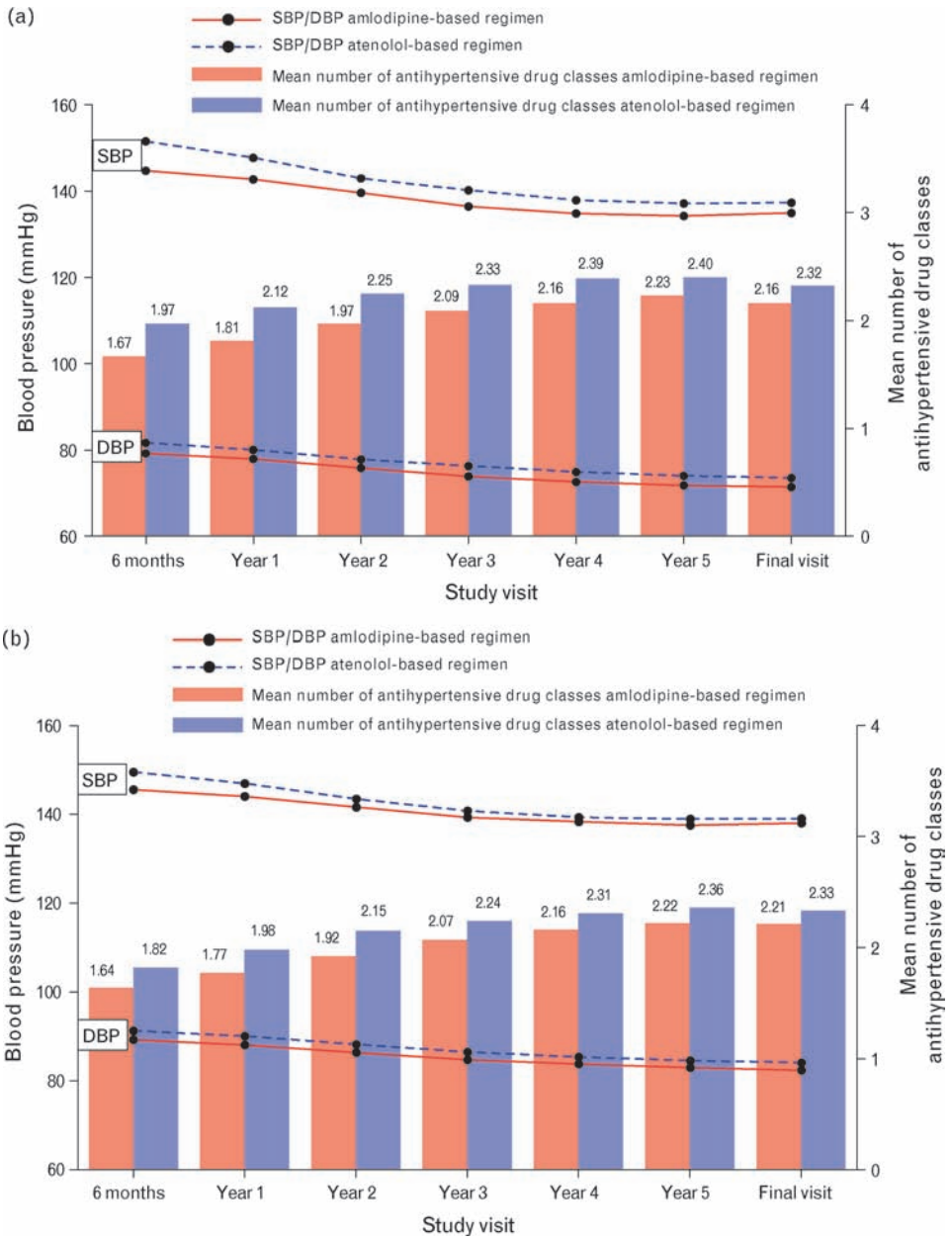
Safety

Overall, older patients reported more serious adverse events (SAEs) than younger patients (42.6 versus 31.3%, respectively). Discontinuation rates due to SAEs were low in both age groups and favoured the amlodipine-based regimen. Among the older group, 0.6% discontinued amlodipine-based therapy and 1.1% discontinued atenolol-based therapy compared with 0.4 and 0.8%, respectively, in the younger group. Furthermore among both the older and younger groups, there were no significant differences between the amlodipine-based and atenolol-based regimens in non-cardiovascular deaths and cancer deaths.

Discussion

The findings of this post-hoc analysis of ASCOT-BPLA suggest that amlodipine-based antihypertensive regimens reduce the risk of cardiovascular events more effectively than atenolol-based regimens in both older (aged ≥65 years) and younger patients (aged <65 years). The relative reduction in cardiovascular events was similar in both age groups (17 and 15%, respectively). However, as the older group was at higher absolute cardiovascular risk compared with the younger group, the absolute benefits of amlodipine-based therapy were greater among older versus younger patients with hypertension.

Fig. 1

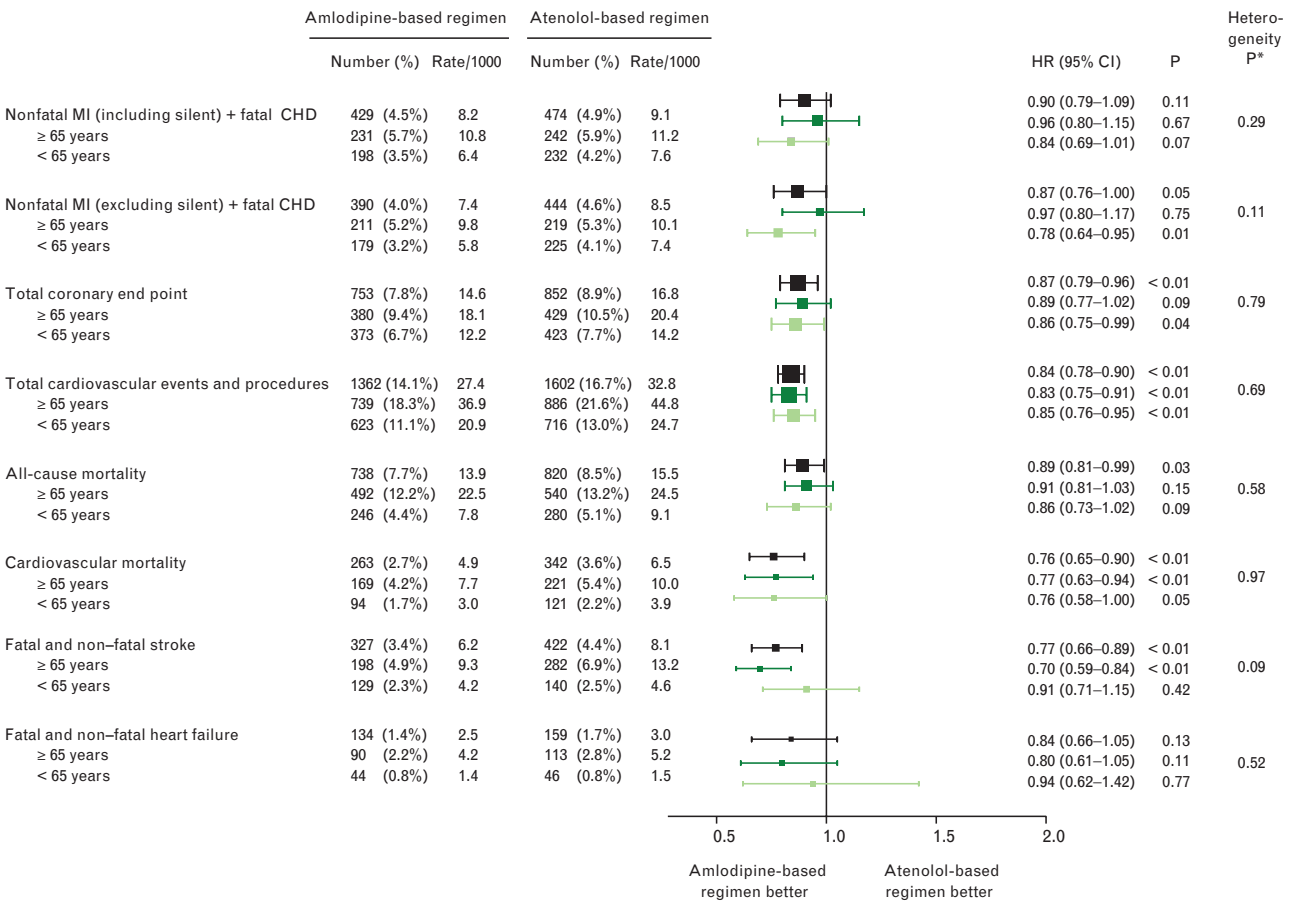


SBP and DBP and mean number of antihypertensive drug classes, by time and study treatment in (a) patients aged at least 65 years and (b) patients aged below 65 years. DBP, diastolic blood pressure; SBP, systolic blood pressure.

In the overall ASCOT-BPLA cohort, BP reductions were greater in those randomized to amlodipine-based compared with atenolol-based regimens. In this post-hoc analysis, we found these differences were greater among those aged 65 years or older compared with those less than 65 years (4.2/2.2 versus 1.7/1.7 mmHg, respectively). These differential BP reductions were observed despite systematic feedback to investigators highlighting patients with inadequate BP control. Furthermore, compared with the amlodipine-based regimen, those randomized to the atenolol-based regimen were prescribed more add-on drugs such as doxazosin [19], spironolactone [20], and moxonidine.

The finding that older patients experienced greater differential BP reduction between the study arms compared with younger patients is consistent with the tendency for older people to have lower renin concentrations than younger people. Thus, antihypertensive drugs that target the renin–angiotensin system, including

Fig. 2



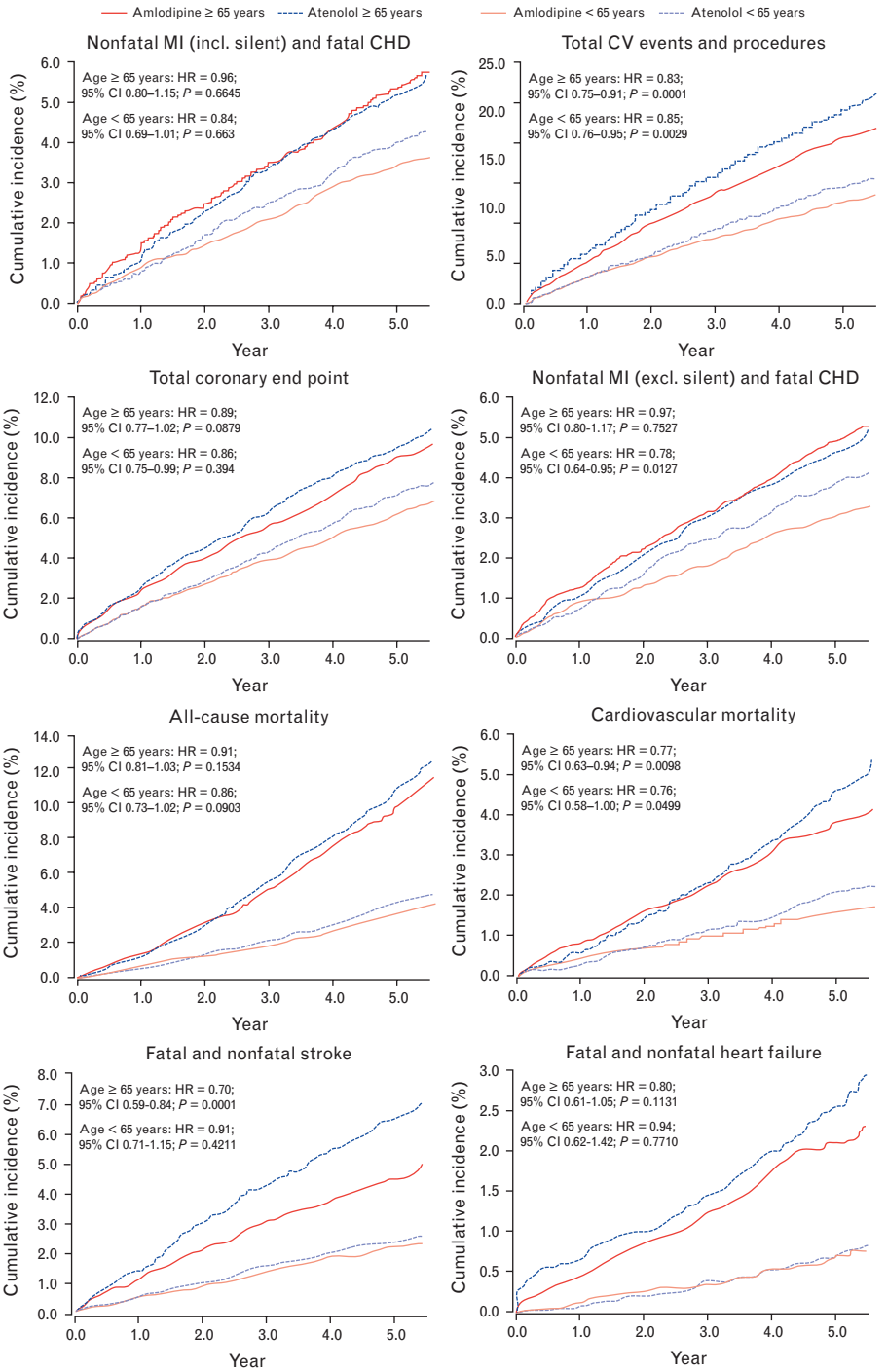
Hazard ratios among all patients, patients aged at least 65 years, and patients aged below 65 years. CHD, coronary heart disease; CI, confidence interval; HR, hazard ratio; MI, myocardial infarction. **P* value for heterogeneity between the older and younger cohorts.

ACE/ARBs and β-blockers, are generally less effective in older patients [2].

The stepped-care protocol in ASCOT-BPLA (Table 1) allowed the addition of the ACE inhibitor perindopril in the amlodipine-based regimen. Thus younger patients, who would be anticipated to have a good BP response to the atenolol-based regimen, would also be more likely than older patients to respond well to the second-line treatment (perindopril) in the amlodipine-based regimen, thereby balancing the BP response between the two treatment arms. On the basis of renin levels, older patients would not be expected to respond as well to atenolol as younger patients but they would be expected to respond well to a diuretic. However, the efficacy of low-dose thiazide diuretics has recently been questioned in a pooled analysis that demonstrated that the decrease in 24-h ambulatory blood pressure was significantly smaller in patients taking hydrochlorothiazide (12.5 to 25 mg) compared with other antihypertensive drugs including ACE inhibitors, ARBs, β-blockers, and CCBs [21]. This may partly explain why the BP difference between the two antihypertensive treatment regimens was greater among older compared with younger patients. Of particular note is the fact that, despite the addition of multiple add-on antihypertensive drugs, the first-line treatment appears to be important in predicting the overall BP reduction. These findings lend support to current British guidance that encourages clinicians to consider age when making decisions about antihypertensive drug treatment [2].

The somewhat surprising finding was that, despite the BP imbalance being greater among older than younger patients, the reductions in the relative risk of cardiovascular events were similar. This is not consistent with previous well established observations that the relationship between BP and cardiovascular risk is positive, continuous, and linear [22]. Our observation may be a spurious finding of an underpowered post-hoc analysis. An alternative explanation is that differences in the baseline cardiovascular risk profile between older and younger patients and changes in these risk factors during the trial made substantial contributions to the observed

Fig. 3



Cumulative incidence for the primary and secondary endpoints among patients aged at least 65 years and patients aged below 65 years. CHD, coronary heart disease; CI, confidence interval; CV, cardiovascular; HR, hazard ratio; MI, myocardial infarction.

relative risk reduction (RRR). Indeed, analyses published alongside the main ASCOT-BPLA results suggested that the BP differences between the treatment arms of ASCOT-BPLA accounted for only part of the observed difference in cardiovascular endpoints [23]. Differences in plasma HDL-C, triglycerides, fasting glucose, and central BP [24] in favour of those receiving amlodipine-based therapy may have also contributed to some of the benefits. In our analyses we found that the lipid effects of the antihypertensive agents differed with age;

atenolol-based therapy led to an observed increase in triglycerides in the younger but not in the older group. The lipid effects of atorvastatin among older and younger patients are considered in more detail in the accompanying study [18].

Our results are consistent with earlier studies comparing the effects of amlodipine in older and younger patients [25]. These studies demonstrated that BP reductions were greater in the elderly, and the rate of adverse events was only slightly higher in older compared with younger patients [25]. Despite lowering BP in both older and younger patients, there are known age-dependent changes in the pharmacokinetic and pharmacodynamic profile of amlodipine [25] and the package insert recommends a lower starting dose for patients aged 65 years or older. The ASCOT-BPLA stepped care protocol made no allowance for a lower starting dose for older patients on amlodipine (amlodipine 2.5 mg was not licensed for use in the UK or Scandinavia at the time the study was conducted) and yet this did not appear to measurably disadvantage older patients.

Although this post-hoc analysis lends support to the use of amlodipine-based antihypertensive therapy in older patients, the study has some limitations. Firstly, ASCOT-BPLA was prematurely terminated before the intended number of primary endpoints was reached due to a significant mortality benefit of amlodipine-based therapy, and this further reduced the power of any subgroup analyses [17]. Secondly, the age-based analysis reported in this study was not an *a priori* hypothesis, and thus the results must be interpreted with appropriate caution. Thirdly, the ASCOT-BPLA study population was predominantly male, white, and the upper age limit for entry into the trial was 79 years [16], hence the age groups reported in this analysis are only separated by an average of 14 years.

The post-hoc analysis of ASCOT-BPLA supports the message that an amlodipine-based regimen reduces the relative risk of cardiovascular events more effectively than an atenolol-based regimen in both older and younger patients. However, given the higher cardiovascular event rates among older patients, the absolute benefits of antihypertensive therapy are greater among older than younger patients.

Acknowledgements

The substudy was an independent analysis funded by Pfizer Inc. A full list of investigators and sponsors of the ASCOT study is available in the primary publication. D.J.C. had full access to all of the data in this study and takes responsibility for the integrity of the data and the accuracy of the data analysis. All authors participated in the design of the study, the interpretation of the data and the development of the manuscript. Editorial support was provided by Dr Papia Das and Dr Sarah Partridge of UBC Scientific Solutions and funded by Pfizer Inc, New York, NY, USA.

Potential conflicts of interest: D.J.C., N.R.P., B.D., P.S.S., H.W. and M.J.C. have served as consultants or received travel expenses, or payment for speaking at meetings, or funding for research from one or more pharmaceutical companies that market blood-pressure-lowering or lipid-lowering drugs. D.J.C., M.J.C., N.R.P. and P.S.S. are grateful for support from the NIHR Biomedical Research funding scheme. J.B. was an employee of Pfizer at the time the study was conducted.

References

1 Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL Jr, *et al.* Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. *Hypertension* 2003; **42**:1206–1252.

2 National Institute of Clinical Excellence. CG34 hypertension management in adults in primary care: pharmacological update. 28 June 2006. www.nice.org.uk/CG34. Accessed December 1, 2009.

3 Mancia G, De Backer G, Dominiczak A, Cifkova R, Fagard R, Germano G, *et al.* 2007 Guidelines for the Management of Arterial Hypertension: The Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *J Hypertens* 2007; **25**:1105–1187.

4 Lloyd-Jones D, Adams R, Carnethon M, De Simone G, Ferguson TB, Flegal K, *et al.* Heart disease and stroke statistics 2009 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. *Circulation* 2009; **119**:e21–e181.

5 Prevention of stroke by antihypertensive drug treatment in older persons with isolated systolic hypertension. Final results of the Systolic Hypertension in the Elderly Program (SHEP). SHEP Cooperative Research Group. *JAMA* 1991; **265**:3255–3264.

6 Staessen JA, Fagard R, Thijs L, Celis H, Arabidze GG, Birkenhager WH, *et al.* Randomised double-blind comparison of placebo and active treatment for older patients with isolated systolic hypertension. The Systolic Hypertension in Europe (Syst-Eur) Trial Investigators. *Lancet* 1997; **350**:757–764.

7 Beckett NS, Peters R, Fletcher AE, Staessen JA, Liu L, Dumitrascu D, *et al.* Treatment of hypertension in patients 80 years of age or older. *N Engl J Med* 2008; **358**:1887–1898.

8 Primatesta P, Poulter NR. Hypertension management and control among English adults aged 65 years and older in 2000 and 2001. *J Hypertens* 2004; **22**:1093–1098.

9 Ostchega Y, Dillon CF, Hughes JP, Carroll M, Yoon S. Trends in hypertension prevalence, awareness, treatment, and control in older U.S. adults: data from the National Health and Nutrition Examination Survey 1988 to 2004. *J Am Geriatr Soc* 2007; **55**:1056–1065.

10 Ko DT, Mamdani M, Alter DA. Lipid-lowering therapy with statins in high-risk elderly patients: the treatment-risk paradox. *JAMA* 2004; **291**:1864–1870.

11 Lewington S, Clarke R, Qizilbash N, Peto R, Collins R. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. *Lancet* 2002; **360**:1903–1913.

12 Lawes CM, Rodgers A, Bennett DA, Parag V, Suh I, Ueshima H, MacMahon S. Blood pressure and cardiovascular disease in the Asia Pacific region. *J Hypertens* 2003; **21**:707–716.

13 Turnbull F, Neal B, Ninomiya T, Algert C, Arima H, Barzi F, *et al.* Effects of different regimens to lower blood pressure on major cardiovascular events in older and younger adults: meta-analysis of randomised trials. *BMJ* 2008; **336**:1121–1123.

14 Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs. diuretic: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *JAMA* 2002; **288**:2981–2997.

15 Wing LM, Reid CM, Ryan P, Beilin LJ, Brown MA, Jennings GL, *et al.* A comparison of outcomes with angiotensin converting enzyme inhibitors and diuretics for hypertension in the elderly. *N Engl J Med* 2003; **348**:583–592.

16 Sever PS, Dahlöf B, Poulter NR, Wedel H, Beevers G, Caulfield M, *et al.* Rationale, design, methods and baseline demography of participants of the Anglo-Scandinavian Cardiac Outcomes Trial. ASCOT investigators. *J Hypertens* 2001; **19**:1139–1147.

17 Dahlöf B, Sever PS, Poulter NR, Wedel H, Beevers DG, Caulfield M, *et al.* Prevention of cardiovascular events with an antihypertensive regimen of amlodipine adding perindopril as required versus atenolol adding bendroflumethiazide as required, in the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA): a multicentre randomised controlled trial. *Lancet* 2005; **366**:895–906.

18 Collier DJ, Poulter NR, Dahlöf B, Sever PS, Wedel H, Buch J, Caulfield MJ. Impact of atorvastatin in older and younger patients in ASCOT-LLA. *J Hypertens* 2010 (in press).

19 Chapman N, Chang CL, Dahlöf B, Sever PS, Wedel H, Poulter NR. Effect of doxazosin gastrointestinal therapeutic system as third-line antihypertensive therapy on blood pressure and lipids in the Anglo-Scandinavian Cardiac Outcomes Trial. *Circulation* 2008; **118**:42–48.

20 Chapman N, Dobson J, Wilson S, Dahlöf B, Sever PS, Wedel H, Poulter NR. Effect of spironolactone on blood pressure in subjects with resistant hypertension. *Hypertension* 2007; **49**:839–845.

21 Messerli FH, Makani H, Bangalore S. Hydrochlorothiazide is inappropriate for first-line antihypertensive therapy. Abstract LB1.3. European Meeting on Hypertension, Milan, Italy; June 12–16, 2009.

22 MacMahon S, Peto R, Cutler J, Collins R, Sorlie P, Neaton J, *et al.* Blood pressure, stroke, and coronary heart disease. Part 1, Prolonged differences in blood pressure: prospective observational studies corrected for the regression dilution bias. *Lancet* 1990; **335**:765–774.

23 Poulter NR, Wedel H, Dahlof B, Sever PS, Beevers DG, Caulfield M, *et al.* Role of blood pressure and other variables in the differential cardiovascular event rates noted in the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA). *Lancet* 2005; **366**:907–913.

24 Williams B, Lacy PS, Thom SM, Cruickshank K, Stanton A, Collier D, *et al.* Differential impact of blood pressure-lowering drugs on central aortic pressure and clinical outcomes: principal results of the Conduit Artery Function Evaluation (CAFE) study. *Circulation* 2006; **113**:1213–1225.

25 Abernethy DR, Gutkowska J, Winterbottom LM. Effects of amlodipine, a long-acting dihydropyridine calcium antagonist in aging hypertension: pharmacodynamics in relation to disposition. *Clin Pharmacol Ther* 1990; **48**:76–86.