Original Paper

Amlodipine Added to Quinapril vs Quinapril Alone for the Treatment of Hypertension in Diabetes: The Amlodipine in Diabetes (ANDI) Trial

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This randomized, comparative, parallel-group trial investigated strategies of blood pressure (BP)–lowering in patients with diabetes and hypertension. Patients not reaching goal BP (<130/80 mm Hg) after 4-week open-label treatment with quinapril 20 mg/d (n=374) received 40 mg/d quinapril (n=167) or 20 mg/d quinapril plus amlodipine besylate (5 mg/d; n=162) for 6 weeks. Patients receiving combination therapy vs monotherapy had significantly greater reductions in mean ± SE sitting systolic BP (9.9±1.0 mm Hg vs 4.3±1.1 mm Hg; P<.001) and diastolic BP (6.5±0.6 mm Hg vs 2.7±0.6 mm Hg; P<.001). No significant differences between groups were observed in percentage of patients achieving goal BP (10.1% with combination therapy vs 8.2% with monotherapy). A clinically neutral effect was observed on high-sensitivity C-reactive protein in both groups. Treatments were well tolerated; fewer than 3% of patients in any group discontinued due to treatment-emergent or treatment-related adverse events. In diabetic hypertensive patients, 20 mg/d quinapril plus 5 mg/d amlodipine besylate was a more effective BP-lowering strategy than monotherapy with 40 mg/d quinapril. (J Clin Hypertens. 2007;9:120–127) ©2007 Le Jacq

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Hypertension and diabetes mellitus frequently occur concomitantly. Approximately 73% of adults with diabetes have hypertension or use antihypertensive medication.[1] Aggressive treatment of hypertension in patients with diabetes is important because reductions in blood pressure (BP) are strongly correlated with reductions in cardiovascular (CV) disease morbidity, CV events, and renal disease in patients with diabetes.[2,3] In patients with increased risk of CV complications, worldwide clinical recommendations specify a more rigorous goal BP of <130/80 mm Hg and the use of angiotensin-converting enzyme inhibitors (ACEIs).[4,5] Despite the established benefit of these recommendations, statistics suggest that only 11% to 20% of patients in the United States with both hypertension and diabetes currently achieve the recommended target BP.[6–8]

The majority of hypertensive patients require more than 1 medication to reach goal BP, and most reports concentrate on initial rather than final combined therapy.[5,9–11] Although many approved medications are available to treat high BP, the

Table I. Patient Demographics

	Open Label		Randomized
	Quinapril 20 mg (n=374)	Quinapril 40 mg (n=167)	Quinapril 20 mg + Amlodipine Besylate 5 mg (n=162)
Sex			
Men	207 (55)	90 (54)	91 (56)
Women	167 (45)	77 (46)	71 (44)
Age, y	60.1±9.1	59.5±8.7	59.8±9.6
Range	25–79	25–75	30–79
Race			
White	364 (97)	162 (97)	158 (98)
Black	2 (1)	0 (0)	1 (0.6)
Asian	3 (1)	3 (2)	0 (0)
Other	5 (1)	2 (1.2)	3 (1.9)
Weight, kg	86.8±15.4	86.5±15.3	86.9±15.6
Range	52.0–139.0	56.0–139.0	52.0–137.0
BMI, mean, kg/m^2	30.9	30.9	31.0
SBP, mm Hg	156.3±11.2*	156.9±11.4	150.5±12.3†
DBP, mm Hg	92.6±7.3*	92.5±7.0	90.8±6.8†
Pulse pressure, mm Hg	63.8±11.4*	64.3±11.2	59.8±11.7†
Heart rate, bpm	74.7±8.8*	74.1±8.8	75.8±8.6†
hsCRP, mg/L	–	3.63±4.02‡	3.64±5.79§

Data are presented as mean ± SD or number (percentage) unless otherwise indicated. BMI indicates body mass index; SBP, systolic blood pressure (BP); DBP, diastolic BP; and hsCRP, high-sensitivity C-reactive protein. *(n=368). †(n=161). ‡(n=162). §(n=158).

best combination is often not readily apparent. In patients with both diabetes and hypertension, ACEIs provide clinical benefits that appear to be independent of BP reduction.[12] For example, in the Fosinopril vs Amlodipine Cardiovascular Events Trial (FACET)[13] in patients with hypertension and diabetes (n=380), the calcium channel blocker amlodipine reduced BP to a greater extent than fosinopril, but those receiving fosinopril were approximately 50% less likely to experience a major CV event than those receiving amlodipine when followed for up to 3.5 years. More important, in the approximately 30% of patients in each group in whom BP was not controlled on monotherapy and who received both drugs in combination, the number of observed vascular events was even lower. In the recently performed Effects of Antihypertensive Agents on Cardiovascular Events in Patients With Coronary Disease and Normal Blood Pressure (CAMELOT) (n=1991),[14] 24 months of treatment with amlodipine significantly reduced the incidence of CV adverse events (AEs) and prevented the progression of atherosclerosis. Placebo-treated patients showed progression and enalapril-treated patients showed a trend for progression of atherosclerosis. The numbers of CV events were also decreased after enalapril treatment compared with placebo in CAMELOT,

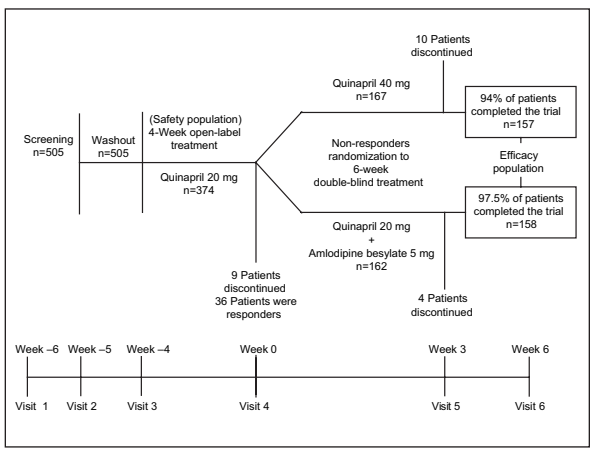

Figure 1. Disposition of patients throughout the trial.

although the decrease was not significant. These studies suggest that the combination of an ACEI with amlodipine might result in better BP control than an ACEI alone, while maintaining the positive benefits of ACEI therapy.

The goal of the Amlodipine in Diabetes (ANDI) trial was to investigate a rational therapy regimen to achieve BP control in patients with hypertension and concomitant diabetes who did not respond adequately to monotherapy with the ACEI quinapril 20 mg. The specific question of whether to increase the dose of the ACEI to 40 mg or to add

Table II. Patient Medications

	Open Label	Randomized	
	Quinapril 20 mg (n=374)	Quinapril 40 mg (n=167)	Quinapril 20 mg + Amlodipine Besylate 5 mg (n=162)
Any concomitant drugs, No. (%)	338 (90.4)	149 (89.2)	142 (87.7)
Antidiabetic	218 (58.3)	101 (60.5)	93 (57.4)
Antihyperlipidemia	143 (38.2)	62 (37.1)	66 (40.7)
Vasodilators	41 (11.0)	14 (8.4)	21 (13.0)
Cerebral	4 (1.0)	0	3 (1.9)
Peripheral	12 (3.2)	6 (3.6)	6 (3.7)
Used in angina pectoris	30 (8.0)	10 (6.0)	15 (9.3)
Antiplatelet	159 (42.5)	81 (48.5)	66 (40.7)
Proportion of patients receiving antihypertensives before study entry, %			
≤2 antihypertensives	73.4	82.6	78.4
≥3 antihypertensives	26.7	17.3	21.6

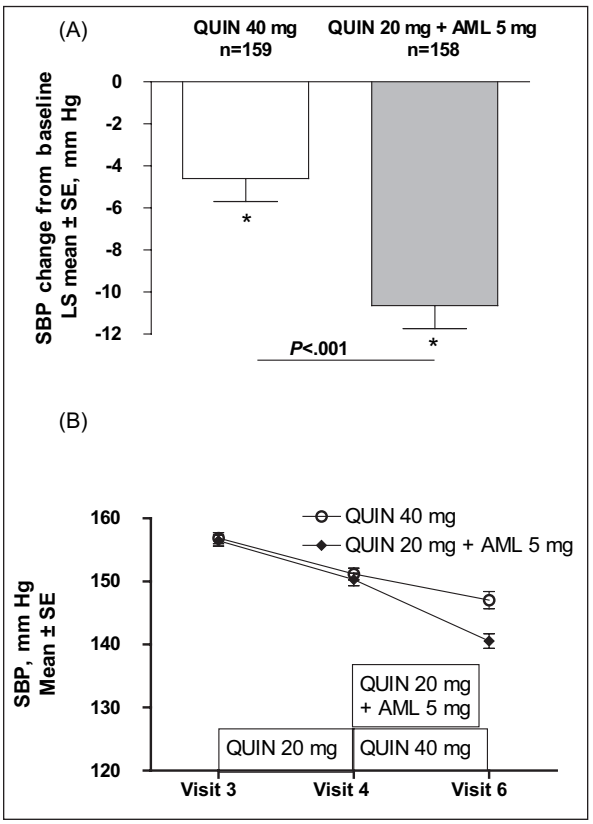

*Figure 2. (A) Changes from baseline (week 0/visit 4 to week 6/visit 6) in systolic blood pressure (SBP). (B) Mean SBP over time. *P<.001 vs baseline. QUIN indicates quinapril; AML, amlodipine besylate; and LS, least squares.*

amlodipine besylate in combination with the lower dose of quinapril was investigated. Assessing tolerability and monitoring the inflammatory marker C-reactive protein (CRP) were secondary goals of the trial.

METHODS

Study Design

Participants. This was a multinational, randomized, comparative, parallel-group, 11-week trial. Patients who had type 2 diabetes mellitus and stage 1 or 2 hypertension were recruited in Canada, France, Spain, Italy, the Netherlands, Belgium, Poland, Romania, the Czech Republic, the Slovak Republic, and Turkey beginning on June 20, 2002. The last patient completed the trial on January 12, 2004. Men and women were between 18 and 75 years of age. Women were included who were not of childbearing potential, had a negative pregnancy test, and agreed to an acceptable form of birth control during the study period. Patients with documented stage 1 (systolic BP [SBP] 140–159 mm Hg or diastolic BP [DBP] 90–99 mm Hg) or stage 2 (SBP 160–179 mm Hg or DBP 100–109 mm Hg) hypertension as measured at the end of the washout period were included. In addition to a previous diagnosis of type 2 diabetes mellitus, patients had to have a fasting serum glucose of ≤180 mg/dL (9.9 mmol/L), glycosylated hemoglobin ≤8%, blood urea nitrogen ≤30 mg/dL (≤10.7 mmol/L), serum creatinine ≤1.5 mg/dL (≤132 μmol/L), and no clinical evidence of overt nephropathy (2 negative and/or trace urine albumin dipstick test results as measured at visits 1 and 2).

Patients who required insulin were excluded; therefore, only patients treated for diabetes with diet or other medication were included. Patients with significant arrhythmia, valvular disease, a diagnosis of heart failure, renal dysfunction (serum creatinine >1.5 mg/dL [>132 μmol/L]), or hepatic dysfunction were excluded. Patients with postural hypotension, stage 3 hypertension, or secondary hypertension were also excluded. Patients were not included if they

Table III. Reasons for Discontinuation

	Open Label	Randomized	
Discontinuations, No. (%)	Quinapril 20 mg (n=374)	Quinapril 40 mg (n=167)	Quinapril 20 mg + Amlodipine Besylate 5 mg (n=162)
Permanent			
All causes	9 (2.4)	6 (3.6)	3 (1.9)
Study drug–related AE	5 (1.3)	4 (2.4)	1 (0.6)
Temporary			
All causes	1 (0.3)	1 (0.6)	0
Study drug–related AE	0	0	0

AE indicates adverse event.

had a history of acute coronary syndrome (unstable angina or myocardial infarction) or congenital heart disease. Patients with a history of acute cerebrovascular syndromes or coronary revascularization (percutaneous transluminal coronary angioplasty/stent, coronary artery bypass graft) within 6 months of the screening visit were excluded.

Intervention. One week after the screening visit (week –6, visit 1), at the start of the 1-week washout period (week –5, visit 2), eligible patients currently treated with antihypertensive therapy discontinued such therapy. If a patient's antihypertensive therapy included β-blockers, the patient entered the 1-week washout period only after β-blocker therapy was tapered off. During the 1-week washout period, patients received single-blind placebo medication. At the end of the washout period, if the patient's BP measurements were still within the parameters defined for stage 1 or 2 hypertension and the patient fulfilled all inclusion criteria, the patient was enrolled in the open-label phase on week –4 at visit 3 (Figure 1). If the BP goal of <130/80 mm Hg was met after the open-label phase, the patient (a responder) was withdrawn from the study. The remaining patients (all nonresponders) who did not reach BP goal after 4 weeks of open-label treatment with quinapril 20 mg/d entered the placebo-controlled, double-blind phase. The end of the open-label phase and the start of the double-blind phase occurred on the same day (week 0, visit 4). Patients were permitted to remain on any concomitant medications with the exception of other antihypertensive medications, tetracycline, or lithium. In the double-blind treatment phase, patients were randomized to quinapril 40 mg/d or combination therapy with quinapril 20 mg/d and amlodipine besylate 5 mg/d. Patients were then monitored at week 3 (visit 5) and at end point (week 6, visit 6).

During the double-blind phase, a double-dummy method was used to maintain the blind. The study medication and placebo tablets were similar in size, color, taste, and appearance. Blinding could be broken only for serious, unexpected, and related AEs, and only for the patient in question, or when required by local regulatory authorities. The investigator was instructed to notify the trial sponsor before unblinding any patient. If the blind was broken for a patient during his or her participation in the study, then the patient was to be discontinued from the study immediately. During the study, blinding documentation was maintained at the site in the investigator's study files.

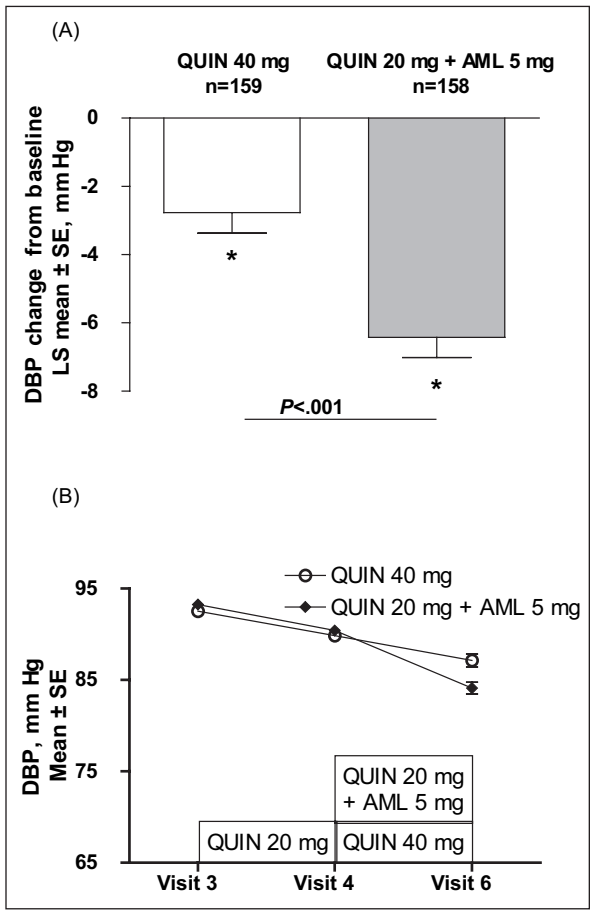

*Figure 3. (A) Changes from baseline (week 0/visit 4 to week 6/visit 6) in diastolic blood pressure (DBP). (B) Mean DBP over time. *P<.001 vs baseline. Abbreviations are expanded in the legend for Figure 2.*

Table IV. Adverse Events Occurring in ≥1% of Patients

	Open Label		Randomized			
	Quinapril 20 mg (n=374)		Quinapril 40 mg (n=167)		Quinapril 20 mg + Amlodipine Besylate 5 mg (n=162)	
Adverse Event, No. (%)	All Causes	Treatment Related	All Causes	Treatment Related	All Causes	Treatment Related
Respiratory tract infection	8 (2.1)	0	8 (4.8)	0	8 (4.9)	0
Headache	6 (1.6)	1 (0.3)	8 (4.8)	1 (0.6)	4 (2.5)	3 (1.9)
Peripheral edema	0	0	0	0	6 (3.7)	6 (3.7)
Increased cough	7 (1.9)	6 (1.6)	5 (3.0)	4 (2.4)	4 (2.5)	4 (2.5)
Hypertension	3 (0.8)	1 (0.3)	3 (1.8)	1 (0.6)	0	0
Chest pain	2 (0.5)	0	2 (1.2)	0	0	0
Procedure	0	0	2 (1.2)	0	2 (1.2)	0
Hypotension	0	0	2 (1.2)	2 (1.2)	0	0
Vomiting	0	0	0	0	2 (1.2)	1 (0.6)
Arthrosis	1 (0.3)	0	1 (0.6)	0	2 (1.2)	0
Myalgia	1 (0.3)	1 (0.3)	2 (1.2)	1 (0.6)	0	0
Anxiety	0	0	0	0	2 (1.2)	0
Dizziness	3 (0.8)	2 (0.5)	2 (1.2)	2 (1.2)	0	0
Somnolence	1 (0.3)	1 (0.3)	2 (1.2)	1 (0.6)	0	0
Rhinitis	0	0	0	0	2 (1.2)	1 (0.6)

Outcomes. The primary efficacy variable was the change from baseline (visit 4) to end point (visit 6) in SBP. The secondary efficacy variables included change from baseline to end point in DBP and heart rate; the percentage of patients reaching BP goal of <130/80 mm Hg at the interim and final visits; and the change from baseline to the final visit in high-sensitivity CRP (hsCRP).

BP determinations were made using a mercury sphygmomanometer and the patient's same arm throughout the course of the study. Three BP readings were to be recorded at each visit, measured in the dominant arm (as defined by the patient), and recorded to the nearest mm Hg. Measurements were to be made with the appropriate size cuff by the same person each time, if possible. Sitting BP (first reading) and heart rate were to be taken after the patient had been in a sitting position for at least 3 minutes, and the second and third BP readings were to be taken 2 minutes following the previous reading.

Safety was assessed by treatment-emergent AEs and serious AEs (SAEs), laboratory measures, vital signs, and use of concomitant medications. Safety was also determined considering completion or discontinuation status.

Statistical Methods

Efficacy analyses comparing 2 treatment arms were performed on all patients who received at least 1 dose of double-blind study medication after the randomization assignment at visit 4, and who completed a baseline (visit 4) and at least 1 post-randomization efficacy measurement. Safety analyses were performed on all patients who received at least 1 dose of study medication.

Change from baseline in SBP and DBP between treatment arms was compared using the analysis of covariance model. The model included treatment and center as main effects and baseline SBP and DBP as covariates, respectively. Center-by-treatment interaction effects were assessed as an exploratory analysis. Percentage of patients who achieved BP goal was compared between treatment arms using the Cochran-Mantel-Haenszel test with center as the strata. Because the data for hsCRP were not normally distributed, comparison for change from baseline within groups was performed using the nonparametric Wilcoxon signed rank test. Results were considered statistically significant if a P value of <.050 was obtained.

The frequency and percentage of patients reporting treatment-emergent AEs were summarized by body system, severity, and cause. Laboratory data were summarized for both treatment groups. The SAEs and clinically significant laboratory abnormalities were carefully reviewed.

The study was conducted in accordance with the Declaration of Helsinki. The protocol, including all amendments and patient informed consent, was approved by all appropriate institutional review boards.

RESULTS

Patients

Patient disposition throughout the trial is summarized in Figure 1. Of the 505 patients screened, 374 patients with stage 1 or stage 2 hypertension were enrolled. Demographics and BP baseline values obtained at visit 3 (after washout) are presented in Table I. Nine patients were withdrawn for protocol variation/noncompliance. Thirty-six patients (9.6%) reached goal BP (<130/80 mm Hg) during the open-label phase on low-dose quinapril 20 mg. The BP (mean ± SD) of the remaining patients with uncontrolled BP entering the double-blind treatment phase (visit 4) was 151.2±11.9/89.9±6.9 mm Hg for those randomized to the high-dose quinapril monotherapy group and 150.3±12.7/90.4±7.0 mm Hg for those randomized to the combination-therapy group.

Most of the patients randomized to treatment with quinapril monotherapy (89.2%) or combination therapy (87.7%) were receiving concomitant medications at study entry; some of those commonly used were antidiabetic, antihyperlipidemic, and vasodilator medications (Table II). Of the patients who entered the treatment phase, approximately 80% in each treatment group received 2 or fewer antihypertensive agents before study entry.

Primary Efficacy Variables

Systolic BP was significantly reduced from baseline in both treatment groups ($P<.001$; Figure 2A). Patients in the combination-therapy group had a significantly greater response to treatment compared with the patients receiving high-dose quinapril (–9.9 mm Hg vs –4.3 mm Hg; $P<.001$). The change in SBP over the course of the study is shown in Figure 2B.

Secondary Efficacy Variables

Reductions in DBP from baseline were significant in both treatment groups ($P<.001$; Figure 3A). Patients receiving combination therapy had a significantly greater response to treatment ($P<.001$). The difference between groups was significant ($P=.034$) in favor of combination therapy. The change in DBP over the course of the experiment is shown in Figure 3B.

No significant difference between groups was observed in heart rate.

At the final visit, BP (mean ± SD) in the quinapril 40-mg group was 147±18/87±9 mm Hg and BP in the combination-therapy group was 141±15/84±8 mm Hg. Of the patients in the quinapril 40-mg group, 13 out of 159 evaluable (8.18%) achieved target BP by the final visit, and of the patients receiving combination treatment, 16 out of 158 (10.13%) achieved target BP by the final visit. The difference between groups was not statistically significant.

Treatment in both groups had a clinically neutral effect on hsCRP. The hsCRP values were not normally distributed; therefore, the median change is more meaningful than mean change. The inflammatory marker was slightly increased from visit 4 to visit 6 in patients receiving combined therapy (n=153; median change 0.10 mg/L; $P=.021$); however, the changes did not appear to be clinically meaningful. In patients receiving quinapril 40 mg, hsCRP was not changed from visit 4 to visit 6 (n=155; –0.68±8.87 mg/L; median change, 0.07 mg/L; $P=.896$).

Tolerability and Safety

Reasons for discontinuations from the trial are shown in Table III. The number of patients who discontinued owing to treatment-emergent, treatment-related AEs was low (fewer than 3% of patients in any treatment group), and there were no unexpected AEs. During the double-blind phase, 10 patients receiving quinapril 40 mg were withdrawn from the study; 6 withdrawals were not related to study drug. Five patients experienced SAEs during or up to 30 days after the last dose of study medication. No SAEs were related to study drug (as assessed by the investigator), and no SAEs resulted in death. Of the patients randomized to combination therapy, 4 patients were withdrawn from the study: 1 was related and 2 were unrelated to study drug and 1 patient was lost to follow-up.

Treatment-emergent AEs (all causes and treatment-related) reported for at least 1% of patients in a treatment group during the open-label or double-blind phases or within 30 days posttreatment are summarized in Table IV.

DISCUSSION

The ANDI study demonstrated that in hypertensive patients with diabetes whose BP was not controlled with 20 mg quinapril alone, initiation of combination therapy by adding 5 mg amlodipine besylate to quinapril 20 mg was more effective in reducing BP than increasing the dose of quinapril to 40 mg.

Worldwide hypertension treatment guidelines recommend an ACEI in the treatment of people with diabetes and hypertension.[4,5,15] The goal of this recommendation includes BP lowering in addition to target organ protection.[16] Long-term blockade of the renin-angiotensin-aldosterone system (RAAS) has been shown to delay progression to end-stage renal disease.[17,18] Renal protection is particularly critical in patients with diabetes because of their accelerated risk of renal dysfunction.[4,5,19] Furthermore, activation of

the RAAS is associated with increased expression of inflammatory mediators; and blockade of the RAAS may provide CV protection in part through reduction of these inflammatory factors.[20] The inflammatory marker CRP has been suggested by some investigators to be associated with an increased risk of developing diabetes[21] and hypertension.[22] Yasunari and coworkers[23] recently reported that inhibition of the RAAS with valsartan in hypertensive patients significantly reduced CRP concentrations and reactive oxygen species formation. In a recent study, quinapril, but not enalapril, was shown to be effective in reducing the increased concentration of CRP in patients following an acute myocardial infarction.[24]

In the Anglo-Scandinavian Cardiac Outcomes Trial–Blood Pressure Lowering Arm (ASCOT-BPLA) study,[10] which compared the efficacy of amlodipine besylate with or without perindopril and atenolol with or without thiazide diuretic, 53% of all patients had reached goal BP (<140/90 mm Hg without diabetes; <130/80 mm Hg with diabetes), whereas only 32% of patients with diabetes achieved goal BP. Additional therapy with doxazosin was allowed if hypertension was not controlled by the 2 primary agents studied. For patients receiving an amlodipine-based regimen, the average number of antihypertensive agents was 2.2, and the average for patients receiving an atenolol-based regimen was 2.3. As expected, many patients required 3 or more antihypertensive drugs in an effort to achieve significant and sustained reductions to goal BP.

Although BP was reduced from baseline in both treatment groups, fewer than 11% in either group achieved the recommended target BP for patients with diabetes mellitus. The low fraction of patients who achieved target BP in ANDI is consistent with what has been reported previously.[6] In clinical practice, patients might have received additional antihypertensive medications in an effort to bring BP to goal, as various clinical trials have demonstrated the benefits of combination therapy to help reach the rigorous target of <130/80 mm Hg in hypertensive diabetic patients.[2,3,11,25,26] Future studies with quinapril and amlodipine besylate that include an additional agent or agents, such as a diuretic, are needed in this patient population to increase the proportion of patients reaching goal BP.

The tolerability profile of the combination of quinapril and amlodipine besylate in the ANDI study compared favorably with that of quinapril alone. During the double-blind treatment phase, the incidence of AEs considered by the investigator to be treatment-related was similar between the 2 treatment groups (6.6% and 10.5%, respectively, for the high-dose quinapril and combination-therapy groups). In addition, 6 patients (3.6%) in the high-dose quinapril group and 2 patients (1.2%) in the combination quinapril/amlodipine group were withdrawn from the study because of an AE. In other studies, quinapril has been demonstrated to be similarly safe and well tolerated in patients with hypertension,[27,28] and additionally has been shown to preserve renal function in patients with diabetes.[29]

A secondary outcome of the ANDI study was to evaluate the effect of quinapril alone compared with quinapril and amlodipine besylate in lowering hsCRP. High hsCRP values (>3 mg/L) have been shown to be associated with increased CV risk.[30] In this study, similar and small changes in hsCRP were observed that were not clinically relevant. Other studies, however, have shown quinapril to be associated with a clear anti-inflammatory effect.[24,31–33] Because drugs such as statins, fibrates, niacin, thiazolidinediones, and antiplatelet agents are also associated with lowering CRP,[34] the neutral effect on CRP observed with quinapril in this study may be a result of the concomitant drugs used in this high-risk patient population.

Limitations

Limitations of this study include the lack of a placebo control group; however, in the population studied, withholding antihypertensive therapy is considered unethical. The short duration of the study allowed a focus only on the surrogate markers of BP and the inflammatory marker hsCRP.

CONCLUSIONS

These data from the ANDI study demonstrated that in hypertensive patients with diabetes who did not respond to 20 mg quinapril, addition of the calcium channel blocker amlodipine besylate provided better BP lowering compared with doubling the quinapril dose. Given that current evidence-based recommendations call for BP control for people with diabetes to <130/80 mm Hg and encourage the use of ACEIs, adding a second agent such as the calcium channel blocker amlodipine besylate to help achieve that control is preferable to pursuing monotherapy with the ACEI at a higher dosage.

Disclosures: This study was sponsored by Pfizer Inc. Dr Tobe has consulted, received honoraria for speaking, or served on an advisory board for Pfizer Inc, AstraZeneca Pharmaceuticals LP, Bristol Myers Squibb Co, and Boehringer Ingelheim Pharmaceuticals, Inc. Dr Zannad has consulted, received honoraria for speaking, or served on an advisory board for Pfizer Inc, Servier Pharmaceuticals, Guidant Corporation, Novartis International AG, and Otsuka Pharmaceuticals. Dr Vetrovec has consulted, received honoraria for speaking, or served on

an advisory board for Pfizer Inc. Dr Patni was an employee of Pfizer Inc at the time the study was performed. Mr Shi is an employee of Pfizer Inc.

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