Review Paper

Prompt, Aggressive BP Lowering in High-Risk Patients

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Various populations with hypertension have been singled out by current treatment guidelines as requiring more specific treatment. These include patients with stage 2 hypertension, black patients, and patients with coexistent diabetes mellitus and coronary heart disease. Hypertension in these groups is often associated with higher risk of cardiovascular morbidity and mortality. This article reviews current knowledge regarding hypertension in high-risk patient populations, with a particular focus on the importance of prompt, aggressive treatment to lower blood pressure and prevent cardiovascular disease progression. Such treatment includes the early use of multiple-drug therapy with agents that have complementary blood pressure–lowering mechanisms and provide protection from target organ damage. While 2- or 3-drug antihypertensive therapy in these high-risk groups has typically included a diuretic, other combinations of agents may be indicated. Evidence suggests that therapy with a calcium channel blocker and an inhibitor of the renin-angiotensin system is one effective strategy for lowering blood pressure and improving outcomes in these populations. (J Clin Hypertens (Greenwich). 2008;10(1 suppl 1):40–48) ©*2008 Le Jacq*

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The importance of hypertension as a continuous, consistent, and independent risk factor for cardiovascular disease (CVD) is well established.[1] Accordingly, recent treatment guidelines have particularly focused on specific subgroups of patients in whom uncontrolled or poorly controlled blood pressure (BP) confers a disproportionately high level of cardiovascular risk.[2,3] These groups include the elderly, patients with stage 2 hypertension (systolic BP ≥160 mm Hg or diastolic BP ≥100 mm Hg), black patients, and hypertensive patients with diabetes mellitus. Hypertension in these populations often poses treatment challenges. In the elderly, for example, age-related changes lead to alterations in the nature of hypertension, as vascular compliance decreases, pulse pressure widens, and isolated systolic BP becomes more prevalent.[4] Although systolic BP plays a predominant role as a predictor of cardiac events in elderly patients, it is also more difficult to control than diastolic BP. (See the article in this supplement on BP control in the elderly by Drs Neutel and Gilderman.)

This article discusses hypertension in 3 other populations that, like the elderly, are considered at high risk, namely, patients with stage 2 hypertension, black patients, and patients with diabetes. These 3 groups are among those identified in the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7)[1] as requiring special consideration. Treatment guidelines emphasize the importance of reaching target BP goals (<140/90 mm Hg, or <130/80 mm Hg in patients with diabetes mellitus or other conditions that confer high risk), with the ultimate aim of reducing cardiovascular morbidity and mortality.[1,5–8] In addition to goal attainment itself, the time to BP control should be

considered. The achievement of prompt BP control has emerged as a goal of treatment based on findings from the Valsartan Antihypertensive Long-Term Use Evaluation (VALUE)[9,10] as well as some other trials. The need for early and adequate drug therapy to rapidly get patients' BP to goal has once again been emphasized by a recent report by an international working group.[11] Meeting BP goals for high-risk patients in a timely fashion will generally require the use of multiple-drug therapy.

CHALLENGES FOR ACHIEVING PROMPT BP CONTROL IN HIGH-RISK PATIENTS

Stage 2 Hypertension

A meta-analysis of data from 1 million adults in 61 prospective studies found that the higher the BP, the greater the risk. Death due to ischemic heart disease, stroke, and other vascular causes doubled with every 20-mm Hg systolic BP and 10-mm Hg diastolic BP increase above 115/75 mm Hg.[12] Evidence from clinical trials indicates that antihypertensive treatment is associated with reductions of 35% to 40% in the risk of stroke, 20% to 25% in myocardial infarction, and >50% in heart failure, with larger BP reductions producing greater reductions in risk.[13–15] Even small changes in BP result in large changes in risk, however, as each 2-mm Hg reduction in systolic BP results in approximately a 10% reduction in cardiovascular events.

Black Patients

Hypertension affects >40% of the adult population, and black persons tend to experience more severe hypertension at an earlier age.[16] As a result, they have an increased risk of virtually every complication of hypertension.[17–19] Black persons have a 1.3 times greater rate of nonfatal stroke, 1.8 times greater rate of fatal stroke, 1.5 times greater rate of heart disease death, 4.2 times greater rate of end-stage kidney disease, and a 50% higher frequency of heart failure than the general population.[19] Because black persons tend to experience an earlier onset and greater severity of hypertension as well as more target organ damage, the International Society on Hypertension in Blacks (ISHIB) Working Group has recommended that early identification of high-normal BP (130–139/85–89 mm Hg) and aggressive treatment are especially important in these patients.[6]

Control of BP in black persons poses distinct clinical challenges. Some studies have raised the possibility that differences based on race/ethnicity[18] may influence response to antihypertensive therapy, whereas other investigators have concluded that the variability observed in patient response to BP medications originates within, not between, racial/ethnic groups.[20] The use of β-blockers and agents that act on the renin-angiotensin system (RAS) has at times been avoided in black patients because some evidence has indicated that they are less effective as monotherapy than are volume-responsive agents such as diuretics and calcium channel blockers (CCBs).[1] Some but not all studies have suggested that these differences may be overcome by the use of higher doses of RAS-inhibiting agents or by the combination of an RAS-inhibiting agent with a diuretic or other drug.[21] Cardiovascular risk and not ethnicity should be used to develop an appropriate antihypertensive regimen for patients with hypertension. Race alone should not be used as a reason to withhold RAS blockade when indicated for treatment of proteinuria and hypertension associated with diabetes or chronic kidney disease. While black patients have a higher relative risk of angioedema from angiotensin-converting enzyme (ACE) inhibitors compared with other patients,[22] the use of ACE inhibitor and angiotensin II receptor blocker (ARB) therapy along with diuretic or CCB treatment will allow for more effective BP control in a greater number of patients, regardless of skin color.

Hypertension and Diabetes Mellitus

Hypertension and diabetes frequently coexist, as hypertension is both a risk factor for and a consequence of diabetes.[3,23] A large prospective study reported that diabetes was nearly 2.5 times as likely to develop in persons with high BP as in their normotensive counterparts, regardless of specific treatment.[24] Other studies show an increased prevalence of hypertension in persons with diabetes.[25] Prevalence estimates vary depending on the defining criteria. For example, a retrospective chart analysis of diabetic patients found that the percentage of patients with concomitant hypertension was 60.2%, 76.5%, and 85.8% at BP thresholds of 140/90, 130/85, and 130/80 mm Hg, respectively.[26] CVD accounts for up to 80% of deaths in persons with diabetes. When hypertension is combined with diabetes, the risk is compounded even further.[25]

A body of evidence from clinical trials has shown that rigorous control of BP is particularly important in patients with hypertension and diabetes. For example, the Hypertension Optimal Treatment (HOT) trial[27] found that lowering diastolic BP to a target level of <80 mm Hg (actual achieved BP level, 81 mm Hg) compared with a

target of <90 mm Hg (actual achieved BP level, 85 mm Hg) in patients with diabetes reduced the risk of CVD events by 51%. This study led to the establishment of lower diastolic BP goals (<80 mm Hg) in diabetic patients. In the United Kingdom Prospective Diabetes Study (UKPDS) 38,[28] diabetic patients in the stricter BP control group (primarily using captopril-based or atenolol-based therapy), in whom a mean BP level of 144/82 mm Hg was achieved, had a 34% (*P*=.019) reduction in risk of developing any macrovascular complication (sudden death, myocardial infarction, stroke, or peripheral vascular disease) compared with patients in the less strict control group, who had a mean BP level of 154/87 mm Hg. There was no difference in outcome between the β-blocker–based and the ACE inhibitor–based treatment groups. The BP difference accounted for the benefit in outcome.

In the subset of diabetic patients in the Losartan Intervention for Endpoint Reduction in Hypertension (LIFE) study,[29] the difference in achieved BP with losartan-based therapy vs atenolol-based therapy was small (146/79 mm Hg vs 148/79 mm Hg, respectively), but losartan use was associated with a 24% relative reduction in risk of CVD (*P*=.031; primarily stroke) compared with atenolol. Once again, seemingly small changes in BP translated into differences in clinical outcome. The LIFE study investigators suggested that in patients with diabetes, the use of an ARB-based regimen might have benefits beyond BP reduction.[29] The first priority, however, in all patients with hypertension, including those with diabetes, is to reduce BP to goal.

Major treatment guidelines recommend a BP target of 130/80 mm Hg in patients with diabetes.[1,5,7] The ongoing Stop Atherosclerosis in Native Diabetics Study (SANDS)[30] and the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial[31] will provide further information on the most appropriate target BP in diabetic patients. The BP arm of the ACCORD trial, for example, will examine the effects on cardiovascular events of lowering systolic BP to a goal of <120 mm Hg, compared with <140 mm Hg, within the context of good glycemic control.

RATIONALE FOR COMBINATION THERAPY

Data from the National Health and Nutrition Examination Survey (NHANES) indicate that BP control rates in the United States remain low, especially in high-risk groups.[16,32–34] For example, the BP control rate in the United States in 2003 to 2004 was only 52.4% among treated non-Hispanic black patients and 37.5% among all treated diabetic patients.[32] Even with appropriate use of lifestyle modifications, most patients with hypertension will require pharmacologic treatment to control BP. In fact, clinical trial results indicate that in most persons with hypertension, ≥2 antihypertensive agents are required to achieve BP targets, and all major treatment guidelines support the use of ≥2 antihypertensive agents in patients at high risk.[1,5,6]

Patients with more severe hypertension, including black persons, usually require ≥2 drugs for BP targets to be reached in a timely manner. According to JNC 7, initial therapy with 2 drugs, separately or as fixed-dose combinations, should be considered when systolic BP is >20 mm Hg or diastolic BP is >10 mm Hg above the desired goal for the patient.[1] The 2007 European Society of Hypertension/European Society of Cardiology practice guidelines state that 2 drugs, separately or in combination, are preferred as first-step treatment in grade 2 (160–179/100–109 mm Hg) or grade 3 (≥180/≥110 mm Hg) hypertension or when total cardiovascular risk is high or very high.[5] A diuretic is often included as one component of combination therapy, since this strategy elicits a greater response than single-agent therapy alone.[35] Whether this strategy is better than using a CCB as one of the components remains unclear. Fixed-dose combinations of a diuretic or CCB plus a wide variety of antihypertensive classes are available and constitute a useful option for patients with stage 2 hypertension. For example, a number of studies have demonstrated the efficacy and tolerability of treatment with a diuretic or CCB plus either an ACE inhibitor or an ARB in stage 2 hypertension.[36–42]

The ISHIB recommends initiating 2-drug therapy in black patients when BP is ≥15/10 mm Hg above goal.[6] As mentioned, monotherapy with RAS blockers is usually considered less effective in black patients. Differences in response, however, may be overcome by the administration of additional antihypertensive therapy, especially a diuretic.[1] As in patients with stage 2 hypertension, the role of diuretic-based combination therapy in black patients is well established and supported by the guidelines.[6] More recently, the use of alternative combinations, such as an RAS blocker with a CCB, has been explored.[36,37,41]

Aggressive BP targets may be particularly difficult to achieve in patients with diabetes mellitus.[1,7,28,43] Although intense nonpharmacologic measures, particularly weight loss and reduction of salt intake, should be encouraged in all hypertensive diabetic patients,[5] combination drug therapy

with ≥2 agents is generally required to achieve appropriate BP targets.[1,5,7]

CLINICAL TRIALS OF CCBs PLUS RAS INHIBITORS IN HIGH-RISK POPULATIONS

By targeting different key mechanisms involved in BP regulation, the combination of a CCB with an RAS blocker offers another possible alternative for prompt and additive BP reductions without an increase in adverse events.[44] Combinations of a CCB with an ACE inhibitor have been available for a number of years, and one such combination is being compared with combined ACE inhibitor/diuretic therapy in the ongoing Avoiding Cardiovascular Events Through Combination Therapy in Patients Living With Systolic Hypertension (ACCOMPLISH) trial.[45] The following section will primarily focus on the newest combination agents, a CCB with an ARB.

Stage 2 Hypertension

Clinical trials in patients with stage 2 hypertension have consistently shown the benefit of combining a CCB with an ACE inhibitor.[35,46,47] Recent trials have also established the efficacy and tolerability of combining an ARB with a CCB in high-risk populations, including patients with stage 2 hypertension.[41,42,48]

A study reporting the results of 2 randomized, double-blind, placebo-controlled, parallel-group 8-week trials in patients with mild to moderate hypertension (mean sitting diastolic BP level >95 mm Hg and <110 mg Hg) demonstrated (as expected) greater BP reductions overall with amlodipine/valsartan combination therapy compared with the monotherapy components.[42] A post hoc subgroup analysis of patients with stage 2 hypertension showed that this combination was associated with greater BP-lowering effects in this population compared with each respective monotherapy and placebo (Figure 1).[48] Patients with stage 2 hypertension generally had greater reductions in mean sitting BP than did patients with stage 1 hypertension.[48] For example, reductions with amlodipine 10 mg plus valsartan 160 mg were 29.6/17.6 mm Hg in patients with stage 2 hypertension compared with 20.3/16.5 mm Hg in patients with stage 1 hypertension; the reductions with amlodipine 10 mg plus a large dose of valsartan (320 mg) were 29.6/18.1 and 22.7/18.2 mm Hg, respectively. The incidence of adverse events in patients with stage 2 hypertension with combination therapy (42.5%) was generally comparable to that with monotherapy (valsartan, 37.4%; amlodipine, 43.0%; placebo, 36.5%).[48]

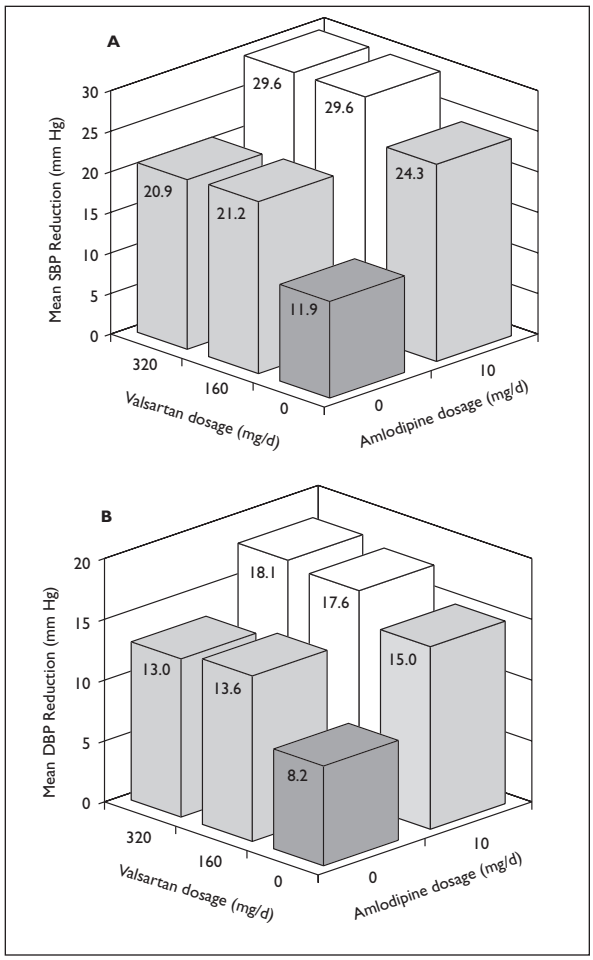

Figure 1. Change from baseline in mean sitting systolic blood pressure (SBP) (A) and mean sitting diastolic blood pressure (DBP) (B) in patients with stage 2 hypertension (baseline systolic blood pressure ≥160 mm Hg and/or baseline diastolic blood pressure ≥100 mm Hg). Patients received amlodipine 10 mg, valsartan 160 or 320 mg, combination therapy with amlodipine and valsartan at these same doses, or placebo. Reprinted with permission from Smith et al.[48]

In another study, therapy with amlodipine plus valsartan was as effective and well tolerated as lisinopril plus hydrochlorothiazide in patients with stage 2 hypertension (mean sitting diastolic BP ≥110 mm Hg and <120 mm Hg).[41] Both treatments were associated with the achievement of BP goals (<140/90 mm Hg) in the majority of patients (67.2% for the amlodipine/valsartan group and 56.1% for the lisinopril/hydrochlorothiazide group).[41] Finally, a trial in 1940 patients with seated diastolic BP levels ≥95 and ≤120 mm Hg reported (again as expected) greater reductions in mean seated systolic BP and diastolic BP values with combinations of amlodipine 5 to 10 mg/d plus olmesartan 10 to 40 mg/d for 8 weeks, compared with the respective monotherapy components.[49]

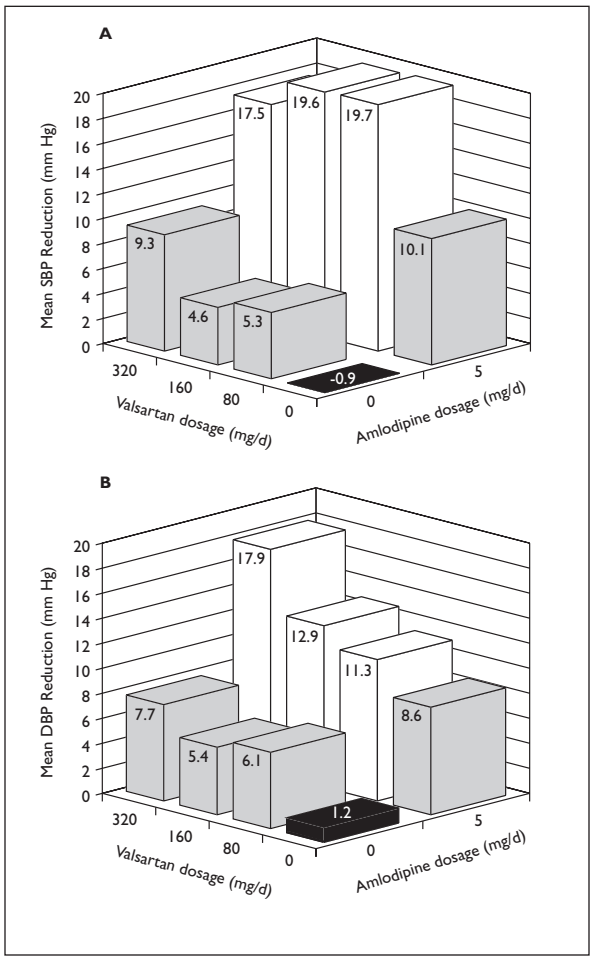

Figure 2. Change from baseline in mean sitting systolic blood pressure (SBP) (A) and mean sitting diastolic blood pressure (DBP) (B) in black patients treated who received amlodipine 5 mg, valsartan 160 or 320 mg, combination therapy with amlodipine 5 mg plus valsartan 160 or 320 mg, or placebo. Adapted from Smith et al.[48]

The greatest reductions in mean seated systolic/diastolic BP occurred with amlodipine 10 mg plus olmesartan 40 mg (–30.1/–19.0 mm Hg vs –4.8/–3.1 mm Hg with placebo and –19.7/–12.7 mm Hg with amlodipine 10 mg).[49]

Black Patients

There is good rationale for including an RAS-blocking agent as one element of combination therapy in black persons who have an increased risk of CVD and are almost twice as likely to develop diabetes as age-matched non-Hispanic whites.[50] Inhibition of the RAS also has renoprotective effects in black patients with hypertensive nephrosclerosis.[51] The combination of an ACE inhibitor or an ARB with a diuretic is established therapy in this population.[6] Evidence is beginning to emerge regarding the potential usefulness of RAS blockers combined with CCBs. A prespecified subgroup analysis by Smith and colleagues[48] showed that amlodipine/valsartan combination therapy was associated with substantial BP-lowering effects in black patients (Figure 2); however, the number of patients in this subset was small. Future trials will need to include more black participants to determine the best combinations of antihypertensive agents in this population.

Diabetes

Major treatment guidelines for patients with concomitant hypertension and diabetes recommend the use of ACE inhibitors or ARBs as one component of therapy because these agents may prevent or delay albuminuria and adverse metabolic outcomes in addition to lowering BP.[1,7] A number of recent trials and meta-analyses have also demonstrated that fewer cases of new-onset diabetes occur when ARBs or ACE inhibitors are used, compared with other agents.[9,52–58] In addition, ACE inhibitors and ARBs have been shown to improve insulin sensitivity[59,60] and to reduce the risk of the development or progression of diabetic nephropathy.[61,62] The guidelines do not provide suggestions as to whether to initiate therapy with an ACE inhibitor or an ARB; however, if either class of RAS-blocking drug is not tolerated (eg, ACE inhibitor–induced cough), an agent from the other class should be used.[7,63] At least 2 drugs will typically be required to achieve the stringent BP goal of <130/80 mm Hg in most diabetic patients.[1,7] An RAS blocker should always be one component of combination therapy in hypertensive patients with diabetes. The other agent might be a diuretic, but CCBs, which do not have adverse effects on the metabolic profile, may also be considered.

The Action in Diabetes and Vascular Disease: Preterax and Diamicron-MR Controlled Evaluation (ADVANCE) trial[64] randomized >11,000 diabetic patients with a history of CVD or one other risk factor for CVD to either a fixed-dose combination of perindopril and indapamide or placebo. Patients could be enrolled whether they were hypertensive or normotensive. With the exception of another ACE inhibitor, all other drugs already being taken at enrollment were continued, and other drugs, except for thiazide diuretics or an ACE inhibitor other than perindopril, could be added during the trial. The mean entry BP value of randomized patients was 145/81 mm Hg, and 41% had BP <140/90 mm Hg. During a mean follow-up of 4.3 years, participants receiving combination therapy with perindopril 2

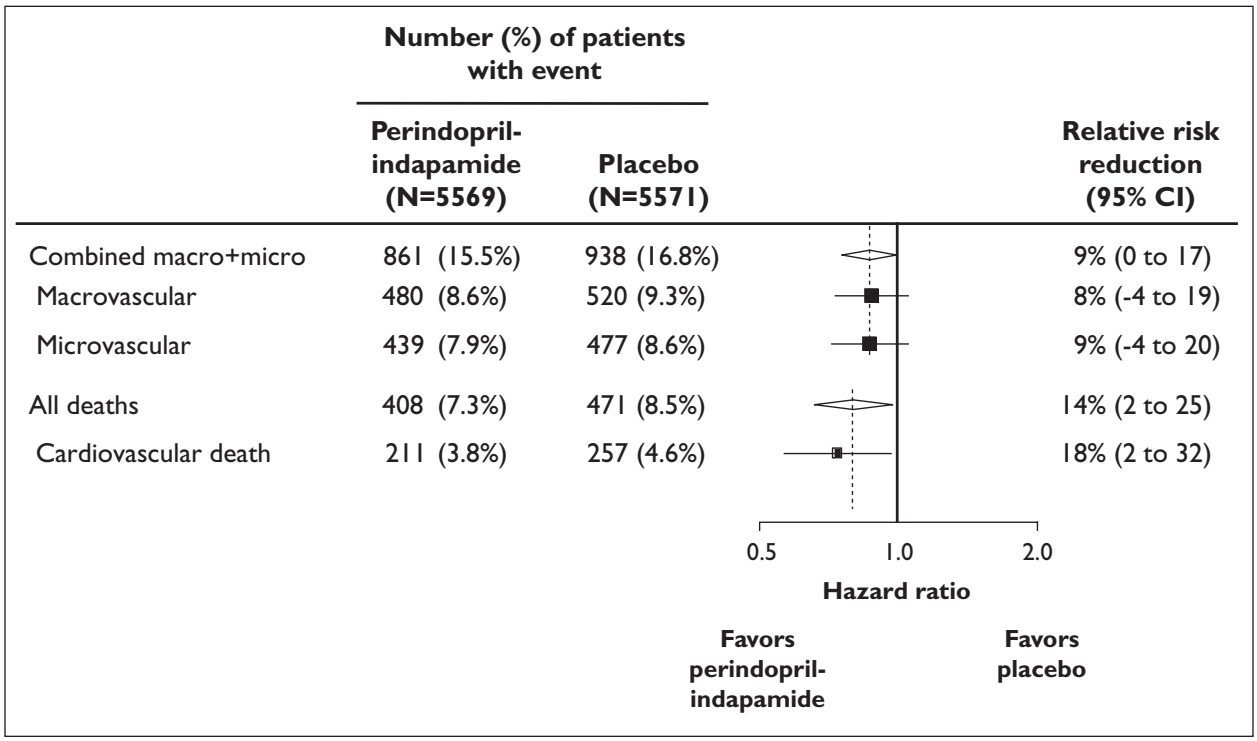

Figure 3. Effects of combination treatment with perindopril plus indapamide vs placebo on deaths and macrovascular and microvascular events in patients with diabetes mellitus in the Action in Diabetes and Vascular Disease: Preterax and Diamicron-MR Controlled Evaluation (ADVANCE) trial. Black squares indicate point estimates; horizontal lines, 95% confidence intervals (CIs); diamonds, point estimate and 95% CIs for overall effects; vertical broken lines, point estimates for overall effect within categories. Adapted with permission from ADVANCE Collaborative Group.[64]

to 4 mg/indapamide 0.625 to 1.25 mg plus other medications had mean reductions of 5.6/2.2 mm Hg, compared with those taking medications other than the specific study drugs, and a 9% reduction in relative risk of major macrovascular or microvascular events (*P*=.04) (Figure 3). The overall risk of death was reduced by 14% in the active-treatment group (*P*=.025 vs placebo).[64]

Support for the utility of fixed-dose CCB/RAS-blocking combination products in achieving prompt BP control is also emerging from preliminary results of the ACCOMPLISH trial.[65] This study has enrolled 11,463 patients with a mean age of 68 years who have a history of coronary disease (46%), stroke (13%), or diabetes (60%). The study objective is to test whether initial combination therapy with an ACE inhibitor and a CCB (benazepril/amlodipine) differs from initial combination therapy with an ACE inhibitor and a diuretic (benazepril/hydrochlorothiazide) on a composite of fatal and nonfatal cardiovascular events.[66] A report of BP-lowering effects during the first 6 months of treatment indicates that the BP control rate was 73% in the overall trial population using initial combination therapy.[65] There is also evidence of excellent systolic BP control at 18 months, with a BP level <140/90 mm Hg achieved in about 76% of the patient population, which is still blinded to treatment group.[67] It is therefore possible that BP had been lowered in a high percentage of patients in both treatment groups.

End point data for the combination of a CCB plus an ARB in hypertensive diabetic patients are not yet available; however, some animal and preclinical studies suggest that this combination may be beneficial in this population. For example, an animal study showed that combined CCB and ARB therapy was more effective than either monotherapy in reducing glucose intolerance.[68] In another study, the addition of valsartan to antihypertensive medications that included an ACE inhibitor or a CCB resulted in improvement in resistance artery remodeling in diabetic hypertensive patients, whereas the addition of atenolol did not.[69]

CONCLUSIONS

Patients with stage 2 hypertension, black patients with hypertension, and patients with both hypertension and diabetes exhibit a disproportionately high level of cardiovascular risk. In addition, these groups pose greater challenges in terms of treatment. BP control in these groups often remains suboptimal, contributing to the burden of CVD morbidity and mortality. Multiple-drug therapy,

either as 2 drugs given separately or as a fixed-dose combination, may result in more prompt achievement of BP goals. Recent evidence indicates that combination therapy with a CCB and an inhibitor of the RAS provides prompt BP reductions and excellent tolerability in patients with stage 2 hypertension, hypertensive black patients, and patients with hypertension and diabetes. The answer to the question of whether and to what extent combined CCB/ARB therapy also decreases the risk of clinical CVD events to the same or greater degree as other agents awaits the performance of future clinical trials.

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