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

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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 (\textgeq 65 years) and younger (<65 years) patients.

Methods In ASCOT-BPLA 19,257 patients (8,137 aged \textgeq 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 (\textit{P} < 0.01). Overall, older patients experienced more cardiovascular events [n = 1,625 (20%)] than younger patients [n = 1,339 (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. \textit{J Hypertens} 29:583–591 © 2011 Wolters Kluwer Health | Lippincott Williams & Wilkins.

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...
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 'Triallists’ Collaboration meta-analysis of BP reduction among 190606 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 cardiovascular effects of two antihypertensive regimens [amlodipine ± perindopril (amlodipine-based) versus atenolol ± thiazide diuretic (atenolol-based)] in 19257 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 10305 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
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 1 Antihypertensive treatment algorithm in ASCOT-BPLA

<table>
<thead>
<tr>
<th>Titration step</th>
<th>Amlodipine-based regimen</th>
<th>Atenolol-based regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Step 1</td>
<td>Start amlodipine 5 mg</td>
<td>Start atenolol 50 mg</td>
</tr>
<tr>
<td>Step 2</td>
<td>Increase amlodipine to 10 mg</td>
<td>Increase atenolol to 100 mg</td>
</tr>
<tr>
<td>Step 3</td>
<td>Add perindopril 4 mg</td>
<td>Add bendroflumethiazide/K⁺ 1.25 mg</td>
</tr>
<tr>
<td>Step 4</td>
<td>Increase perindopril to 8 mg</td>
<td>Increase bendroflumethiazide/K⁺ to 2.5 mg</td>
</tr>
<tr>
<td>Step 5</td>
<td>Add doxazosin gastrointestinal transport system 4 mg</td>
<td>Add additional antihypertensive drugs (suggestions included moxonidine and spironolactone) at the investigator’s discretion</td>
</tr>
</tbody>
</table>

### Table 2 Baseline characteristics

<table>
<thead>
<tr>
<th>Demographic and clinical characteristics</th>
<th>Patients aged ≥65 years</th>
<th>Patients aged &lt;65 years</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Amlodipine-based regimen</td>
<td>Atenolol-based regimen</td>
</tr>
<tr>
<td></td>
<td>n = 4042</td>
<td>n = 4095</td>
</tr>
<tr>
<td></td>
<td>Amlodipine-based regimen</td>
<td>Atenolol-based regimen</td>
</tr>
<tr>
<td></td>
<td>n = 5597</td>
<td>n = 5523</td>
</tr>
<tr>
<td>Men, n (%)</td>
<td>2974 (73.6)</td>
<td>3009 (73.5)</td>
</tr>
<tr>
<td>Age, years, mean (SD)</td>
<td>71.1 (4.0)</td>
<td>71.1 (4.0)</td>
</tr>
<tr>
<td>White, n (%)</td>
<td>3906 (96.6)</td>
<td>3941 (96.2)</td>
</tr>
<tr>
<td>Current smoker, n (%)</td>
<td>961 (23.8)</td>
<td>911 (22.2)</td>
</tr>
<tr>
<td>SBP, mean mmHg (SD)</td>
<td>168.4 (18.7)</td>
<td>167.8 (18.6)</td>
</tr>
<tr>
<td>DBP, mean mmHg (SD)</td>
<td>92.0 (10.5)</td>
<td>91.8 (10.5)</td>
</tr>
<tr>
<td>Heart rate, mean beats/min (SD)</td>
<td>70.1 (12.3)</td>
<td>70.3 (12.6)</td>
</tr>
<tr>
<td>BMI, mean kg/m² (SD)</td>
<td>27.9 (4.2)</td>
<td>28.0 (4.2)</td>
</tr>
<tr>
<td>Glucose, mean mg/dl (SD)</td>
<td>111.7 (36.0)</td>
<td>111.7 (37.8)</td>
</tr>
<tr>
<td>Creatinine, mean mg/dl (SD)</td>
<td>1.2 (0.2)</td>
<td>1.2 (0.2)</td>
</tr>
<tr>
<td>Medical history</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Previous stroke or TIA, n (%)</td>
<td>640 (15.8)</td>
<td>622 (15.2)</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>1148 (28.4)</td>
<td>1166 (28.5)</td>
</tr>
<tr>
<td>ECG abnormalities (not LVH), n (%)</td>
<td>703 (17.4)</td>
<td>719 (17.6)</td>
</tr>
<tr>
<td>LVH (on ECG or ECHO), n (%)</td>
<td>921 (22.8)</td>
<td>850 (23.2)</td>
</tr>
<tr>
<td>Peripheral vascular disease, n (%)</td>
<td>334 (8.9)</td>
<td>333 (8.1)</td>
</tr>
<tr>
<td>Number of risk factors, mean (SD)</td>
<td>3.8 (0.9)</td>
<td>3.8 (0.9)</td>
</tr>
<tr>
<td>Drug therapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No previous antihypertensive use, n (%)</td>
<td>681 (16.8)</td>
<td>677 (16.5)</td>
</tr>
<tr>
<td>Aspirin use, n (%)</td>
<td>1066 (26.4)</td>
<td>1046 (25.5)</td>
</tr>
</tbody>
</table>

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 cardiovascular 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.
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
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 amlopidine-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 amlopidine-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
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 amldopine 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 amldopine [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 amldopine (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 amldopine-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 amldopine-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 amldopine-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.

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References


