Uptitrating amlodipine significantly reduces blood pressure in diabetic patients with hypertension: a retrospective, pooled analysis

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Abstract: Diabetic patients with hypertension are approximately twice as likely to develop cardiovascular disease as non-diabetic patients with hypertension. Given that hypertension affects ~60% of patients with diabetes, effective blood pressure (BP) management is important in this high-risk population. This post-hoc analysis pooled data from six clinical studies to quantify additional BP efficacy achieved when titrating hypertensive diabetic patients from amlodipine 5 mg to 10 mg. Approximately half of the diabetic patients were male (44/98; 44.9%) with a mean (standard deviation [SD]) age of 60.6 (9.6) years and a baseline mean (standard error [SE]) systolic blood pressure/diastolic blood pressure (SBP/DBP) of 150.8 (1.30)/87.5 (0.94) mmHg while on amlodipine 5 mg (159.1 [1.40]/92.6 [0.94] mmHg prior to treatment). In comparison, 350/610 (57.4%) non-diabetic patients were male with a mean (SD) age of 58.7 (11.1) years and baseline mean (SE) SBP/DBP of 150.3 (0.62)/90.9 (0.41) mmHg while on amlodipine 5 mg (160.0 [0.67]/96.2 [0.45] mmHg prior to treatment). Increasing amlodipine from 5 mg to 10 mg lowered sitting SBP by −12.5 mmHg (95% confidence interval (CI): −15.5, −9.5; P<0.0001) and DBP by −6.0 mmHg (−7.4, −4.6; P<0.0001) in diabetic patients; and SBP by −12.4 mmHg (−13.5, −11.3; P<0.0001) and DBP by −7.3 mmHg (−8.0, −6.7; P<0.0001) in non-diabetic patients. In total, 12.0% (95% CI: 6.4, 20.0) of diabetic patients achieved their BP goal versus 46.4% (42.4, 50.4) of non-diabetic patients after titration to amlodipine 10 mg. Overall, 22.0% of diabetic patients experienced 31 adverse events (AEs) and 28.9% of non-diabetic patients experienced 282 AEs. Serious AEs were reported by one (1.0%) diabetic and five (0.8%) non-diabetic patients. In this analysis, increasing amlodipine from 5 mg to 10 mg produced a clinically significant reduction in the BP of diabetic hypertensive patients, similar to non-diabetic patients, highlighting the importance of optimizing amlodipine titration in this high-risk population.

Keywords: hypertension, diabetes, calcium channel blockers, cardiovascular disease prevention, efficacy

Background

Hypertension and diabetes each represent a major public health challenge worldwide. They frequently co-exist, thus compounding the risk of vascular morbidity and mortality associated with these conditions individually. The worldwide prevalence of hypertension in the year 2000 was estimated to be 26.4% (972 million adults), with a predicted rise of approximately 60% to a total of 1.56 billion adults (29.2%) by 2025.1 Recent estimates put global diabetes prevalence in the year 2011 at 8.3% (366 million adults), increasing to 9.9% (552 million adults; approximately 50% rise) by 2030.2

Higher levels of blood pressure (BP) are a powerful predictor of cardiovascular disease (CVD), including coronary heart disease (CHD) and stroke.3-4 Hypertension...
affects approximately 60% of patients with diabetes, and is
twice as likely to occur in diabetic patients compared with
their age-matched non-diabetic counterparts. Compared
with diabetic individuals who are normotensive, those with
concomitant hypertension exhibit about a two-fold increase
in the risk of cardiovascular events and death. Moreover,
hypertension has been found to be a stronger predictor of
cardiovascular events as compared with diabetes.

Given the high prevalence of hypertension in diabetic
patients, combined with the observed increased cardio-
vascular risk attributable to hypertension, appropriate BP
management strategies should be employed to mitigate the
risk of future CVD events. The Joint National Committee
on Prevention, Detection, Evaluation, and Treatment of
High Blood Pressure (JNC 8) advocate a sitting BP goal of
140/90 mmHg for hypertensive patients with diabetes and/or
chronic kidney disease patients. Similarly, the American
Diabetes Association (ADA) guidelines and joint guide-
lines from the European Society of Hypertension (ESH)/
European Society of Cardiology (ESC) recommend a BP
goal of <140/80 mmHg and <140/85 mmHg, respectively, for patients with diabetes. The caveat is that a lower
systolic blood pressure (SBP) target (ie, <130 mmHg)
may be appropriate for some diabetic individuals, such as
younger patients or those at higher risk of stroke, if it can
be achieved with fewer drugs and without adverse effects.
A similarly revised BP goal of <140/85 mmHg has been
proposed for those with diabetes in the latest joint guide-
lines for hypertension management from the ESH/ESC. However, effective therapeutic control of BP in patients with
concomitant diabetes and hypertension can be challenging,
and many patients are not achieving desired BP goals despite
antihypertensive medication use.

Antihypertensive regimens based on angiotensin-
converting-enzyme inhibitors (ACEIs), angiotensin II recep-
tor blockers (ARBs), calcium channel blockers (CCBs),
and diuretics/beta-blockers are all broadly comparable for
reducing cardiovascular risk in patients with and without
diabetes. Amlodipine (Pfizer Inc., New York, NY, USA)
is a well-established, long-acting CCB for the treatment of
hypertension, including patients with diabetes. Studies
in hypertensive patients have highlighted the additional
benefit of titrating amlodipine from 5 mg to 10 mg once daily
with regard to lowering BP, including Asian patients. However, because the efficacy of increasing amlodipine dose
from 5 mg to 10 mg has thus far only been evaluated in a
small number of patients with hypertension and diabetes,
we conducted this post-hoc analysis of 710 patients with
known diabetic status from six clinical trials, which included
100 diabetic patients. The objective of this analysis was to
assess the incremental effect of amlodipine titration to 10 mg
daily on BP-lowering efficacy in patients with concomitant
diabetes and hypertension who had not responded sufficiently
to treatment with the 5 mg dose.

Methods

Study selection criteria

Studies selected for this analysis were all Pfizer-
sponsored studies of amlodipine treatment for mild to
moderate hypertension for which there was patient-level
data, diabetic status was known, and dose was titrated
from 5 mg to 10 mg.

Study design and participants

This post-hoc analysis used pooled data from six random-
ized controlled or open-label clinical studies assessing the
efficacy and safety of amlodipine 5 mg daily titrated to
10 mg daily in patients with mild or moderate hypertension
(Table 1). Although total study durations varied depending
on the design, patients in this analysis received amlodipine
at a dose of 5 mg daily for 4–8 weeks followed by titration
up to 10 mg daily as required for an additional 4–8 weeks.
Patients were stratified into two subgroups based on their
diabetes status at the time of entry into the study (those with
diabetes versus those without diabetes), derived from their
medical history.

Study endpoints and assessments

Efficacy endpoints were change from baseline in sitting SBP
diastolic blood pressure (DBP) to the specified time point,
and proportion of patients who achieved the sitting BP goal at
follow-up. Depending on the study, sitting BP was measured
once or twice at each visit. Each patient’s response for a given
visit was the average of the multiple measurements, or the
single measurement if only one sitting BP was available.
The sitting BP goal was <130/80 mmHg for patients with
diabetes and <140/90 mmHg for patients without diabetes.
The BP goal was also assessed according to recently revised
guidelines of a sitting BP goal of <140/80 mmHg (ADA
guidelines) and a sitting BP goal for age <60 years,
140/90 mmHg; age ≥60 years, 150/90 mmHg (JNC 8
guidelines) for both subgroups.

Safety endpoints were frequency of treatment-emergent
adverse events (AEs) (all causality), treatment-emergent
serious AEs (all causality), and AEs resulting in withdrawal from treatment (all causality).

Statistical analyses
Patients without a diabetes status at study entry were excluded from the analysis. The efficacy analysis included all patients in the intent-to-treat population who received at least one dose of amlodipine, were titrated from 5 mg to 10 mg; where applicable, total study duration included screening, baseline, and multiple study phases; these trials started before September 2008, before clinical studies were registered at http://www.clinicaltrials.gov; NCT Number, ClinicalTrials.gov Identifier.

Results
Study population
A total of 710 patients with known diabetic status were included in this analysis (693 with complete BP data). Of the 100 patients (14.1%) with diabetes at study entry, four patients (4.0%) discontinued from the study; all four discontinuations were due to AEs. Of the 610 patients (85.9%) without diabetes at study entry, 44 patients (7.2%) discontinued from the study. Reasons for discontinuation among non-diabetic patients included: AEs (n=33; 5.4%), no longer willing to participate (n=4; 0.7%), protocol violation (n=2; 0.3%), insufficient clinical response (n=1; 0.2%), and other reason (n=4; 0.7%).

Patients with diabetes were mostly female (55.1%) with a mean (standard deviation [SD]) age of 60.6 (9.6) years and a baseline mean (standard error [SE]) SBP/DBP prior to amlodipine treatment of 159.1 (1.40)/92.6 (0.94) mmHg (Table 2); mean (SE) SBP/DBP was 150.8 (1.30)/87.5 (0.94) mmHg while on amlodipine 5 mg treatment. Patients without diabetes were mostly male (57.4%) with a mean (SD) age of 58.7 (11.1) years and a baseline mean (SE) SBP/DBP prior to amlodipine treatment of 160.0 (0.67)/96.2 (0.45) mmHg

### Table I Studies used in the pooled analysis

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Study number/ NCT number (if applicable)</th>
<th>With diabetes (N=100)</th>
<th>Without diabetes (N=610)</th>
<th>Patient population</th>
<th>Total study duration</th>
<th>Study dates</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Randomized, multicenter, double-blind, parallel group</td>
<td>A0531004&lt;sup&gt;a&lt;/sup&gt;</td>
<td>10</td>
<td>70</td>
<td>Washed out of antihypertensives or treatment naïve</td>
<td>18 weeks</td>
<td>6 March 2001–14 October 2003</td>
</tr>
<tr>
<td>2</td>
<td>Single arm, multicenter, open, non-intervention</td>
<td>A0531044&lt;sup&gt;a&lt;/sup&gt;</td>
<td>38</td>
<td>134</td>
<td>Washed out of antihypertensives or treatment naïve</td>
<td>12 weeks</td>
<td>1 November 2001–31 March 2002</td>
</tr>
<tr>
<td>3</td>
<td>Randomized, multicenter, double-blind, parallel group</td>
<td>A0531085 NCT00415623</td>
<td>26</td>
<td>125</td>
<td>Uncontrolled on current antihypertensive at screening, doses stable throughout the study</td>
<td>16 weeks</td>
<td>6 January 2007–20 October 2007</td>
</tr>
<tr>
<td>4</td>
<td>Single arm, long-term extension for NCT00415623</td>
<td>A0531086 NCT0043456</td>
<td>12</td>
<td>57</td>
<td>Uncontrolled on current antihypertensive at screening, doses stable throughout the study</td>
<td>44 weeks</td>
<td>2 May 2007–11 June 2008</td>
</tr>
<tr>
<td>5</td>
<td>Randomized, multicenter, double-blind, parallel group</td>
<td>A053R0510&lt;sup&gt;c&lt;/sup&gt;</td>
<td>12</td>
<td>121</td>
<td>Washed out of antihypertensives or treatment naïve</td>
<td>18 weeks</td>
<td>Study dates unavailable</td>
</tr>
<tr>
<td>6</td>
<td>Single arm, multicenter, open, non-intervention</td>
<td>AML-NY-93002&lt;sup&gt;c&lt;/sup&gt;</td>
<td>2</td>
<td>103</td>
<td>Uncontrolled on current antihypertensive at screening, doses stable throughout the study, or treatment naïve</td>
<td>14 weeks</td>
<td>20 November 1993–30 April 1995</td>
</tr>
</tbody>
</table>

Notes: All Pfizer-sponsored studies of amlodipine treatment for mild to moderate hypertension for which there were patient-level data, diabetic status was known, and dose was titrated from 5 mg to 10 mg; where applicable, total study duration included screening, baseline, and multiple study phases; these trials started before September 2008, before clinical studies were registered at http://www.clinicaltrials.gov; NCT Number, ClinicalTrials.gov Identifier. All Pfizer-sponsored studies of amlodipine treatment for mild to moderate hypertension for which there were patient-level data, diabetic status was known, and dose was titrated from 5 mg to 10 mg; where applicable, total study duration included screening, baseline, and multiple study phases; these trials started before September 2008, before clinical studies were registered at http://www.clinicaltrials.gov; NCT Number, ClinicalTrials.gov Identifier.
Table 2 Baseline characteristics of the study population stratified by diabetes status

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>With diabetes (N=100)</th>
<th>Without diabetes (N=610)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male, n (%)</td>
<td>44 (44.9)ᵃ ³ ³ ³</td>
<td>350 (57.4)</td>
</tr>
<tr>
<td>Mean age, years (SD)</td>
<td>60.9 (6.4)</td>
<td>58.7 (11.0)</td>
</tr>
<tr>
<td>Mean SBP/DBP, mmHg (SE)</td>
<td>159.1 (1.40)</td>
<td>160.0 (0.67)</td>
</tr>
<tr>
<td>Mean weight, kg (SD)</td>
<td>82.1 (16.80)¹</td>
<td>75.4 (16.68)</td>
</tr>
<tr>
<td>Mean BMI, kg/m² (SD)</td>
<td>30.3 (4.60)</td>
<td>27.0 (4.36)</td>
</tr>
<tr>
<td>History of CHD, n (%)</td>
<td>7 (7.0)</td>
<td>24 (3.9)</td>
</tr>
<tr>
<td>Prior antihypertensive use, n (%)</td>
<td>64 (64.0)</td>
<td>312 (51.1)</td>
</tr>
<tr>
<td>Prior antihypertensive use by class, n (%) ³ ³ ³</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACEI</td>
<td>42 (42.0)</td>
<td>139 (22.8)</td>
</tr>
<tr>
<td>ARB</td>
<td>4 (4.0)</td>
<td>49 (8.0)</td>
</tr>
<tr>
<td>Alpha receptor agonist/antagonist</td>
<td>2 (2.0)</td>
<td>10 (1.6)</td>
</tr>
<tr>
<td>Alpha2-Adrenergic Agonist</td>
<td>2 (2.0)</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>BB</td>
<td>14 (14.0)</td>
<td>64 (10.5)</td>
</tr>
<tr>
<td>CCB</td>
<td>37 (37.0)</td>
<td>140 (23.0)</td>
</tr>
<tr>
<td>Centrally-acting antihypertensive</td>
<td>5 (5.0)</td>
<td>8 (1.3)</td>
</tr>
<tr>
<td>Diuretics</td>
<td>10 (10.0)</td>
<td>80 (13.1)</td>
</tr>
<tr>
<td>Ergot alkaloid</td>
<td>1 (0.2)</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>Vasodilator</td>
<td>1 (0.2)</td>
<td>1 (0.2)</td>
</tr>
</tbody>
</table>

Notes: N=98 (two patients with sex not specified); ³ patients could have been taking more than one medication; P<0.05.
Abbreviations: BMI, body mass index; CHD, coronary heart disease; DBP, diastolic blood pressure; SBP, systolic blood pressure; SD, standard deviation; SE, standard error; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BB, beta blocker; CCB, calcium channel blocker.

(Table 2); mean (SE) SBP/DBP was 150.3 (0.62)/90.9 (0.41) mmHg while on amlodipine 5 mg treatment. Patients with diabetes weighed more and had a higher body mass index than their non-diabetic counterparts (Table 2).

Blood pressure levels and goal attainment

In patients with diabetes, titration of amlodipine 5 mg to 10 mg lowered sitting SBP by −12.5 mmHg (95% CI: −15.5, −9.5, P<0.0001) and DBP by −6.0 mmHg (95% CI: −7.4, −4.6; P<0.0001) from baseline (established while patients were on amlodipine 5 mg treatment) to follow-up (Figure 1A). Mean (SE) SBP/DBP at follow-up in diabetic patients was 138.3 (1.35)/81.5 (0.86) mmHg. Similarly, in patients without diabetes, titration to amlodipine 10 mg lowered sitting SBP by −12.4 mmHg (95% CI: −13.5, −11.3; P<0.0001) and DBP by −7.3 mmHg (95% CI: −8.0, −6.7; P<0.0001) from baseline (established on amlodipine 5 mg treatment) to follow-up (Figure 1B). Mean (SE) SBP/DBP at follow-up in non-diabetic patients was 137.9 (0.56)/83.5 (0.36) mmHg.

Not surprisingly, fewer patients with diabetes achieved their desired BP goal compared with non-diabetic patients. In total, 12/100 patients with diabetes (12.0%; 95% CI: 6.4, 20.0) attained a BP <140/80 mmHg; 283/610 patients without diabetes (46.4%; 95% CI: 42.4, 50.4) attained a BP <140/90 mmHg. Slightly more diabetic patients (25/100 [25%; 95% CI: 16.9, 34.7]) achieved the newly revised ADA target BP levels of <140/80 mmHg. Even more diabetic patients (64/100 [64%; 95% CI: 53.8, 73.4]) achieved the new JNC 8 target BP goals of 140/90 (aged ≤60 years) or 150/90 (aged ≥60 years) mmHg.

Safety

Overall, 22/100 patients with diabetes (22.0%) experienced 31 AEs and 176/610 patients without diabetes (28.9%) experienced 282 AEs (Table 3). The AEs most frequently reported by patients with diabetes were: peripheral edema (n=4; 4.0%), sinusitis (n=2; 2.0%), and upper respiratory tract infection (n=2; 2.0%). The AEs most frequently reported by patients without diabetes were: peripheral edema (n=46; 7.5%), nasopharyngitis (n=24; 3.9%), back pain (n=8; 1.3%), and upper respiratory tract infection (n=6; 1.0%).

Serious AEs were reported by one patient (0.1%) with diabetes (event: ankle fracture) and five patients (0.8%) without diabetes (events: cardiomyopathy, pneumonia, facial bone fracture, intervertebral disk protrusion, gingival cancer, cerebrovascular accident, cerebrovascular disorder, Table 3). Three patients with diabetes (3.0%) and 20 patients without diabetes (3.3%) withdrew from treatment due to an AE (Table 3). Adverse events that led to treatment withdrawal in patients with diabetes included: peripheral edema (n=1; 1.0%), headache (n=1; 1.0%), and hypertension (n=1; 1.0%). AEs that led to treatment withdrawal in patients without diabetes included: peripheral edema (n=8; 1.3%), joint swelling (n=2; 0.3%), and dyspnea (n=2; 0.3%).

Discussion

This retrospective, pooled analysis has shown that increasing amlodipine from 5 mg to 10 mg daily provided a clinically and statistically significant incremental reduction in sitting SBP and DBP in patients with concomitant diabetes and hypertension who had not responded sufficiently to treatment with the 5 mg dose. Furthermore, the incremental benefit on BP lowering achieved with amlodipine titration was similar in both diabetic and non-diabetic patient populations. This is similar to what has previously been observed in other patient populations, such as Asian patients with hypertension. Amlodipine 10 mg was also well tolerated in patients with diabetes, demonstrating a safety profile similar to that observed in the non-diabetic patient group and previous studies involving high-dose amlodipine.23,24,26,29,30
Up titrating amlodipine in diabetic patients with hypertension

The age-adjusted prevalence of diagnosed diabetes in the general US adult population has recently been estimated at 8.5%. However, in this analysis, diabetes prevalence in this patient population with mild or moderate hypertension was nearly double that of the current national estimate, at 14.1%.

Patients with hypertension have been shown to have a 2.5-fold excess risk of developing diabetes over 6 years of follow-up compared with non-hypertensive individuals (relative risk: 2.43; 95% CI: 2.16, 2.73). Similarly, hypertension is twice as likely to occur in patients with diabetes versus those

Figure 1 Systolic blood pressure at baseline and follow-up in (A) patients with diabetes and (B) patients without diabetes titrated from amlodipine 5 mg to 10 mg.

Notes: Analyses were conducted using the intent-to-treat population. Baseline was established while patients were on amlodipine 5-mg treatment; follow-up was determined using a last-observation-carried-forward analysis.

Abbreviations: BP, blood pressure; CI, confidence interval.
without diabetes, with prevalence in diabetic patients of approximately 60%. Although hypertension and diabetes individually predict cardiovascular morbidity and mortality, the comorbidity of these two conditions only serves to exacerbate the cardiovascular risk associated with either condition in isolation. Hence, appropriate management of cardiovascular risk factors, with particular emphasis on the early detection and effective treatment of hypertension in patients with diabetes, is paramount to reduce CVD burden in these high-risk individuals.

Even modest reductions in BP have the potential to substantially reduce cardiovascular morbidity and mortality. A meta-analysis of data from 61 prospective observational studies on deaths from vascular disease among individuals with no known vascular disease at baseline found that a 2 mmHg reduction in SBP could lower mortality from stroke by 10% and from ischemic heart disease or other vascular causes by 7%. Similarly, the results of a prospective, observational study in patients with diabetes showed that a 10 mmHg decrease in SBP was associated with reductions in the risk of diabetes-related complications (including myocardial infarction, sudden death, angina, and stroke; relative risk reduction: 12%; 95% CI: 10%, 14%; *P* < 0.0001), diabetes-related deaths (including death from myocardial infarction, sudden death, and stroke; relative risk reduction: 15%; 95% CI: 12%, 18%; *P* < 0.0001), and myocardial infarction (relative risk reduction: 11%; 95% CI: 7%, 14%; *P* < 0.0001). Thus, the observed incremental reduction in BP by up titrating amlodipine to 10 mg (−12.5 mmHg in SBP, −6.0 mmHg in DBP) in diabetic patients would be expected to drastically reduce the occurrence of diabetes-related complications.

Numerous clinical trials of antihypertensive agents have demonstrated the benefit of BP lowering on cardiovascular outcomes in a range of patient populations, including patients with diabetes. The UK Prospective Diabetes Study compared tight control of BP to <150/85 mmHg with less rigorous control of BP to <180/105 mmHg in hypertensive patients with diabetes. Patients allocated to tight BP control experienced a 24% reduction in the relative risk of diabetes-related endpoints (including sudden death, myocardial infarction, angina, and stroke; 95% CI: 8%, 38%; *P* = 0.0046), a 32% reduction in diabetes-related deaths (including death from myocardial infarction, sudden death, and stroke; 95% CI: 6%, 51%; *P* = 0.019), and a 44% reduction in the risk of stroke (95% CI: 11%, 65%; *P* = 0.013) compared with patients allocated to less rigorous BP control. The Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE) trial demonstrated that significant reductions in SBP and DBP (−5.6 mmHg and −2.2 mmHg, respectively; both *P* < 0.001) to mean follow-up levels of 134.7/74.8 mmHg reduced the relative risk of major macrovascular or microvascular events (including CVD death, non-fatal stroke, and non-fatal myocardial infarction) by 9% (hazard ratio [HR]: 0.91; 95% CI: 0.83, 1.00; *P* = 0.04), and CVD death by 18% (HR: 0.82; 95% CI: 0.68, 0.98; *P* = 0.03). A subgroup analysis of 1,501 patients with diabetes enrolled in the Hypertension Optimal Treatment (HOT) trial, where hypertensive patients were randomly assigned to a target DBP, showed that the risk of major cardiovascular events (non-fatal myocardial infarction, non-fatal stroke, and cardiovascular death) was halved in those randomized to a DBP ≤80 mmHg compared with ≤90 mmHg (relative

Table 3 Incidence of all-cause adverse events in patients with and without diabetes titrated from amlodipine 5 mg to 10 mg

<table>
<thead>
<tr>
<th>Parameter</th>
<th>With diabetes (N=100)</th>
<th>Without diabetes (N=610)</th>
<th>Difference (%)</th>
<th>95% CI‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of AEs</td>
<td>31</td>
<td>282</td>
<td>−1.3</td>
<td>[−2.7, 2.1]</td>
</tr>
<tr>
<td>Patients with AEs, n (%)</td>
<td>22 (22.0)</td>
<td>176 (28.9)</td>
<td>−3.9</td>
<td>[−5.9, −0.5]</td>
</tr>
<tr>
<td>Patients with serious AEs, n (%)</td>
<td>1 (1.0)</td>
<td>5 (0.8)</td>
<td>2.0‡</td>
<td>[0.2, 7.0]</td>
</tr>
<tr>
<td>Patients withdrawn from treatment due to AEs, n (%)</td>
<td>3 (3.0)</td>
<td>20 (3.3)</td>
<td>1.0</td>
<td>[−1.0, 5.6]</td>
</tr>
</tbody>
</table>

Notes: Analyses were conducted using the safety population. Baseline was established while patients were on amlodipine mg treatment. *P* < 0.05, null hypothesis is that the percentage of patients with the given AE is equal between the two subgroups, versus not equal; ‡those with an incidence ≥1.0% in either subgroup; ‡difference between the two subgroups in the percentage of most common AEs (those with diabetes minus those without), and associated 95% confidence interval.

Abbreviations: AEs, adverse events; CI, confidence interval.
risk for 90 mmHg versus 80 mmHg: 2.06; 95% CI: 1.24, 3.44; P for trend = 0.005).36

However, recent results from the Action to Control Cardiovascular Risk in Diabetes (ACCORD)37 and International Verapamil SR-Trandolapril Study (INVEST)38 trials have questioned the clinical benefit obtained with aggressive control of SBP levels to <120 mmHg, or even <130 mmHg. For example, the ACCORD trial, where patients with diabetes were randomized to a SBP <120 mmHg versus <140 mmHg, failed to demonstrate a significant reduction in the relative risk of major cardiovascular events, although a significant reduction in the relative risk of stroke was observed (HR: 0.59; 95% CI: 0.39, 0.89; P = 0.01).37 Moreover, the incidence of serious AEs attributed to antihypertensive treatment was significantly higher in the intensive-therapy group (3.3%) compared with the standard-therapy group (1.3%; P<0.001), indicating the potential for harm with aggressive BP lowering to within the normotensive range in this patient population. With this in mind, recent updates to treatment guidelines for the management of BP in patients with diabetes have seen therapeutic targets revised to <140/80 mmHg (ADA),11 or <140/85 mmHg (ESH/ESC),12 with the option of a lower SBP goal (ie, <130 mmHg) for some individuals, such as younger patients or those at very high risk of stroke, if it can be achieved with few drugs and without adverse effects.11

For patients with diabetes, current clinical practice guidelines advocate the use of renin–angiotensin system (RAS) inhibitors such as an ACEI or an ARB, with the addition of a CCB such as amlodipine, and/or hydrochlorothiazide, as needed to achieve BP goals.11 Studies in hypertensive patients have highlighted the incremental benefit of titrating amlodipine up to 10 mg on BP lowering.23–26 Moreover, higher doses of amlodipine have been shown to be equally effective or superior, either as monotherapy or in combination with another agent, in reducing cardiovascular outcomes compared with other treatment regimens,23–26 even in patients with diabetes.16 The Avoiding Cardiovascular Events Through Combination Therapy in Patients Living With Systolic Hypertension (ACCOMPLISH) trial16 demonstrated that combination therapy with benazepril and amlodipine (mean achieved BP: 131.5/72.6 mmHg) reduced the relative risk of a cardiovascular event (cardiovascular death, myocardial infarction, stroke, hospitalization for angina, resuscitated arrest, and coronary revascularization) by 21% compared with benazepril and hydrochlorothiazide (mean achieved BP: 132.7/73.7 mmHg) in patients with concomitant diabetes and hypertension (HR: 0.79; 95% CI: 0.68, 0.92; P = 0.003).

This analysis of pooled data from trials investigating the incremental effect of amlodipine titration to 10 mg daily on BP-lowering efficacy in patients with concomitant diabetes and hypertension has revealed that increasing amlodipine from 5 mg to 10 mg daily significantly lowered sitting SBP by −12.5 mmHg and DBP by −6.0 mmHg. Reductions in SBP and DBP of this magnitude are likely to translate to meaningful clinical reductions in cardiovascular outcomes in this high-risk patient group, however, the lack of information on cardiovascular events is an obvious limitation of this study. Nevertheless, the ability to increase amlodipine dose may provide a safe and effective strategy through which to achieve an incremental improvement in BP levels before adding to the medication burden of this patient group, where the average number of antihypertensive medications used to achieve BP goals may be as high as 4.3.43

Conclusion

This retrospective, pooled analysis demonstrates that a significant, incremental improvement in sitting SBP and DBP levels can be safely achieved in patients with and without concomitant diabetes and hypertension by increasing amlodipine dose from 5 mg to 10 mg once daily. Thus, the use of amlodipine as a therapeutic option can be extended in the effective management of hypertension in patients with diabetes.

Author contributions

Barrett W Jeffers, Rahul Bhambri, and Jeffery Robbins were involved in the design of the study. Jeffery Robbins performed the statistical analysis of the data. Barrett W Jeffers, Rahul Bhambri, and Jeffery Robbins interpreted the data, were involved in the drafting of the manuscript, and critically reviewed the manuscript for important intellectual content and accuracy, and made revisions. All authors have approved the final version to be published.

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