

REVIEW

Initial combination therapy for rapid and effective control of moderate and severe hypertension

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Moderate (grade 2) and severe (grade 3) hypertension are important public health problems associated with high cardiovascular risk. Blood pressure (BP) control becomes more difficult to achieve as hypertension progresses. Therefore, early and effective treatment is essential to prevent hypertensive urgencies and emergencies and reduce cardiovascular risk. Currently, less than 50% of patients being treated for moderate or severe hypertension in the United States achieve their BP goal as recommended by treatment guidelines. This review examines the cardiovascular risk and

physician inertia associated with moderate and severe hypertension, and concludes that increased use of initial combination therapy can overcome many of the barriers to effective BP control. Furthermore, initial combination therapy with a renin-angiotensin system (RAS) inhibitor and diuretic has the potential to rapidly and effectively reduce BP across a range of baseline BPs, with a comparable adverse event profile to monotherapy.

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Introduction

Although mild hypertension has the highest attributable risk for cardiovascular disease as compared with higher grades or stages of hypertension, moderate and severe hypertension remain important public health problems. The 2007 European Society of Hypertension-European Society of Cardiology (ESH-ESC) guidelines define moderate hypertension as 'grade 2' (systolic blood pressure (SBP) 160–179 mmHg and/or diastolic blood pressure (DBP) 100–109 mmHg), and severe hypertension as 'grade 3' hypertension (SBP \geq 180 mmHg and/or DBP \geq 110 mmHg).¹ In contrast, The Joint National Committee (JNC) has down-graded the severe forms of hypertension. Very severe hypertension, stage 4 (SBP \geq 210 mmHg or DBP \geq 120 mmHg), was eliminated in JNC-6 in 1997;² and severe hypertension, stage 3 hypertension (SBP \geq 180 mmHg or DBP \geq 110 mmHg) was eliminated in JNC-7 in 2003.³ JNC-7 recognizes only two levels of hypertension: 'stage 1 hypertension' (SBP 140–159 mmHg or DBP 90–99 mmHg), and 'stage 2 hypertension'

(SBP \geq 160 mmHg or DBP \geq 100 mmHg), which includes all patients with grade 2 (moderate) and grade 3 (severe) hypertension, as defined by the ESH-ESC guidelines.¹

According to National Health and Nutrition Examination Survey III,⁴ approximately 4% of the US population with hypertension is in the category of severe or very severe hypertension. Of these, $1.2 \pm 0.2\%$ (2.4 million people) were diagnosed with severe (formally grade 3) hypertension,⁴ a condition associated with a high risk of hypertensive urgencies and emergencies, including hospitalization for hypertensive crises, congestive heart failure, intracranial haemorrhage, progression of hypertensive retinopathy and nephropathy, and rupture of aneurysms.^{5,6} Astonishingly, more than 900 000 of these individuals in the United States with severe hypertension were not receiving anti-hypertensive therapy in the 1990s.⁴ Furthermore, treatment of patients with severe hypertension has been shown to be inadequate with less than 50% of patients having controlled hypertension.³ As blood pressure (BP) control becomes increasingly more difficult to achieve as hypertension progresses,⁷ early and effective treatment is essential for the prevention of hypertensive urgencies and emergencies and for the overall reduction of cardiovascular risk. The reasons for poor BP control rates in moderate and severe hypertension are complex. Many times BP is

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extremely variable—changing from minute to minute, hour to hour, week to week and from visit to visit, and thus, physicians frequently wait for many patient visits before taking action. This review examines the cardiovascular risk and physician inertia associated with moderate and severe hypertension and concludes that increased use of initial combination therapy can overcome many of the barriers to effective BP control.

Moderate to severe hypertension is associated with a high cardiovascular risk

The level of cardiovascular risk increases exponentially with increasing levels of BP (Figure 1).^{8,9} Across the BP range from 115/75 to 185/115 mm Hg, the risk of death from ischaemic heart disease and stroke increases linearly for people aged 40–89 years.⁹ For those aged 40–69 years, mortality from ischaemic heart disease and stroke doubles for every 20 mm Hg increase in SBP or 10 mm Hg increase in DBP.⁹ Data analysed from the Veteran Administration Cooperative Studies of 1967¹⁰ and 1972¹¹ and the National Heart, Lung, and Blood Institute Study of 1966¹² of very severe hypertension showed an excess risk of cardiovascular events although patients were receiving placebo treatment of 27, 11, and 14% per patient-year, respectively. To place this in perspective, the Framingham Heart Study guidelines recommend initiating anti-hypertensive therapy when there is a cardiovascular event risk of 2% per year or higher, that is., a 10-year risk $\geq 20\%$. Preston *et al.*⁵ in 1999, reported on 3000 consecutive emergency room visits at Jackson Memorial Hospital, of which 4.9% were for severe hypertension. Of the 74 patients with severe hypertension who were managed as outpatients, 50 were lost to follow-up. Of the 24 who did return, 22 had persistent severe hypertension and 10 had new cardiovascular events, which included stroke, heart failure and new retinopathy; the average time for patients to return

for further care was 33 days. Studies by Bender *et al.*¹³ and Karras *et al.*¹⁴ identified patients with severe hypertension as being non-compliers, largely ethnic minorities and with risk factors that included obesity, metabolic syndrome and smoking. These authors also noted deficient emergency room medical care, such as incomplete evaluation for target organ damage (no ordering of an electrocardiogram, urinalysis or serum creatinine), that patients were sent home on baseline medications or on a single anti-hypertensive agent, and that there was no scheduling for a prompt return visit. The significant increase in cardiovascular risk in patients with moderate and severe hypertension emphasizes the need for more effective strategies for successful management.

The benefits of early and aggressive BP lowering in subjects with moderate to severe hypertension

Numerous clinical trials have demonstrated that BP lowering can produce rapid reductions in vascular disease risk in people with any degree of hypertension.^{9,15–20} Even small, persistent reductions of just a few mm Hg in average BP have the potential to avoid large absolute numbers of premature deaths and disabling strokes in the long term.^{9,17} Vascular changes that occur during cardiovascular disease generally precede the onset of hypertension and often continue even after hypertension is diagnosed and controlled.^{21–24} Early, aggressive and sustained BP lowering has the potential to reduce progression from pre-hypertension to hypertension,^{25,26} to reduce progression to more severe hypertension,²⁷ and to reduce long-term cardiovascular consequences.^{18,25,27} A meta-analysis of seven clinical trials examining the benefits of anti-hypertensive therapy in more than 26 000 patients showed that hypertension progressed from moderate (SBP 140–179; DBP 90–109 mm Hg) to severe (SBP > 180 mm Hg; DBP > 110 mm Hg) in only 0.7% of patients receiving active treatment vs 11.2% in the placebo group.²⁷ In this study, relative reductions in left ventricular hypertrophy and heart failure of 35 and 52%, respectively, were achieved.

Early studies in people with severe hypertension demonstrated that reducing severely elevated BP to more moderate levels can prevent the majority of hypertensive crises in this high cardiovascular risk patient group.²⁸ In the Veterans Administration Cooperative study¹⁰ carried out in patients with a mean baseline DBP of 121 mm Hg, severe hypertensive complications occurred in 27 patients in the placebo group (one crisis per 4 patient-years) and in none of the patients in the combination anti-hypertensive treatment group. The study was stopped early, after 1.3 years on placebo, because of the dramatic benefit of initial combination therapy vs placebo in reducing hypertension-related

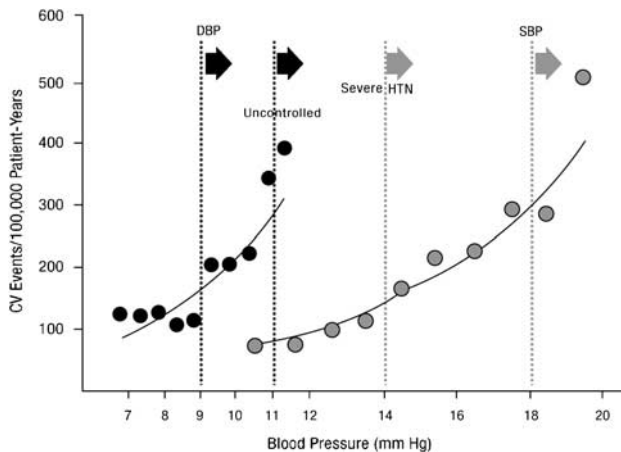


Figure 1 Cardiovascular event rates in the Framingham study.⁸ Reproduced with permission from the *Lancet*.

cardiovascular events (1 vs 21) after a mean follow-up of 11 months. Importantly, the benefit in preventing hypertensive crises was immediate (within 2 months). In a similar study by the National Heart, Lung, and Blood Institute (NHLBI),¹² significant and early (within 6 months) benefits were observed in patients with severely elevated levels of BP (mean baseline DBP 109.5 mmHg) who were treated with combination therapy vs placebo. In the aggregate, these data support a more aggressive treatment strategy for reaching goal therapy, especially in those patients with moderate to severely elevated BP.

Guidelines for the management of patients with moderate to severe hypertension

The current treatment guidelines recommend reducing BP to <140/90 mmHg in most patients and to <130/80 mmHg in those with diabetes and kidney disease.^{1,3,29} Considering global cardiovascular risk, the recent American Heart Association guidelines³⁰ have lowered the treatment threshold to <130/80 for coronary heart disease, coronary heart disease equivalents, peripheral artery disease, carotid artery disease, abdominal aortic aneurysm and high-risk patients with a 10-year Framingham risk score $\geq 10\%$. Furthermore, the 2007 European Society of Hypertension and Cardiology Guidelines¹ for the Management of Hypertension advocate a goal of <130/80 mmHg for stroke survivors.

Hypertension treatment guidelines now recommend initiating treatment using a two-drug combination in patients with BP $\geq 20/10$ mmHg above their target.^{1,3} This concept of initial treatment with combination agents was first introduced in a review by Epstein and Bakris in 1996.³¹ Indeed, clinical trial evidence shows that most patients with moderate, severe, or complicated hypertension will require ≥ 2 drugs to achieve their targets, and many will require the addition of a third or even a fourth drug.^{3,15,16,20,32–34} Increased use of initial combination therapy in these difficult-to-treat patients, therefore, has the potential to overcome many of the barriers to effective BP control and improve goal attainment rates without increasing the incidence of adverse effects. However, despite these new treatment guidelines, many physicians still fail to initiate therapy with multiple agents and/or prescribe additional anti-hypertensive medication when necessary.^{26,35,36}

Why do physicians fail to treat moderate and severe hypertension aggressively? Commonly, follow-up visits are inadequate, as they can be inconvenient and costly. Some health plans encourage prescription refills but do not give incentives for doctor visits. Practitioners reviewing prescriptions in multi-doctor settings may not be aware of the original treatment goal, and simple treatment regimens are preferred by both patients and

physicians, so adequate therapy may not be prescribed.^{37,38} In a study of patient visits in a Medicare setting, pharmacological therapy was initiated or changed at only 38% of visits, despite documented hypertension for at least 6 months before patient visits.³⁸ The use of combination therapy, either as initial treatment or much earlier in the course of treating hypertensive patients, has the potential to overcome this and many of the other barriers to attaining goal BP.

Specific anti-hypertensive drug classes

Most guidelines suggest that initial combination treatment should include a thiazide diuretic and either an angiotensin converting enzyme inhibitor (ACE-I), angiotensin receptor blocker (ARB), calcium channel blocker (CCB), or β -blocker. As some anti-hypertensive drug classes have specific cardiovascular benefits beyond BP reduction, the choice of initial treatment should depend on a patient's comorbidities. For example, renin-angiotensin system inhibitors are renoprotective^{33,39–42} and have a beneficial cardiometabolic profile, which has the potential to prevent new onset diabetes.^{16,43–46} Treatment guidelines, which are based on clinical trial data, therefore recommend treating patients with hypertension and chronic renal disease or type 2 diabetes with a combination of agents that includes an ACE-I or an ARB.^{3,20,33,47–49} Indeed, in the Avoiding Cardiovascular Events through Combination Therapy in Patients Living with Systolic Hypertension trial, which included over 10 000 hypertensive subjects 60% of whom were diabetic, 6-month control rates after benazepril/amlodipine or benazepril/hydrochlorothiazide (HCTZ) treatment was 73% in the overall trial, 43% in diabetic subjects and 40% in patients with renal disease.⁴⁹ These rates, as expected, are higher than those reported in other trials with monotherapies.

Interestingly, although ACE-Is and ARBs are routinely combined with HCTZ, some studies suggest that the choice of the secondary agent may be more complex. For example, in the Study of Trandolapril/Verapamil SR and Insulin Resistance (STAR) study of patients with hypertension and impaired glucose tolerance, treatment with trandolapril/verapamil was superior to treatment with losartan/HCTZ in reducing new-onset diabetes for similar BP control.⁵⁰ In the Gauging Microalbuminuria Reduction with Lotrel in Diabetic Patients with Hypertension (GUARD) study, in patients with mild hypertension (mean baseline sitting SBP/DBP of 151/88 mmHg), a greater reduction in albuminuria was noted with benazepril/HCTZ combination than with the benazepril/amlodipine combination, whereas greater BP reductions were noted with benazepril/amlodipine than with benazepril/HCTZ.⁵¹ Together these data suggest that although the data supporting the addition of HCTZ to an

ARBs or ACE-Is is solid both in terms of efficacy and safety considerations, use of a CCB as a secondary agent should be considered too. Efficacy and safety in specific subtypes such as moderate and severe hypertensive patients remain to be investigated.

The current directive in most managed care organizations is to use an ACE-I first, then switch to an ARB if the ACE-I fails. However, these choices were based on evidence from clinical trials that were carried out during the development of ACE-Is and ARBs. The ACE-I trials have typically included patients with uncomplicated hypertension whose BP was relatively easy to control, whereas the ARB trials included higher proportions of patients with diabetes, high cardiometabolic risk and chronic renal disease. As ARBs are well tolerated in a wide range of patient groups with side effects resembling that of placebo,^{52,53} the initial use of an ARB combined with a thiazide diuretic might be considered in many patient groups. Such considerations are supported by the results of the recently published ONgoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET), a head-to-head comparison of telmisartan and ramipril in hypertensive patients at high risk of having a cardiovascular event.⁵⁴ Although, efficacy with ramipril and telmisartan was similar, patients taking telmisartan experienced fewer side effects including significantly lower cough rates and lower angioedema rates. Similarly, in The Blood Pressure Reduction and Tolerability in Comparison with Lisinopril Study (PREVAIL) in patients with mild to severe hypertension, both valsartan and lisinopril were equally effective in controlling BP, but the valsartan-based regimen was associated with a significantly reduced risk for adverse events such as cough.⁵⁵

Initial fixed combination therapy in people with moderate to severe hypertension

Compared to multiple single agents, fixed-dose combinations offer greater cost-effectiveness and improved treatment compliance due to simplified dosing regimens, reduced pill burden, greater response rates, improved tolerability, attenuation of adverse events and greater efficacy across a broad population of patients.^{53,56–60} Combinations of anti-hypertensive agents that reduce BP through different mechanisms, such as thiazide diuretics and ARBs or ACE-Is, can have additive anti-hypertensive effects on BP reduction. Furthermore, combining drug classes with opposite adverse effects has the potential to improve safety and tolerability. For example, diuretic-induced alterations in potassium, serum cholesterol and fasting glucose can be offset by the concomitant administration of an ACE-I or ARB.⁶¹ The use of low-dose combination therapy is associated with fewer adverse events than the higher doses of single agents that would be required to

achieve the same level of BP.⁶² Similarly, persistence rates can be improved by combining drug classes.

In the 9-month Strategies of Treatment in Hypertension: Evaluation study, an initial combination therapy approach using perindopril and indapamide was superior to stepped care (valsartan 40 mg titrated to 80 mg, co-administered with HCTZ, if necessary) or sequential monotherapy (atenolol replaced by losartan and then by amlodipine) in subjects with a baseline BP $\geq 160/95$ mm Hg.⁶³ The percentage of patients achieving their goal BP without experiencing drug-related adverse events was 56% in the low-dose combination group compared to 42% in the sequential monotherapy ($P=0.002$) and the stepped-care groups ($P=0.004$). The reasons why patients initiated on monotherapy fail to catch up with those starting on combination therapy are thought to include inadequate follow-up visits, a preference for simple treatment regimens, variations in BP between visits, and failure to initiate early treatment and to intensify existing treatment even when hypertension is severe.³⁵

The benefit/risk profile of initial fixed combination therapy including an ARB in people with moderate to severe hypertension

Data from numerous clinical trials have consistently shown that, compared to monotherapy, combination anti-hypertensive treatments including ACE-Is or ARBs provide superior BP lowering and allow a higher proportion of patients with moderate to severe hypertension and/or additional cardiovascular risk factors to achieve their BP goal. For example, a 6-week, double-blind trial carried out in 585 patients with severe hypertension (mean seated (Se) DBP >110 mm Hg and mean SeSBP <220 mm Hg) randomized to either losartan/HCTZ combination therapy or losartan monotherapy, titrated as necessary, showed that the proportion of patients who achieved their goal BP (mean SeDBP <90 mm Hg) at 4 weeks was more than double in those receiving combination therapy than in those receiving monotherapy (Figure 2).⁶⁴ Similarly, the percentage of patients achieving goal BP at 6 weeks was more than double after two steps of combination therapy titration than after three steps of monotherapy titration.⁶⁴ In an 8-week, randomized, double-blind, forced-titration trial comparing losartan/HCTZ with ACE-I monotherapy in 312 patients with BP 20/10 mm Hg above the recommended goal, greater week 4 reductions were observed with combination therapy (15.4/10.2 mm Hg) than with monotherapy (9.2/6.4 mm Hg; $P<0.001$).⁶⁵ Combination treatment also provided higher rates of goal BP attainment; DBP ≤ 80 mm Hg (30.5 vs 14.4%; $P<0.001$) and SBP ≤ 130 mm Hg (29.8 vs 14.4%; $P<0.001$) at weeks 4 and 8. In a randomized double-blind study in patients with stage 2 or 3 hyperten-

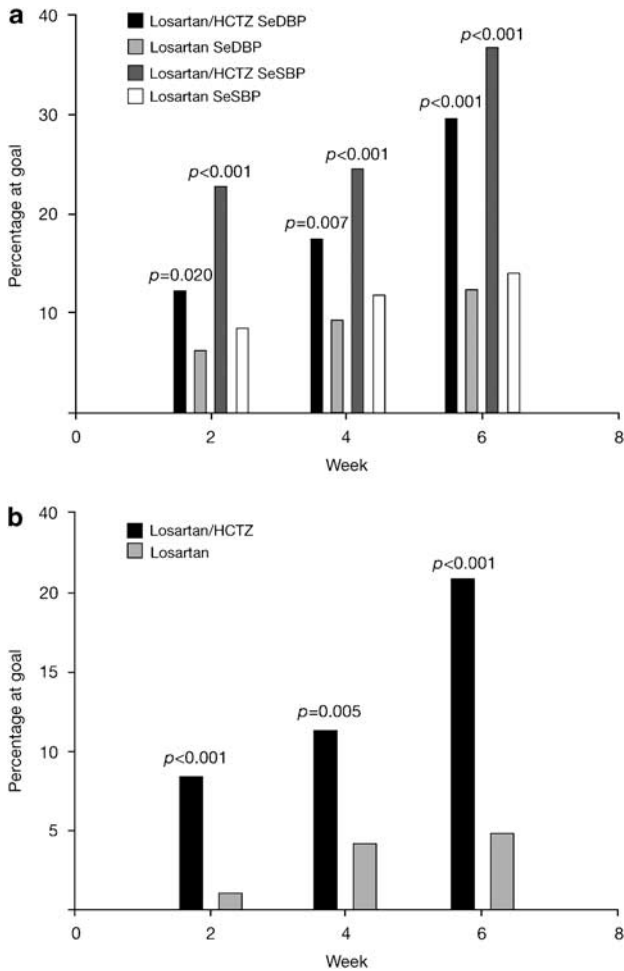


Figure 2 Percentage of patients reaching goal systolic blood pressure (SBP) or diastolic blood pressure (DBP) (a) and goal SBP/DBP 140/90 mmHg (b) in the losartan/hydrochlorothiazide (HCTZ) and the losartan groups.⁶⁴ Reproduced with permission from the *Journal of Clinical Hypertension*.

sion (SBP ≥ 160 and ≤ 200 mm Hg), with or without other cardiovascular risk factors, monotherapy with valsartan 160 mg was effective, but significant additional reductions in SBP and DBP and an increase in responder rates were achieved by the addition of HCTZ 12.5 and 25 mg, with no significant effect on tolerability.⁶⁶

Similarly, initial irbesartan/HCTZ combination therapy has been shown to be significantly more effective than irbesartan monotherapy in achieving rapid and sustained BP reduction in patients with untreated or uncontrolled moderate (SeSBP 160–180 mm Hg or SeDBP 100–110 mm Hg)⁶⁷ or severe (SeSBP ≥ 110 mm Hg)⁵³ hypertension (Figure 3). In both the individual studies and in a post hoc pooled analysis,⁷ irbesartan/HCTZ was generally associated with a greater likelihood of achieving a SeSBP < 140 mm Hg or SeDBP < 90 mm Hg (Figure 4) relative to irbesartan or HCTZ monotherapies across the range of BPs studied. The proportion of patients who achieved their BP goal decreased as their baseline BP increased (Figure 4). Results were

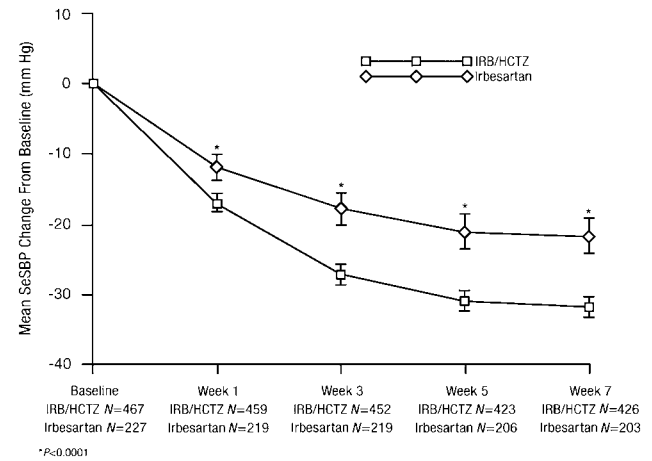


Figure 3 Mean change from baseline in seated (Se)SBP during 7 weeks double-blind treatment with irbesartan/hydrochlorothiazide (HCTZ) and irbesartan monotherapy in patients with severe hypertension.⁵³ Reproduced with permission from the *Journal of Clinical Hypertension*.

consistent for a variety of target goals, regardless of age, obesity and type 2 diabetes status.⁶⁰ Nevertheless, many patients would have required a third or even a fourth drug to reach goals of $< 130/80$ mm Hg.

A time-point analysis of the irbesartan/HCTZ vs irbesartan monotherapy study in patients with severe hypertension⁶⁸ showed that SeDBP and SeSBP control rates were significantly greater for combination therapy vs monotherapy at all time points (weeks 3, 5 and 7) and that the BP reductions achieved with irbesartan monotherapy at week 7 were surpassed by irbesartan/HCTZ approximately 1 month earlier. Over 7 weeks, the probability of having SeDBP ≥ 110 mmHg at least once during follow-up was 24.9% with monotherapy vs 16.4% with combination therapy, an absolute difference of 8.5%. For every 12 patients treated with combination vs monotherapy, one case of SeDBP ≥ 110 mmHg was avoided and for every 100 patients treated with combination therapy vs monotherapy, exposure to SeDBP ≥ 110 mmHg was reduced by 26 weeks ($P = 0.004$). The investigators therefore conclude that initial treatment with RAS inhibitor/diuretic combination therapy has the potential to decrease the risk of hypertensive urgencies/emergencies and reduce the long-term adverse clinical outcomes by reducing BP more rapidly and thereby reducing the length of exposure to severely elevated levels of BP.

Despite increasing the magnitude and rate of BP reduction, the incidence of adverse events did not increase with combination therapy vs monotherapy in any of the studies mentioned above. This is important because many physicians are cautious about reducing BP too far, too quickly because of the risk of hypotension, dizziness and syncope. Overall, the results of these studies support the current treatment guidelines that recommend initial combi-

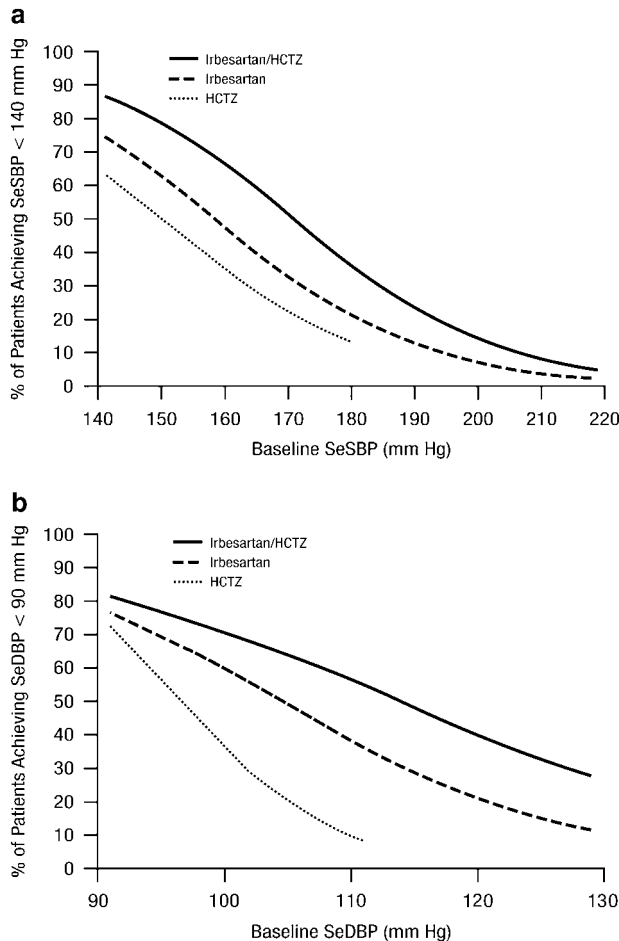


Figure 4 Probability of achieving a systolic blood pressure (SBP) < 140 mmHg (a) or a diastolic blood pressure (DBP) < 90 mmHg (b) in subjects with moderate or severe hypertension using irbesartan/hydrochlorothiazide (HCTZ) combination therapy vs either agent alone.⁷ Reproduced with permission from the *Journal of Clinical Hypertension*.

nation therapy including a RAS inhibitor in patients with moderate to severe hypertension.^{1,3}

In summary, early and effective BP control has the potential to significantly reduce cardiovascular risk in general and hypertensive urgencies and emergencies in particular, in those patients with moderate and severe (grade 3) hypertension. The current hypertension treatment guidelines recommend lowering BP to < 130/80 mmHg in high-risk individuals with complicated hypertension and to < 140/90 mmHg in the general population without other risk factors. As the majority of patients will require more than one anti-hypertensive agent to achieve their BP goal, guidelines suggest initiating treatment in patients with moderate to severe hypertension with combination therapy. A review of the literature suggests that an increased use of initial combination therapy could overcome many of the barriers to effective BP control. Furthermore, initial combination therapy including a RAS inhibitor has the potential to rapidly and effectively reduce BP with a comparable adverse event profile to monotherapy.

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