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Controversies in blood pressure goal guidelines and masked hypertension

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In uncomplicated hypertension, <140/90 mmHg is the treatment goal for individuals aged 18–79 and between 140 mmHg and 150 mmHg in those 80 years of age. Inhibitors of the renin–angiotensin–aldosterone system, as well as calcium channel blockers, are universally accepted as first-line therapy in uncomplicated hypertension, but controversy exists over the role of thiazide diuretics and beta blockers. Because at similar blood pressure (BP) levels, African Americans have more target organ damage than whites, a lower goal of <135/85 mmHg is recommended. In patients with coronary artery disease, diabetes, and chronic kidney disease, <130/80 mmHg is recommended. Masked hypertension, defined as normal clinic BP with a high average self-monitored or ambulatory BP, is prevalent in those with chronic kidney disease, diabetes, and obstructive sleep apnea. Masked hypertension is associated with worse outcome. Ambulatory BP monitoring for those at risk for masked hypertension needs to be incorporated into guidelines.

Keywords: blood pressure; guidelines; masked hypertension; essential hypertension

Introduction

Over the past decade, multiple guidelines and consensus statements on the treatment of essential hypertension (HTN) have been issued from the United States, the United Kingdom, Japan, Europe, Canada, and international organizations.[1–7] The focus of this review is to critically assess blood pressure (BP) goal guidelines and explore controversies in uncomplicated essential HTN in the elderly, African Americans, diabetics, chronic kidney disease (CKD), and coronary artery disease (CAD). In addition, first-line antihypertensive therapy, combination therapy, and the emerging problem of masked hypertension will be briefly reviewed.

Uncomplicated hypertension

There is universal agreement that BP should be <140/90 mmHg in patients <80 years of age.[1–7] However, the basis for this position in patients age ≥65 with isolated systolic hypertension is scant, as no trial has achieved an average systolic BP <143 mmHg. Those individuals who achieved an SBP <140 mmHg in these trials may not have had incremental benefit. For example, in the Systolic Hypertension in the Elderly Program (SHEP), where the entry criteria was a systolic BP (SBP) >170 mmHg, those who achieved an SBP <160 mmHg had a 33% reduction in stroke, and a further 5% reduction was accrued in those with SBP <150 mmHg.[8] However, there was no further benefit seen in those who achieved an SBP <140 mmHg. Nevertheless, all guidelines have an SBP goal of <140 mmHg in those aged <80.

In those aged ≥80, guidance is available from the Hypertension in the Very Elderly Trial (HYVET).[9] The study hypothesis was that in patients age ≥80 with SBP between 160 and 199 mmHg, antihypertensive therapy with a BP goal of <150/80 mmHg would be efficacious. The primary endpoint of the trial was any stroke (fatal or nonfatal), excluding TIAs. Secondary endpoints included death from any cause, death from cardiovascular causes, death from cardiac causes, and death from stroke.

HYVET randomized a total of 3,845 patients from Europe, China, Australia, and Tunisia to either

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indapamide 1.5 mg sustained release (SR) or placebo. At each visit (or at the discretion of the investigator), if needed to reach the target BP (SBP <150 mmHg and DBP <80 mmHg), perindopril 2 mg or 4 mg or matching placebo could be added. At two years, 25.8% of patients in the active treatment group were receiving indapamide alone, 23.9% were receiving indapamide and perindopril 2 mg, and 49.5% were receiving indapamide and perindopril 4 mg. At two years, mean standing BP levels had decreased by 13.6/7.0 mmHg in the placebo group (demonstrating once again the power of placebo), and by 28.3/12.4 mmHg in the active treatment group, where the SBP was on average 143 mmHg.

At the two-year follow-up, compared to placebo, antihypertensive drug therapy with indapamide, plus perindopril if needed, reduced all-cause mortality by 21%. This is the first major hypertension trial to show a reduction in mortality. In addition, fatal or nonfatal stroke was reduced by 30%, fatal stroke by 39%, cardiovascular death by 23%, and heart failure by 64%.

HYVET results have been incorporated into two guidelines. Basing their recommendation on the SBP goal in HYVET, the U.K. NICE guidelines recommend a BP <150 mmHg,[2] whereas the American College of Cardiology (ACC)/American Heart Association (AHA) recommend a more aggressive target SBP goal of 140–145 mmHg.[4]

Initiation of antihypertensive therapy in uncomplicated HTN: Where is the debate?

In uncomplicated hypertension, all guidelines recommend either an angiotensin-converting enzyme inhibitor (ACEI), an angiotensin receptor blocker (ARB), or a calcium channel blocker (CCB) as first-line therapy (Table 1).[1–7] Virtually all guidelines, with the exception of UK NICE,[2] also recommend diuretic as a potential first-line therapy. Because of concerns of metabolic disturbances associated with thiazide diuretics (particularly hyperglycemia), in the absence of heart failure, NICE relegate thiazides to second-line therapy for patients of African descent, and third line in other ethnic groups. NICE recommends addition of sprionolactone as fourth-line therapy.

Recommendations regarding β blockers are mixed, as some guideline committees are more concerned than others about their relative ineffectiveness compared to other agents in stroke prevention in the elderly, and the concern about their potential to exacerbate diabetes. After review of the data, and recognizing the pharmacological and possible clinical heterogeneity of β blockers, the European Society of Hypertension recommended continued use of β blockers as first-line therapy.[6] The Japanese Society of Hypertension and the Canadian Hypertension Education Program recommend β blockers in young patients, but recommends other drugs in the elderly or in those with glucose intolerance or diabetes.[5,7] The NICE guidelines have relegated β blockers to fourth-line therapy, except in young patients with "an intolerance or contraindication to ACE inhibitors and angiotensin II antagonists or women of child-bearing potential or people with evidence of increased sympathetic drive."[2]

Table 1. Recommendations for initiation of antihypertensive therapy according to guidelines/consensus statements issued from national and international organizations

Country/region	ACEI/ARB/ CCB	Diuretic	β blocker
USA-JNC 7[1]	Yes	Yes	Yes
Europe[6]	Yes	Yes	Yes
Japan[5]	Yes	Yes	Yes/no
Canada[7]	Yes	Yes	Yes/no
USA – ACC[4]	Yes	Yes	No
International (Blacks)[3]	Yes	Yes	No
UK[2]	Yes	No	No

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCB, calcium channel blocker.

Combination therapy

While the choice of initial therapy is important, since most patients require at least two drugs for BP control (JNC 7), more emphasis needs to be placed on determining the most efficacious drug combination. Combining drugs with different mechanisms of actions is a physiological approach associated with more effective BP lowering (Fig. 1).[5] The most effective combinations include an ACEI or an ARB combined with a CCB or thiazide diuretic, or a β blocker combined with a CCB. Because of the increased incidence of diabetes, the combination of β blocker and thiazide diuretic is not recommended

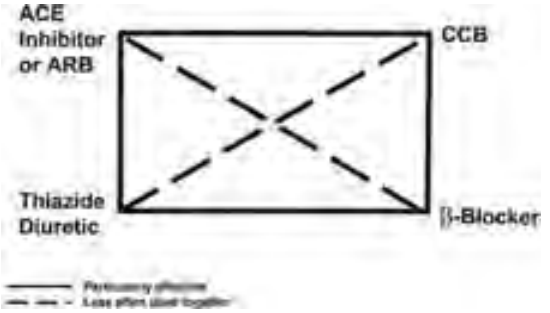

Figure 1. Physiological combinations of antihypertensive medications. Combining drugs at adjacent corners of the figure is particular effective. ACE, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCB, calcium channel blocker. Adapted with permission.[34]

by the Japanese Society of Hypertension or the NICE guidelines.[2,5]

An alternative approach is to base combination therapy on an outcome/trial-based approach. Unfortunately, there are very few trials in this area. The randomized, double-blind Avoiding Cardiovascular Events through Combination Therapy in Patients Living with Systolic Hypertension (ACCOMPLISH) trial prospectively compared the effects of two antihypertensive combinations, benazepril/hydrochlorothiazide (HCTZ) (force titrated to 40/12.5 mg) and amlodipine besylate/benazepril (force titrated to 5/40 mg), as initial therapy, on the clinical endpoints of survival and cardiovascular outcomes.[10] ACCOMPLISH enrolled 11,506 patients at high risk for a cardiovascular event and comorbidities were common. Fifty percent of the patients enrolled were obese, and 60% had diabetes. Sixty-eight percent of patients were taking lipid lowering therapy, and 63% of patients were on antiplatelet therapy.

The primary endpoint in ACCOMPLISH was the time to first event of composite cardiovascular morbidity and mortality. Cardiovascular morbidity was defined as nonfatal, clinically evident, acute MI, nonfatal stroke, hospitalization for unstable angina, resuscitated sudden cardiac death, or coronary revascularization procedures. Cardiovascular mortality was defined as death due to sudden cardiac death, fatal MI, fatal stroke, death due to coronary intervention, or death due to CHF or other cardiovascular causes.

The amlodipine-based regimen lowered office-based BP slightly more effectively (1 mmHg), but 24-h BP control was slightly better (1.6 mmHg) with the HCTZ-based regimen.[11] Despite the aggressive treatment given to enrolled patients before study randomization (e.g., 75% of patients were treated with two or more antihypertensive agents), only 37.3% were controlled to the BP goal of <140/90 mmHg.

In ACCOMPLISH, the risk for the primary endpoint was reduced by 20% in the group receiving the CCB amlodipine plus the ACEI benazapril when compared to the group receiving benazapril plus hydrochlorothiazide ($P = 0.0002$). The composite primary endpoint was driven by fewer fatal and nonfatal MIs in the ACEI/CCB group than the ACEI/HCTZ group (RR 21.5%, $P = 0.04$) and 13.9% reduction in coronary revascularization procedures ($P = 0.04$). ACCOMPLISH is the first large-scale randomized trial that suggests that an ACE/CCB-based therapy is superior to an ACE/thiazide-based regimen. ACCOMPLISH has been criticized for its use of HCTZ rather than chlorthalidone, which is known to have superior BP lowering effects and is the thiazide used in most randomized trials.[12] While this is a valid point, the fact is that the overwhelming majority of clinically available current fixed-dose combination ACEI/diuretic products have HCTZ as the diuretic, and despite slightly better 24-h BP control in ACCOMPLISH with the ACEI/HCTZ combination, the ACEI/CCB combination had fewer cardiovascular events.

Treatment of African Americans

For every level of BP, African Americans have more target organ damage than other ethnic groups.[13] Because of this, the International Society of Hypertension in Blacks has suggested a goal of <135/85 mmHg for African Americans.[3] There is controversy regarding this recommendation since only one trial, the African American Study of Kidney Disease and Hypertension (AASK), has randomized African Americans to different BP goals.[14]

Type 2 diabetes

All current guidelines are recommending a target BP <130/80 mmHg in patients with diabetes. In the Hypertension Optimal Treatment (HOT) study, participants with diabetes who were randomized to a goal of <80 mmHg BP (achieved, 82.6 mmHg) had a 50% reduction in major CV events compared to those randomized to the <90 mmHg BP group.

The Appropriate Blood Pressure Control in Diabetes (ABCD) normotensive study was designed to evaluate the effect of intensive versus moderate DBP control on vascular and renal complications in 480 normotensive patients with type 2 diabetes and stage 2 CKD.[15] Patients were randomized to one of two BP target groups: either to a moderate goal of 80–89 mmHg, or to a goal of 10 mmHg below the baseline DBP. After a mean follow-up of 5.3 years, the BPs in the two groups was 137/81 mmHg and 128/75 mmHg, ($P < 0.0001$). Fewer patients in the intensively treated group progressed from normo- to microalbuminuria ($P = 0.012$) and micro- to overt albuminuria ($P = 0.028$). There was less progression of diabetic retinopathy ($P = 0.019$) and a lower incidence of strokes ($P = 0.03$).

The Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial has challenged the <130/80 mmHg recommendation.[17] ACCORD randomized 4,734 patients with type 2 diabetes to a systolic BP goal of either <120 mmHg (intensive therapy) or <140 mmHg (standard therapy). The mean duration of follow-up for the rate of death was 5.0 years. There was no difference in the primary outcome, which was a composite of nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular disease (1.87%/year vs. 2.09%/year, intensive vs. standard, $P = 0.20$). In addition, in the intensive group there was twice the incidence of adverse events, which were primarily reversible metabolic and hypotensive events. Although the stroke event rate was low, there was a significant reduction in the stroke incidence in the intensive group (0.32% per year vs. 0.53%/year, HR 0.59 (95% CI: 0.39–0.89, $P = 0.01$). Over a 5-year period, 89 patients would need to be treated to the intensive goal to prevent one stroke.

Published after the results of ACCORD, the 2011 NICE guidelines, as well as the 2011 Canadian Hypertension Education Program, have maintained a goal of <130/80 mmHg in patients with diabetes.[2,7] This appears to be a prudent approach because the <120 mmHg goal is associated with more side effects, and 89 patients need to be treated to the intensive goal to prevent a stroke over five years.

Chronic kidney disease

Current recommendations in patients with CKD is a BP goal of <130/80 mmHg. [1–7] Based on the results of the AASK, this goal may only be necessary in those whose CKD is accompanied by a protein/24 h of >300 mg.[14] A urinary protein/24 h of ≥300 mg/dL corresponds to a urinary protein/urinary creatinine (P:C) ratio of ≥0.22 or a spot urine P:C ratio of >300 mg/g.[18] AASK randomized 1,094 African Americans with GFR between 20 and 65 mL/min/m^2 to an intensive BP goal of MAP <92 mmHg (BP ∼125/75) and a usual goal of MAP 102–107 mmHg (∼140/90 mmHg). Although there was no difference in the composite outcome (renal function decline, ESRD, or death) between the randomized groups at the end of five years, the patients continued to be followed as a cohort. At the end of 10 years, those who were initially assigned to the intensive arm had better outcome only if their baseline protein excretion was >300 mg/24 h (Fig. 2). Since the absolute reduction in events was 10%, only 10 patients with this level of proteinuria need to be treated (NNT) over 10 years to achieve benefit. In those with ≤300 mg/24 h, there was no difference in outcome between the intensive and standard group. Importantly, the more intensively treated group did not have more adverse events. Consistent with the findings in AASK, a recent systematic review in patients with CKD concluded that "evidence does not conclusively show that a currently recommended blood pressure target of less than 130/80 mmHg improves clinical outcomes more than a conventional target of less than 140/90 mmHg in adults with CKD. A lower target may be beneficial in persons with proteinuria greater than 300–1,000 mg/day."[19]

Coronary artery disease

Current guidelines and recommendations for patients with coronary artery disease is a goal of <130/80 mmHg. However, this recommendation is based on very limited trial data. Perhaps the best data are from the CAMELOT trial, where patients with CAD (rather liberally defined as >20% coronary stenosis) and diastolic BP <100 mmHg (average BP 129/78 mmHg) were randomized to treatment with either amlodipine (CCB) or enalapril (ACEI) versus placebo and followed for 24 months.[20] A substudy of 274 patients measured the effect of achieved BP on progression of atherosclerosis as assessed by intravascular ultrasound (IVUS).

Results of the trial showed that the achieved SBP level was a significant determinant of progression of coronary atherosclerosis. Individuals with BP in the hypertensive range (average: 147/80 mmHg) had an

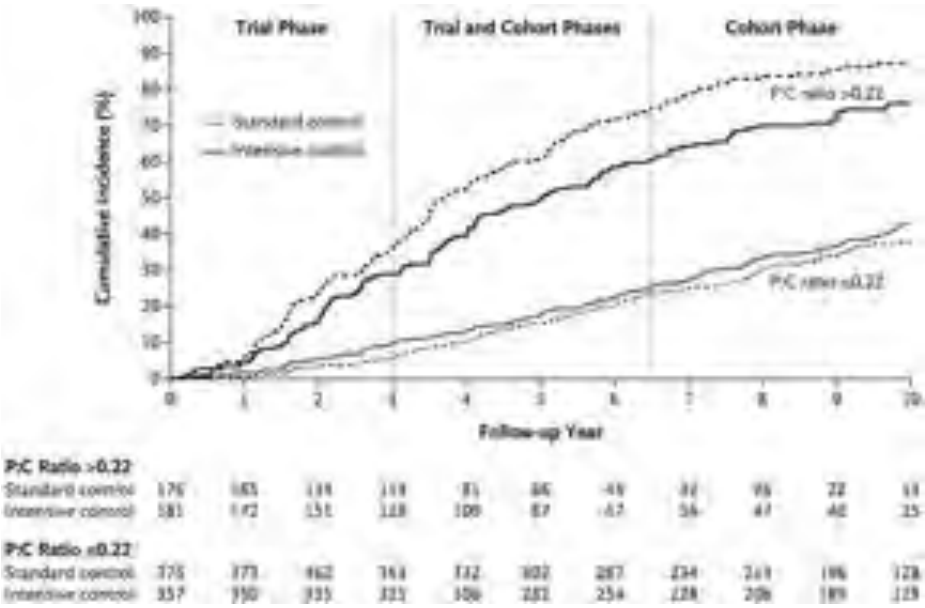

Figure 2. **Cumulative incidence of the composite primary outcome, according to baseline proteinuria status in the AASK study. Among patients with baseline proteinuria, which was defined as a urinary protein-to-creatinine (P:C) ratio of >0.22, those who received intensive blood-pressure control during the randomized phase of the study had a significantly lower cumulative incidence of the composite primary outcome (a doubling of the serum creatinine level, end-stage renal disease, or death) than those who received standard blood-pressure control. However, the between-group difference was not significant among patients with a P:C ratio of < 0.22. The values at the bottom of the graph are numbers of patients. With permission from the *New England Journal of Medicine*.[14]**

increase of 12.0 ± 3.6 mm^3 in atheroma volume, whereas individuals with prehypertension (average: 128/76 mmHg) had no major change, and those with normal BP levels (average: 114/71 mmHg) had a decrease of 4.6 ± 2.6 mm^3 in atheroma volume.[21] The investigators concluded that the therapeutic target goal of BP <140/90 mmHg recommended by JNC 7 for the general population may not be optimal in patients with CAD. Hence, the recommendation by the AHA that BP in patients with CAD be <130/80 mmHg.[22]

Observational data suggests that there is a J-curve with relation to achieved diastolic BP and CV events. In the INVEST study, which compared efficacy of β-blocker strategy versus CCB strategy, there was a nadir in events at an achieved diastolic BP of 84 mmHg. Below this level, CV event rates began to increase.[23] Similar types of data come from Syst-Eur, which was a study of BP lowering in patients with isolated systolic hypertension. In Sys-Eur, risk began to increase in patients with CAD at an achieved diastolic BP < 80 mmHg. The hazard ratio (HR) was 1.1 at a diastolic of 70, which led the authors to conclude that it was prudent not to lower patients with CAD below a diastolic of 70 mmHg.[24] The ROADMAP study, which randomized patients with type 2 diabetes to receive the ARB olmesartan or placebo, also suggests that a J-curve may exist.[25] Target BP of <130/80 mmHg was achieved in nearly 80% of those on olmesartan, and compared to placebo there was a marked and significant reduction in onset of microalbuminuria, the primary endpoint. However, there were more fatal cardiovascular events in the ARB group. Exploratory analysis found that there was a trend toward higher death rate in those in the lowest quartile and the highest quartile of achieved BP, suggesting that excessive BP lowering and the J-curve effect might have been the cause of increased cardiovascular events in the ARB group.

Masked hypertension: definition, incidence, and potential treatment

Masked hypertension is a relatively recently recognized phenomena, characterized by normal clinic BP with a high average ambulatory (ABP) or self-

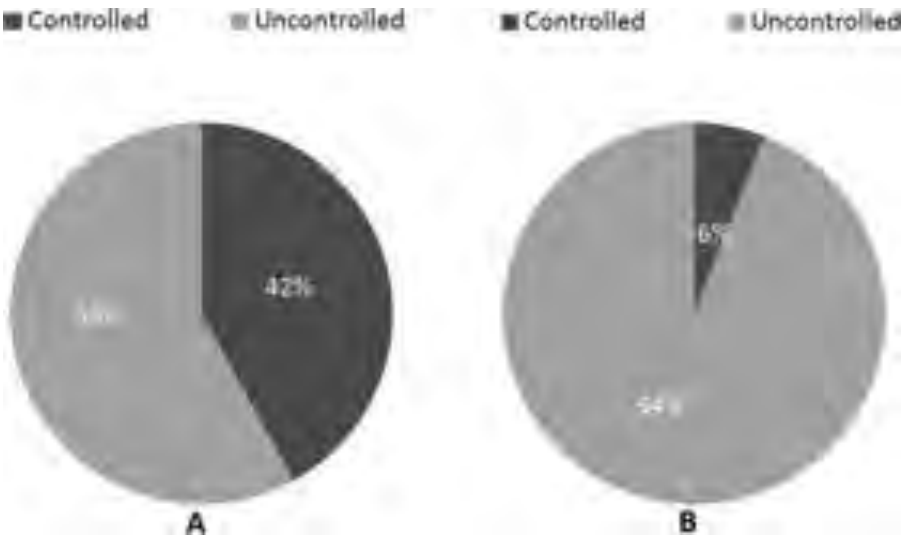

Figure 3. Percentage of patients with chronic kidney disease and masked hypertension with adequate BP control during awake hours (A) and sleep (B).[29] If only daytime measurements are obtained, 42% of patients with masked hypertension would not be detected, as their BP is normal during the day, but elevated at night (A). By contrast, 94% of patients with masked hypertension have elevated BP during sleep (B).

monitored BP.[26] Conditions associated with masked hypertension include smoking,[27] diabetes,[28] CKD,[29] microalbuminuria,[29] LVH,[29] and obstructive sleep apnea.[30] Target organ damage and CV events in masked hypertensives are greater than those with sustained normotension and similar to those with sustained hypertension. For example, in the AASK study, despite intensive drug treatment to lower BP, 42% of the subjects had masked hypertension.[29] This was associated with significantly more LVH and nearly threefold greater incidence of microalbuminuria compared to those whose BP was normal. Nonmodifiable factors associated with masked hypertension in AASK were older age and male gender. Modifiable risk factors included increased sodium intake, microalbuminuria, and decreased exercise. In a study of 4,939 elderly Parisians with hypertension, over a three-year period of follow-up, risk for a CV event was twofold greater in those with masked hypertension compared to those with normal office and home BP.[31]

Since masked hypertension is associated with adverse outcomes, it is important to identify those with the condition. ABP monitoring is required to detect masked hypertension because self-measured home BP, which can only be obtained in awake hours, will miss a significant number of patients. This was demonstrated in the AASK Cohort study, in which 42% of patients with normal daytime BP had masked hypertension on the basis of elevated nocturnal BP (Fig. 3).[29] If only self-measured daytime BPs had been obtained, masked hypertension would have been missed in these patients. To identify patients with white coat hypertension, the UK NICE guidelines have recommended that ABP monitoring be obtained in all patients with office BP $>140/90$.[2] Similarly, it appears prudent that in those patients at risk for masked hypertension that an ABP monitor be obtained to identify these patients.

At the current time there is no treatment for masked hypertension that is based on trial data. Since nearly all patients with masked hypertension have elevated nocturnal BP (94% in the AASK Cohort, Fig. 3), in the absence of trial data, there are several reasons why dosing medication at bedtime to lower nocturnal BP is a reasonable and safe approach. Studies have shown that lower nocturnal BP does not increase risk of stroke and that bedtime dosing is also associated with lower awake BP. Lower nocturnal BP is associated with reduced proteinuria and there is some evidence from the Heart Outcomes Prevention Evaluation (HOPE) trial that it is also associated fewer CV events.

The HOPE study tested hypothesis that compared to a placebo, addition of an ACEI (ramipril) will reduce major cardiovascular events compared to placebo in high-risk patients.[32] The study involved 9,297 patients with CAD, stroke, peripheral vascular

disease (PVD) or diabetes mellitus plus one or more additional cardiovascular risk factors, but without left ventricular dysfunction.

In 75% of participants, ramipril was dosed at night, and therefore this study can be considered a nocturnal BP treatment trial. ABP measurements were taken in a subgroup of 38 patients from the HOPE study with PVD, defined as a history of intermittent claudication and an ankle-to-brachial systolic pressure index of <0.9 by Doppler ultrasonography at rest. ABP measurements were taken for 24 h at baseline before study randomization and then after one year of randomized treatment.

Twenty-four-hour ABP was significantly reduced in the ramipril group compared with the placebo group (12/5 mmHg vs. 2/1 mmHg, $P = 0.03$). A marked reduction in BP was observed in the ramipril group at night (16/7 mmHg, $P < 0.001$). Daytime ABP measurements also showed a reduction in BP in the ramipril group compared with the placebo group; however, the between-group comparison was not significant.[33] The reduced nocturnal BP most likely influenced the outcome of the trial.

In the overall trial, ramipril reduced the occurrence of the primary endpoint, MI, stroke, or death from cardiovascular causes (14% vs. 17.8%, relative risk [RR] 0.78, $P < 0.001$). Among secondary outcomes, ramipril versus placebo reduced the rate of death from any cause (10.4% vs. 12.2%, RR 0.84, $P = 0.005$), death from cardiovascular causes (6.1% vs. 8.1%, RR 0.74, $P < 0.001$), complications related to diabetes (6.4% vs. 7.6%, RR 0.84, $P = 0.03$), hospitalization for heart failure (3.0% vs. 3.4%, RR 0.88, $P = 0.25$), and revascularization procedures (16% vs. 18.3%, RR 0.85, $P = 0.002$). Ramipril also significantly reduced the occurrence of MI, heart failure, and stroke versus placebo (all $P < 0.001$).

Conflicts of interest

The author declares no conflicts of interest.

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