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Research Article

Efficacy and safety of perindopril arginine + amlodipine in hypertension

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Abstract

To study the efficacy and safety of a new combination of perindopril arginine and amlodipine besylate, 837 subjects were enrolled in a three–arm, prospective, 59–center, randomized clinical trial. For 42 days, subjects (average seated blood pressure [BP], 158 ± 12/101 ± 5 mm Hg; age, 52 ± 10 years; 52% male; 34% black; 20% diabetic) received amlodipine/perindopril arginine (10/14 mg/d), perindopril erbumine (16 mg/d), or amlodipine (10 mg/d). Goal BP was <140/90 or <130/80 mm Hg in diabetics, per JNC 7 guidelines. The combination showed the largest change in seated BP (−23.7/−15.7 vs. −13.7/−9.5 vs. −19.3/−13.2 mm Hg, respectively; $P < .0001$), the highest proportion at goal BP (51% vs. 26% vs. 37%; $P < .0001$), and a lower incidence of pedal edema and adverse events compared with amlodipine. No deaths or significant differences across groups in early discontinuation, serum potassium, or rates of total or serious adverse events or glomerular filtration, were observed. J Am Soc Hypertens 2015;9(4):266–274. © 2015 American Society of Hypertension. All rights reserved.

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Introduction

Hypertension is an important modifiable risk factor and validated surrogate for cardiovascular risk. Blood pressure (BP) reduction is associated with both a reduced cardiovascular event rate and slowed progression of chronic kidney disease. Despite recent national[1–3] and international[4,5] guidelines, often based on abundant data from randomized clinical trials,[6–8] and widespread availability of many generic antihypertensive drug therapies,[1,9] BP control in many large populations remains suboptimal.[10,11] A recent report from a large managed care organization attributed successful control of hypertension to easier access to BP measurements, simpler dose titration, and broader use of combination antihypertensive drug therapy.[12]

Recent hypertension guidelines have recommended a trial of lifestyle modifications, with consideration of initiating drug therapy if BP is persistently ≥140/90 mm Hg, using an angiotensin–converting enzyme (ACE) inhibitor, an angiotensin receptor blocker, calcium channel blocker,

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or low–dose thiazide–type or thiazide–like diuretic, depending on age and race/ethnicity.[1–7] All guidelines issued during the past decade include single–pill combination drug therapy as a therapeutic option for patients with BPs >160/100 mm Hg, or those who do not achieve goal BPs with monotherapy.[1–7,13]

The randomized clinical trial evidence–base supporting initial therapy with single–pill combination therapy for cardiovascular risk reduction in high–risk hypertensive patients is limited.[8,14–16] Most randomized clinical trials in hypertension have pre–specified a stepwise addition of agents from different therapeutic classes if the target BP was not achieved, so abundant clinical trial evidence has been accumulated with several regimens that combine two drugs from different pharmacologic classes.[6–8] Of the ACE–inhibitors, ramipril and perindopril have accumulated the most cardiovascular and renal outcomes,[17,18] whereas 11 trials that reported cardiovascular outcomes have included the calcium antagonist, amlodipine.[18]

This article reports the results of a three–arm, multicenter, double–blinded, prospective, Phase 3 randomized clinical trial that compared the safety and efficacy of the new arginine salt of perindopril, in combination with amlodipine (which has become common practice[19]) to amlodipine alone and to the highest US Food and Drug Administration (FDA)–approved daily dose of the old erbumine salt of perindopril.

Methods

Eligible subjects were hypertensive adult men or women, aged 18–75 years, who had signed a local institutional review board–approved informed consent document. At screening, each subject was provided with an automated home BP monitor (but home readings are not included in this report). Excluded were subjects who worked the night shift, those with known or suspected secondary hypertension or volume depletion, baseline seated mean systolic BP ≥180 mm Hg, ischemic heart disease, heart failure, significant cardiac dysrhythmias, chronic kidney disease Stage ≥3, known chronic viral infection, major surgery in the prior 3 months, cancer in the prior 5 years (excluding squamous skin cancers), abnormal liver function tests (alanine aminotransferase [ALT] or aspartate aminotransferase [AST] ≥3 times, or serum bilirubin >2 times the upper limit of the reference range), serum potassium ≤3.0, or >5.1 mEq/L, prior history of intolerance to ACE–inhibitors or amlodipine, pregnancy (or plans to soon become pregnant), breastfeeding, arm size that precluded the use of a large BP cuff, major psychiatric disorder (including substance abuse), or treatment with any investigational drug or device in the prior 30 days. Prohibited during the randomized treatment period were: any antihypertensive medication, vasoactive drugs (except for stable doses of nitrates), antithyroid drugs, amphetamines or other weight loss medications, aspirin >325 mg/d, potassium supplements, lithium, gold, gentamicin, or strong inhibitors of CYP3A4 (eg, ritonavir, –azole antifungals). Subjects discontinued all antihypertensive drug therapy, and were observed during a 2–3 week washout period. Treatment-naïve individuals who met all eligibility criteria were randomized after only 7 days of observation. Subjects with mean seated diastolic BP between 95 and 115 mm Hg (inclusive), with acceptable baseline screening blood and urine tests (including, for women with reproductive potential, a negative serum pregnancy test and practicing adequate contraceptive techniques) were randomized in a 1:1:1 ratio to one of the three double–blind treatment arms. Randomization was accomplished using a centralized interactive voice response system, stratified by: presence or absence of type 2 diabetes, race/ethnicity (black vs. non–black), and baseline diastolic BP (<100 or ≥100 mm Hg).

After randomization, subjects received, in identical packaging in a double–blind fashion, perindopril erbumine (16 mg/d), amlodipine besylate (10 mg/d), or perindopril arginine + amlodipine (14 mg + 10 mg/d). An interval visit was scheduled after 21 ± 3 days of therapy, and the final visit occurred after 42 ± 3 days of therapy, as maximal BP reduction occurred with these medications after 6 weeks in prior studies. All medications were to be taken in the morning, after BP measurements (at home or in the office). Laboratory safety testing (blood, urine, electrocardiogram) was performed in the fasting state, prior to randomization and at day 42 of therapy. Seated BPs and heart rates were measured in triplicate by an automated BP monitor in the arm with the higher BPs at baseline, using an appropriately sized BP cuff (large adult cuff for those with mid–humeral circumference >42 cm). Adherence was based on pill counts of returned medications at days 21 and 42 of therapy. Subjects were encouraged to measure home BPs in the morning, in triplicate, more than 30 minutes after awakening, at least every other day during treatment, and whenever dizziness, lightheadedness, or other unusual symptoms occurred, and to notify a clinical site if their mean seated BPs were outside the range of 90/60–180/115 mm Hg.

The pre–specified primary efficacy measure was the change in mean seated office trough diastolic BP from baseline to day 42 (or end–of–treatment, in the case of early withdrawal), analyzed in the intent–to–treat population (which included all randomized subjects who had taken at least one dose of study medication, and had at least one post-baseline office BP measurement). This was evaluated using analysis of covariance with treatment assignment as the main effect, with type 2 diabetes, race/ethnicity, and baseline office diastolic BP as covariates, using the last observation carried forward for subjects who withdrew early. Because there were two pair–wise comparisons for the perindopril + amlodipine group, the level of significance (α) was set at 0.025; one–sided *P*–values were used because it was expected a priori that the combination