American Journal of Therapeutics 22, 278–287 (2015)

OPEN

Incremental Blood Pressure–Lowering Effect of Titrating Amlodipine for the Treatment of Hypertension in Patients Including Those Aged ≥55 Years

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Small reductions in blood pressure reduce the risk of cardiovascular events. Here, we report 2 post hoc pooled analyses assessing the antihypertensive effect of amlodipine in patients who had not responded to 5 mg and were uptitrated to 10 mg. The first analysis assessed subgroups of patients aged either younger than 55 years or 55 years or older and the second analysis pooled all patients irrespective of age. Of 706 patients in the age-related analysis, a statistically significant decrease in blood pressure from baseline was observed {for younger than 55 years [N = 253]: systolic blood pressure = −12.8 [standard error (SE) = 0.90] mm Hg, diastolic blood pressure = −8.0 [SE = 0.55] mm Hg; for 55 years or older [N = 453]: systolic blood pressure = −12.1 [SE = 0.66] mm Hg, diastolic blood pressure = −6.7 [SE = 0.39] mm Hg; all $P < 0.0001$}. In total, 45.8% and 39.3% of patients aged younger than 55 and 55 years or older, respectively, achieved their blood pressure goals. Adverse events were experienced by 62 (24.5%) patients aged younger than 55 years and 136 (30.0%) patients aged 55 years or older. Similar efficacy and safety results were seen in the all patient pooled analysis. Titration of amlodipine from 5 mg to 10 mg significantly decreased blood pressure in older hypertensive patients, which is clinically relevant because increased age is associated with hypertension and cardiovascular events.

Keywords: amlodipine, hypertension, blood pressure, blood pressure variability, age

INTRODUCTION

High blood pressure (≥140/90 mm Hg) is a serious public health care problem and a major risk factor for cardiovascular disease and stroke.[1–3] The incidence of hypertension increases with age affecting approximately 30%–45% of adults worldwide, and by age 60 approximately two-thirds of the population will develop the disease.[4–7] In the Framingham Heart Study, 90% of adults who had normal blood pressure at age 55 years then went on to develop hypertension.[3] Current clinical practice guidelines from the Joint National Committee (JNC) on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 8), published in December 2013, advocate general sitting blood pressure goals of 140/90 mm Hg for hypertensive patients younger than 60 years of age and 150/90 mm Hg for patients aged 60 years or older.[8]

Small changes in blood pressure are known to reduce the risk and mortality from cardiovascular events and stroke.[1,2,9,10] Small decreases in blood pressure (10 mm Hg systolic; 5 mm Hg diastolic) are known to lower the risk of stroke and heart failure by up to 50% and myocardial infarction by up to 25%.[9,11–14] Furthermore, the risk of mortality associated with stroke and ischemic heart disease has been estimated to double with each 20 mm Hg increase in

Pfizer Inc, New York, NY.
The studies included in these analyses were funded by Pfizer Inc. Editorial support was provided by Sarah Knott and Abegale Templar, PhD, of Engage Scientific, and funded by Pfizer Inc.
B. W. Jeffers, R. Bhambri, and J. Robbins are employees of Pfizer Inc.

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systolic blood pressure or with each 10 mm Hg in diastolic blood pressure from normotensive readings.[2]

Recent post hoc analyses have also emphasized the importance of an increased visit-to-visit variability of blood pressure in predicting cardiovascular events. Rothwell et al showed that visit-to-visit blood pressure variability was an independent and strong predictor of cardiovascular events.[15,16] To prevent stroke most effectively, blood pressure–lowering drugs should reduce mean blood pressure without increasing variability; ideally, they should reduce both.[16]

Data from randomized controlled trials suggest that treating hypertension in older patients, including octogenarians, may substantially reduce the risk of cardiovascular disease and death.[17] For example, the combined results of 6 major randomized controlled studies in patients aged 60–96 years demonstrated that the treatment of hypertension reduced the incidence of all cardiovascular complications by approximately 30%, fatal coronary events by 26%, and fatal stroke by 33%.[18] However, treatment still remains challenging in aging patients because of other comorbidities, age-related changes, and problems with compliance and adherence, particularly in those taking multiple medications.[17]

Calcium channel blockers, such as amlodipine, are an effective treatment option for hypertension because both the risk of cardiovascular events and all-cause mortality are reduced.[19–21] Furthermore, calcium channel blockers may have better efficacy for preventing stroke than other classes of antihypertensive agents,[13] including in older and elderly hypertensive patients.[22] Much of this advantage may be related to their robust blood pressure–lowering effects[9,23] and their beneficial effects on blood pressure variability compared with other antihypertensive classes.[16]

Calcium channel blockers are recommended in several international clinical guidelines as a first-line treatment for hypertension including patients 55 years or older.[1,7,24,25] Furthermore, the recent National Institute of Clinical Excellence (NICE) guidelines recommend calcium channel blockers as the first-line agent of choice in all patients aged 55 years or older or of African descent (Figure 1). Amlodipine has been shown to be an effective well-tolerated antihypertensive agent in older patients,[26–28] and its efficacy is not affected by age.[26]

Despite these well-documented benefits, hypertension remains a public health problem and is still frequently undiagnosed, untreated, or inadequately controlled, particularly among older individuals and the elderly.[17,29–32] In a recent large multinational study with 142,000 participants (mean age 50.4 years) conducted in 17 countries, 40.8% had hypertension. Of these, less than half (46.5%) were aware of their diagnosis, with blood pressure being controlled in only 32.5% of those being treated.[33]

As hypertension is still inadequately controlled in most patients, 2 post hoc pooled analyses of clinical studies using similar methodology were conducted to quantify any incremental benefit achieved when titrating hypertensive patients (including older patients, 55 years or older) from amlodipine 5 to 10 mg daily.

MATERIALS AND METHODS

Study design

This was an analysis of the safety and efficacy of amlodipine 5 mg titrated to 10 mg daily in patients with mild or moderate hypertension taken from 2 post hoc pooled analyses. Both analyses pooled data from the same patient groups included in 6 randomized controlled or open-label studies [A0531004, A053R0510, A0531085, A0531086, AML-NY-93-002, A0531044 (Pfizer data on file)] to increase the precision around blood pressure estimates (Table 1). Eligible patients were male and female, aged 18 years or older with mild or moderate hypertension (diastolic blood pressure: $\geq$95 to $\leq$120 mm Hg; systolic blood pressure: $>$140 to $<$200 mm Hg). The 6 studies included in this analysis enrolled patients who mirrored actual clinical practice. Namely, they were a mixture of treatment-naive patients and those who were uncontrolled on prior antihypertensive medication. All patients remained on stable treatment throughout the study.

The first analysis compared a subgroup of patients aged younger than 55 years with patients aged 55 years or older. The second analysis assessed patients of all age groups (mean age, 58.9 years). Although total study durations varied depending on the design, patients received amlodipine at a dose of 5 mg daily for 4–8 weeks and were then allowed to titrate up to 10 mg daily as required for an additional 4–8 weeks.

Analysis sets

The efficacy analysis included all patients in the intent-to-treat (ITT) population who received at least 1 dose of amlodipine and were titrated from 5 to 10 mg daily and had both a baseline (while on 5 mg) and follow-up (4–8 weeks after dose titration) blood pressure measurement. The safety analysis included all patients who received a least 1 dose of amlodipine and were titrated from 5 to 10 mg daily.

Study end points

Efficacy end points were the change from baseline in sitting systolic and sitting diastolic blood pressure and

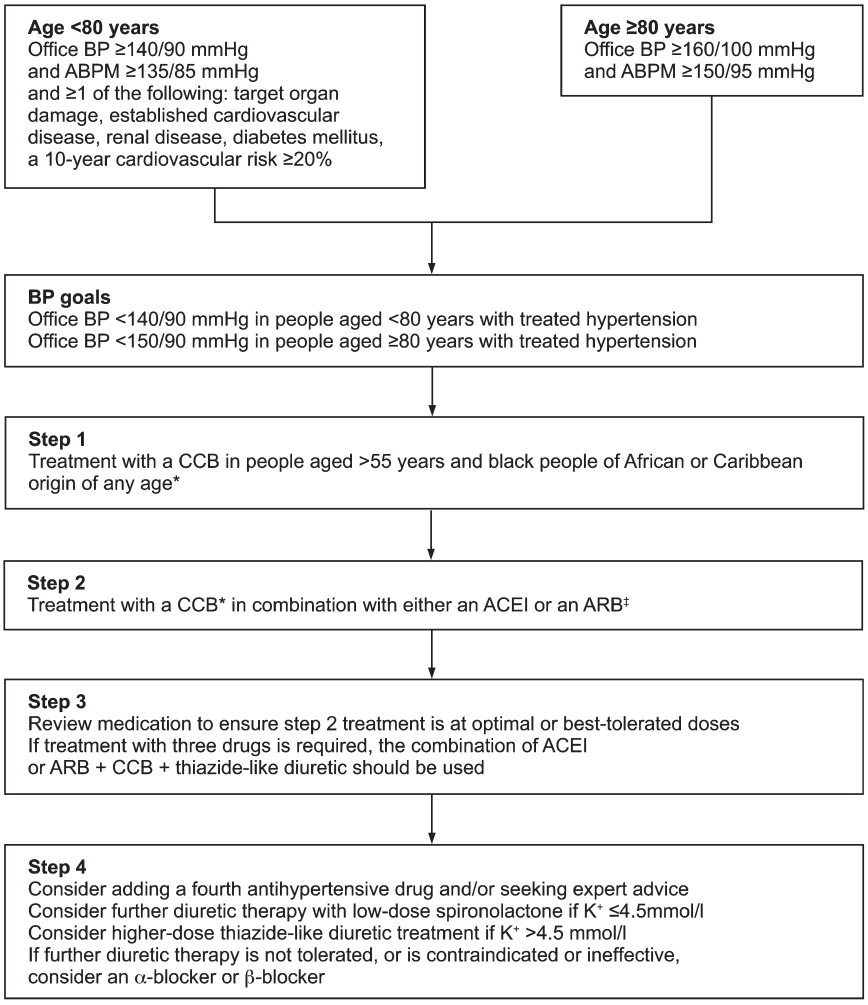

FIGURE 1. Algorithm for treatment of hypertension in older patients according to the 2011 NICE guideline recommendations.[25] *If a CCB is not suitable for treatment, for example, because of edema or intolerance, or if evidence or a high risk of heart failure exists, offer a thiazide-like diuretic (preference for chlorthalidone or indapamide). ‡For people of African or Caribbean family origin, consider an ARB in preference to an ACEI, in combination with a CCB. ABPM, ambulatory blood pressure monitoring; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BP, blood pressure; CCB, calcium channel blocker; NICE, National Institute for Health and Clinical Excellence.

the proportion of patients achieving their sitting blood pressure goal (140/90 mm Hg) at follow-up. Baseline was established before titration, that is, after patients had received amlodipine 5 mg daily for 4–8 weeks. The blood pressure goal was also assessed according to the recently revised JNC 8 guidelines of sitting blood pressure goal for persons aged younger than 60 years in general of 140/90 mg Hg and of 150/90 mm Hg for those aged 60 years or older.[8]

Safety was assessed by measurement of the frequency of treatment-emergent adverse events, treatment-emergent serious adverse events, and adverse events resulting in withdrawal from treatment.

Statistical analysis

The efficacy results were analyzed using descriptive statistics, single-sample paired *t* tests, and corresponding confidence intervals. The usual *t*-distribution confidence interval was applied to mean values. An exact confidence interval based on the binomial distribution was used for proportions.

RESULTS

Age-related pooled analysis

Of 706 patients included in the age-related patient analysis, 253 (35.8%) were aged younger than 55 years

Table 1. Studies used in the aged pooled analysis.

Study	Design	Study number/NCT number (if applicable)	Age <55 years (N = 253)	Age ≥55 years (N = 453)	Treatment duration, wk*
1	Randomized, multicenter, double-blind, parallel group	A0531004	0	80	18
2	Single arm, multicenter, open, noninterventional	A0531044	76	93	12
3	Randomized, multicenter, double-blind, parallel group	A0531085/NCT00415623	39	112	16
4	Single arm, long-term extension for A0531085	A0531086/NCT00443456	19	50	44
5	Randomized, multicenter, double-blind, parallel group	A053R0510	64	69	18
6	Single arm, multicenter, open, noninterventional	AML-NY-93-002	55	49	14

*Where applicable, total study duration included screening, baseline, and multiple study phases.
NCT number, http://www.clinicaltrials.gov/identifier.

and 453 (64.2%) aged 55 years or older (Table 2). The majority (391; 55.4%) were male, with a mean age of 47.2 years for patients younger than 55 years and 65.5 years for patients aged 55 years or older. Baseline (5 mg) mean systolic blood pressure and diastolic blood pressure were 147.4 [standard error (SE) 0.91] and 95.0 (SE 0.52) mm Hg, respectively, in patients aged younger than 55 years and 151.8 (SE 0.69) and 87.8 (SE 0.48) mm Hg, respectively, in patients aged 55 years or older.

Titration of amlodipine 5 to 10 mg daily resulted in a statistically significant decrease in both systolic blood pressure and diastolic blood pressure for both age subgroups. Amlodipine lowered mean blood pressure by (1) younger than 55 years: −12.8 mm Hg (SE = 0.90) for systolic blood pressure and −8.0 mm Hg (SE = 0.55) for diastolic blood pressure and (2) 55 years or older: −12.1 mm Hg (SE = 0.66) for systolic blood pressure and −6.7 mm Hg (SE = 0.39) for diastolic blood pressure (all $P < 0.0001$; Figure 2). In total, 45.8% and 39.3% of patients aged younger than 55 and 55 years or older, respectively, achieved their blood pressure goals. Applying the new JNC 8 hypertension guidelines (sitting blood pressure goal for age younger than 60 years is 140/90 mg Hg and for age 60 years or older is 150/90 mm Hg)[8] to our data, 51.0% of patients

Table 2. Baseline characteristics of the pooled populations.

Characteristic	Age pooled analysis		All patient pooled analysis*
	Age <55 years (N = 253)	Age ≥55 years (N = 453)	N = 710
Male, n (%)	150 (59.3); n = 253	241 (53.3); n = 452	394 (55.6); n = 708
Age, yr, mean (SD)	47.2 (5.36); n = 253	65.5 (7.00); n = 453	58.9 (10.9); n = 706
Weight, kg (SD)	80.5 (17.4); n = 250	74.0 (16.1); n = 453	76.3 (16.8); n = 705
BMI, kg/m² (SD)	28.1 (4.57); n = 249	27.2 (4.49); n = 451	27.5 (4.53); n = 701
Baseline (5 mg) blood pressure, mm Hg (SE)			
Systolic	147.4 (0.91)	151.8 (0.69)	150.3 (0.56)
Diastolic	95.0 (0.52); n = 246	87.8 (0.48); n = 443	90.4 (0.38); n = 693
Diabetes, n (%)	26 (10.3); n = 253	72 (15.9); n = 453	100 (14.1); n = 710
History of CHD, n (%)	5 (2.0); n = 253	26 (5.7); n = 453	31 (4.4); n = 710
Prior antihypertensive drug use, n (%)	130 (51.4); n = 253	243 (53.6); n = 453	376 (53.0); n = 710

*Analysis included 4 additional patients of an unspecified age.
BMI, body mass index; CHD, coronary heart disease.

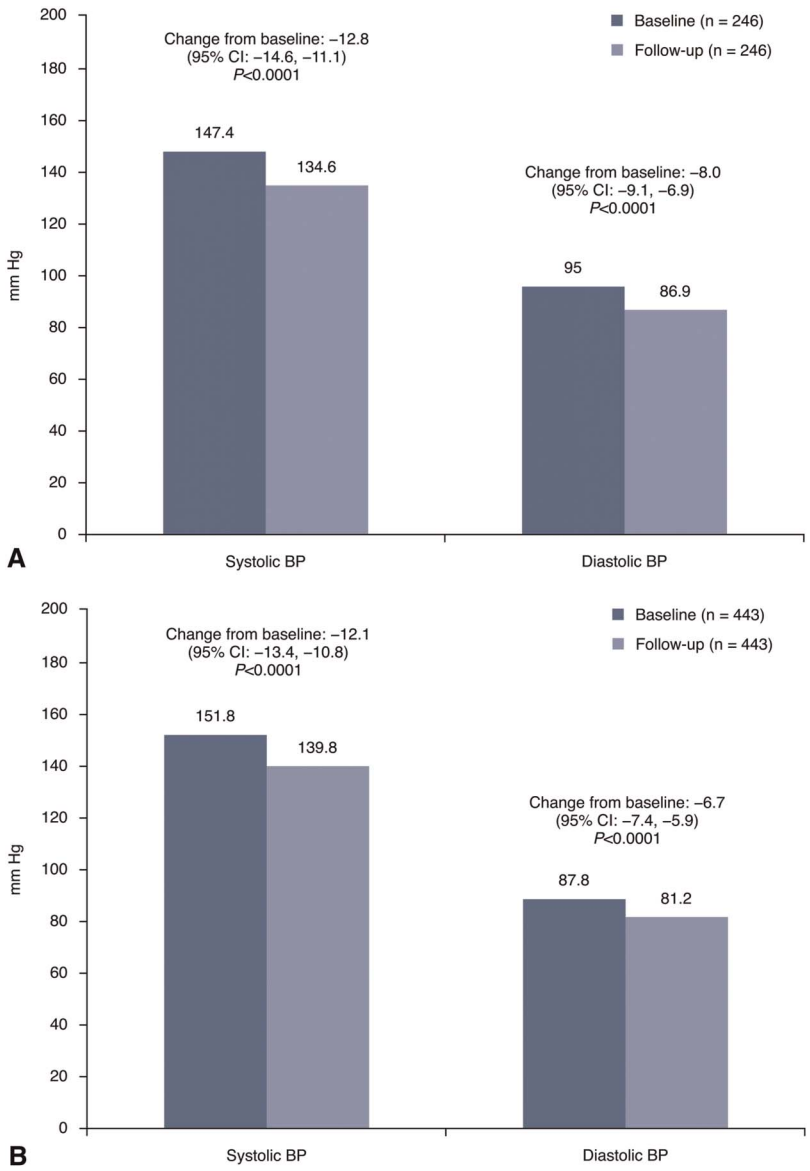

FIGURE 2. Change in blood pressure (baseline established on 5 mg) in patients aged (A) younger than 55 years and (B) 55 years or older titrated from amlodipine 5 to 10 mg. Analyses conducted using the intent-to-treat population. *P* values and corresponding CIs were computed using Student single-sample paired *t* test. CI, confidence interval; BP, blood pressure.

in the group of younger than 55 years and 64.2% of patients in the age group of 55 years or older achieved these blood pressure goals.

A total of 239/253 (94.5%) patients younger than 55 years completed the study and 14 (5.5%) discontinued, similarly 419/453 (92.5%) patients of age 55 years or older completed the study and 34 (7.5%) discontinued. Reasons for discontinuation included adverse events [n = 37 (5.2%)]; withdrawal of consent and other reasons [both n = 4 (0.6%)], protocol violation [n = 2 (0.3%)], and insufficient clinical response [n = 1 (0.15%)].

In total, 62 (24.5%) patients aged younger than 55 years experienced 96 adverse events, of which, system organ class general disorders (7.1%), infections (6.3%), gastrointestinal disorders (4.7%), and musculoskeletal disorders (4.3%) were the most common; 9 patients (3.6%) discontinued treatment due to an adverse event (Table 3), with peripheral edema being the reason for withdrawal in 2 or more patients. In all, 136 (30.0%) patients aged 55 years or older experienced 217 adverse events, of which general disorders (10.4%), infections (8.6%), gastrointestinal disorders (4.6%), and musculoskeletal disorders (4.2%) were

Table 3. Incidence of adverse events.

Characteristic	Age pooled analysis		All patient pooled analysis* (N = 710)
	Age <55 years (N = 253)	Age ≥55 years (N = 453)	
Number of adverse events	96	217	313
Patients with adverse events, n (%)	62 (24.5)	136 (30.0)	198 (27.9)
Patients with serious adverse events, n (%)	1 (<1.0)	5 (1.1)	6 (0.8)
Patients discontinued due to adverse events, n (%)	9 (3.6)	14 (3.1)	23 (3.2)
Most common all-cause adverse events, n (%)			
General disorders	18 (7.1)	47 (10.4)	65 (9.2)
Infections	16 (6.3)	39 (8.6)	55 (7.7)
Gastrointestinal disorders	12 (4.7)	21 (4.6)	33 (4.6)
Musculoskeletal disorders	11 (4.3)	19 (4.2)	30 (4.2)

*Analysis included 4 additional patients of an unspecified age.

most common; 14 patients (3.1%) discontinued treatment due to an adverse event (Table 3), with peripheral edema, chest pain, joint swelling, headache, hypoesthesia, and dyspnea all resulting in the discontinuation of treatment in 2 or more patients.

All patients pooled analysis

Given that results were consistent between the 2 age subgroups, data were also pooled to increase the level of precision for the end points. A total of 710 patients (includes 4 additional patients of unspecified age) were included in the ITT analysis (Table 2). The majority were male [394/710 (55.6%)] with a mean age of 58.9 (SD = 10.9) years. At baseline (5 mg), mean systolic blood pressure was 150.3 (SE = 0.56) mm Hg and diastolic blood pressure was 90.4 (SE = 0.38) mm Hg.

Titration of amlodipine from 5 to 10 mg daily in patients not responding to treatment with the 5 mg dose resulted in a statistically significant decrease in blood pressure: systolic blood pressure by −12.4 mm Hg (SE = 0.53) and diastolic blood pressure by −7.2 mm Hg (SE = 0.32) (both $P < 0.0001$; Figure 3). Overall,

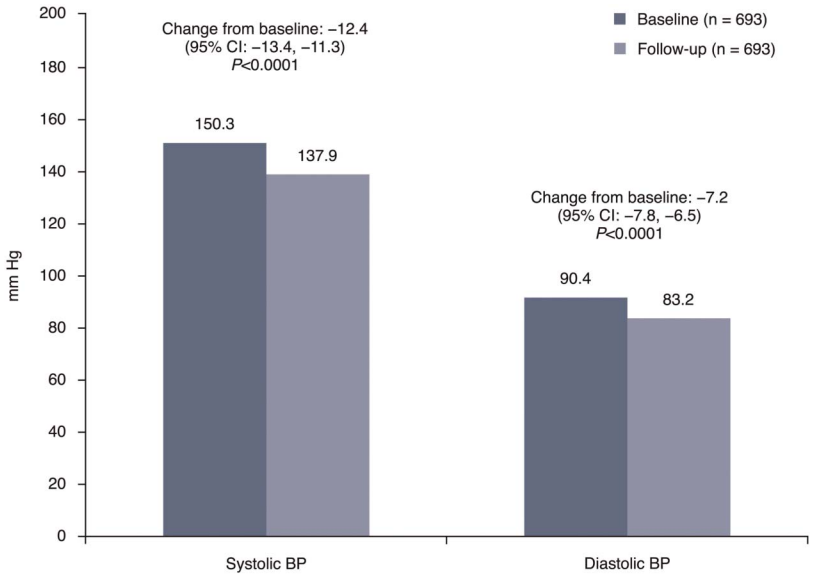

FIGURE 3. Change in blood pressure from baseline (established on 5 mg) to follow-up in hypertensive patients titrated from amlodipine 5 to 10 mg once daily. Analyses conducted using the intent-to-treat population. *P* values and corresponding CIs were computed using Student single-sample paired *t* test. Baseline established while on amlodipine 5 mg. Analysis included 4 additional patients of an unspecified age.

295/710 (41.5%) patients achieved their blood pressure goal. Using the new JNC 8 hypertension guidelines (sitting blood pressure goal for age younger than 60 years is 140/90 mg Hg and for age 60 years or older is 150/90 mm Hg), 59.4% of patients younger than 55 years achieved their blood pressure goals.

A total of 662 (93.2%) patients completed the study and 48 (6.8%) discontinued. Reasons for discontinuation included adverse events [n = 37 (5.2%)] and withdrawal of consent and other reasons [both n = 4 (0.6%)].

In total, 313 adverse events were reported by 198/710 (27.9%) patients (Table 3). The most common adverse events were general disorders [n = 65 (9.2%)], infections [n = 55 (7.7%)], gastrointestinal disorders [n = 33 (4.6%)], and musculoskeletal disorders [n = 30 (4.2%)]. Serious adverse events were reported by 6 (0.6%) patients. Twenty-three (3.2%) patients discontinued treatment due to an adverse event with chest pain, joint swelling, peripheral edema, headache, hypoesthesia, and dyspnea all resulting in the discontinuation of treatment in 2 or more patients.

DISCUSSION

Hypertension remains a public health concern, despite numerous outcome trials demonstrating the benefits of blood pressure lowering among older individuals with hypertension; high blood pressure is more prevalent, less well controlled, and more severe in this patient population.[4] Compared with younger patients with similar blood pressure, older and elderly hypertensive patients have lower cardiac output, higher peripheral resistance, wider pulse pressure, lower intravascular volume, and lower renal blood flow.[34] They are also more likely than younger patients to suffer from the complications of hypertension (such as stroke and myocardial infarction) and have multiple comorbidities.[17] Older patients are also more prone to have resistant hypertension and thus require multiple drugs to control their blood pressure, with many drug-related adverse effects.[17] All these factors should be considered when treating older patients with hypertension.

Many outcome trials in older and elderly patients have been based on the use of thiazide diuretics or β-blockers. These agents may aggravate coexisting diseases, such as hyponatremia, peripheral vascular disease, insulin sensitivity, and weight gain, and are often unsuitable for older and elderly patients.[20,35] Short-term studies have shown that calcium channel blockers seem to be most effective in reducing cardiovascular disease outcomes in older hypertensive patients.[36] They have the following advantages as antihypertensive agents: maintenance of cerebral, coronary, renal, and peripheral circulations at good levels despite showing a secure antihypertensive effect and an absence of adverse effects on glucose and lipid metabolism.

Calcium channel blockers have performed particularly well in preventing stroke in older hypertensive patients, which is of major interest for both patients and their physicians. A recent meta-analysis found that dihydropyridine calcium channel blockers reduced stroke by 10% compared with other active therapies.[22] Much of this advantage may be related to their strong blood pressure–lowering effects, which were evident in both the Valsartan Antihypertensive Long-term Use Evaluation (VALUE) and Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) trials, where 4–5 lower brachial artery systolic blood pressure levels were noted in the first few months of therapy compared with angiotensin receptor antagonists or β-blocker-based treatment.[9,23]

Amlodipine has been shown to be an effective antihypertensive agent in older patients and the elderly.[27] Indeed, in a recent large community-based study in the US, amlodipine was actually more effective in elderly patients compared with those aged younger than 65 years.[26] Tolerability has been shown to be good or excellent in most patients[20,37] and, because amlodipine is slowly absorbed, the tendency for vasodilatory side effects is reduced. It also has low hepatic metabolism (including first-pass metabolism) and a long elimination half-life, which allows effective blood pressure control with once-daily dosing, an important promoter of compliance,[38] particularly in older patients who are likely to be taking several medications. In contrast to short-acting calcium channel blockers, trial data suggest that amlodipine may be used in hypertensive patients with concomitant heart failure.[39] Available data also suggest a greater capability of calcium channel blockers, such as amlodipine, in comparison to other therapeutic classes to attenuate long- and short-term blood pressure variability.[16,40]

These 2 post hoc analyses showed that titration of amlodipine from 5 mg to 10 mg daily significantly ($P < 0.0001$) decreased systolic and diastolic blood pressure in younger and older age groups whose blood pressure did not reach target levels. This incremental change in systolic blood pressure of approximately 12 mm Hg is vital in reducing the potential occurrence of future cardiovascular and cerebrovascular events. Just by titrating the amlodipine dose to 10 mg, blood pressure goals were achieved in approximately 40% of patients aged younger than 55 years or 55 years or older. Amlodipine 10 mg was well tolerated in both analyses with a low incidence of adverse events. Peripheral

edema occurred in approximately 7.1% of patients overall, consistent with previous findings.[41]

The present analysis is subject to several limitations. First, it was a post hoc analysis pooled from 6 studies with differing designs (randomized controlled and open-label), in which there were large differences in sample sizes. When the studies vary in size, the larger studies can have a greater influence on the pooled results. Three of the trials included (accounting for 342 of the 706 participants in the analysis) were open-label and could be subject to types of bias commonly associated with such designs. Finally, it should be noted that the trials used in this analysis may have had differences in characteristics of participants (ie, receiving monotherapy or combination therapy—although any background therapy was kept constant during the assessment period, treated blood pressure or treatment naive, comorbidities, etc.).

These results are similar to another post hoc analysis, where the titration of amlodipine from 5 to 10 mg daily significantly decreased both systolic blood pressure and diastolic blood pressure in Asian patients with mild-to-moderate hypertension.[42] Amlodipine 10 mg lowered systolic blood pressure by −13.3 mm Hg (95% CI: −15.5 to −11.0) and diastolic blood pressure by −9.2 mm Hg (95% CI: −10.6 to −7.8) at the final visit ($P < 0.0001$ for both).

The results also support those of large-scale clinical studies in patients with hypertension where amlodipine uptitrated to 10 mg once daily controlled blood pressure and suppressed cardiovascular events.[9,23,43–45] The wealth of studies reporting not only the dangers of sustained hypertension in older patients on the risk of cardiovascular events but also the benefits of uptitration to amlodipine 10 mg in reducing elevated blood pressure highlights the importance of encouraging this strategy in prescribing patterns.

Increasing amlodipine from 5 to 10 mg could also provide an alternative to initiate combination therapy, especially in patients with very high blood pressure and those at greater cardiovascular risk. Indeed, recent guidelines, such as NICE, still advocate the use of monotherapy with a calcium channel blocker in the older patient population (55 years or older) before initiating combination therapy.[25] Our results showed that not only will this result in clinically meaningful incremental blood pressure lowering but that a significant portion of the patents will also achieve their blood pressure targets.

CONCLUSIONS

Titration of amlodipine from 5 to 10 mg once daily significantly decreased both systolic blood pressure and diastolic blood pressure in patients with hypertension across both age subgroups (younger than 55 years vs. 55 years or older). Blood pressure goals were achieved safely in ~40% of patients. This is clinically relevant as advancing age is associated with hypertension and an increased risk of nonfatal and fatal cardiovascular events and stroke.

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