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EXPERT REVIEW

The Efficacy and Tolerability of Fixed Dose Irbesartan/ Hydrochlorothiazide in the Management of Hypertension

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Abstract: Hypertension is one of the most important and prevalent major cardiovascular risk factors. It is also a risk factor for medical problems leading to a marked increase in cardiovascular risk. Thus, appropriate and efficacious management of patients with hypertension is important. There is also an ongoing debate regarding whether major drug subgroups differ in their ability to protect against total cardiovascular risk or etiology-specific cardiovascular events, such as stroke and myocardial infarction. Hypertension guidelines, based on experience from clinical trials, recognize that many individuals will require ≥2 antihypertensive agents at appropriate doses, either in fixed combination or as separate prescriptions, to achieve their BP goal, particularly in patients at high cardiovascular risk. If possible, initiation of fixed-dose combinations should be chosen, because of the advantages for compliance to treatment. In this context, we aimed to review fixed-dose combinations of irbesartan/hydrochlorothiazide in the management of hypertension.

Keywords: hypertension, medication, irbesartan, hydrochlorothiazide

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Clinical Impact of Hypertension and Problems in Management

Hypertension accounts for one of the most important epidemiological concerns and is associated with increased morbidity and mortality. It is a heterogeneous disorder, with different patient profiles that lead to increased blood pressure (BP).[1] Despite the burden of disease associated with uncontrolled hypertension and the availability of several different classes of antihypertensive medications, few patients reach their target BP level. Analysis of the 2001–2010 United States National Health and Nutrition Examination Survey database revealed that in 2009 to 2010, only 47.2% of hypertensive patients had controlled blood pressure and only 60.3% of patients treated for hypertension achieved BP control.[2] These data suggests that current management of hypertension is often not optimal. Uncontrolled hypertension may lead to subsequent cardiovascular diseases, such as stroke, myocardial infarction, and heart failure, and other conditions such as kidney disease, all of which are associated with significant morbidity and mortality.[3,4] Because of the its worldwide burden and associated medical conditions causing high morbidity and mortality, hypertension should be prioritized in research and practice to find immediate and appropriate management.

Although there are different classes of antihypertensive medications, BP control seems inadequate in many patient populations. Wolf-Maier and colleagues[5] reported rates of BP control ranging from 5%–50% in European countries, 17% in Canada and 29% in the US. Although BP control rates have improved over years, more than half of patients still fail to reach BP targets, and are therefore at increased risk of cardiovascular morbidity and mortality. Hypertension control is difficult partly due to patient incompliance, and partly due to the complexity of the pathophysiology of hypertension and cardiovascular diseases. Not only are multiple pathways and feedback mechanisms involved, but hypertension and cardiovascular diseases are often associated with diabetes and renal dysfunction, which are also tightly linked to the regulation of the renin-angiotensin system.

Angiotensin II is a potent vasoconstrictor and is the main end-product of the renin-angiotensin system (RAS), which plays a central role in the regulation of BP.[6] Angiotensin II binds to the angiotensin II type 1 (AT1) receptor, which mediates the pathways that lead to vasoconstriction and water retention, increases in renal tubular sodium reabsorption and endothelial dysfunction. 24-hour (h) blood pressure control, rapid treatment response, and excellent tolerability profiles are 3 important characteristics of angiotensin receptor blockers (ARBs) that significantly contribute to treatment success. ARBs have proven efficacy in treating hypertension,[7] and have a tolerability profile similar to placebo.[8] Furthermore, the initial use of one of these agents has been shown to increase long-term patient adherence rates compared with those for patients initially prescribed angiotensin-converting-enzyme (ACE) inhibitors, calcium channel antagonists, beta-blockers, or thiazide diuretics.[9,10]

In addition, blood pressure reductions have been noted as early as 2 weeks after the initiation of treatment,[11] and in an irbesartan trial, 33% of severely hypertensive patients reached the primary outcome of BP control (diastolic blood pressure < 90 mm Hg) after 5 weeks of treatment.[12] Overall, side-effect profiles resemble those of placebo, and patient compliance and treatment persistence rates are high.[13,14] Commonly reported adverse events include dizziness, back pain, and fatigue in similar proportions to placebo patients.[13–15]

Caution is nonetheless required in specific patient populations. As ARBs modulate the RAS, the development of hypotension and hyperkalemia should be monitored carefully. Hypotension, for example, has been observed in volume- or salt-depleted patients, and dose adjustments should be considered for patients with impaired hepatic or renal function. ARBs are also contraindicated in pregnancy, hyperkalemia, and bilateral renal artery stenosis.[1]

Thus, targeting deficient pathways in hypertensive patient management is one of the main aspects of BP control. Improvement in patient compliance should be the primary target of all physicians during initiation and maintenance of the therapy. The second target should be safe and effective blockage of the main pathophysiological pathways in hypertension. An important evolution to reach these targets has been the development of fixed-dose (FD) combination therapies, since most patients require at least two medications to achieve BP targets.[16,17]

Fixed-Dose Combination Therapy

In recently updated guidelines, combination therapies that target multiple pathways are recommended

to obtain better BP control.[1,16–18] ARBs are routinely combined with the diuretic hydrochlorothiazide (HCTZ). This approach has proven beneficial in a wide range of patients, specifically those who were unresponsive to initial monotherapy.[19–21] In the single-arm irbesartan/HCTZ Blood Pressure Reductions in Diverse Patient Populations (INCLUSIVE) trial (n = 1005), which included difficult-to-treat hypertensive patients, treatment with irbesartan/HCTZ for 16 weeks normalized BP in 69% of patients who had been uncontrolled on HCTZ alone.[20]

As with single ARB therapies, ARB/HCTZ combinations start taking effect rapidly and compliance rates are high.[19,22] In an ambulatory BP monitoring trial of patients with mild-to-moderate hypertension, 65% to 69% of patients treated with irbesartan/HCTZ had normalized by 8 weeks. The combination of an ARB and a diuretic is particularly attractive in the diabetic population. The ARB blocks the activation of the RAS, thereby reducing BP and damage to the kidneys. The diuretic helps counteract the tendency of patients with diabetes to retain sodium. Indeed, in the subgroup analysis of patients with type 2 diabetes or metabolic syndrome (MS) in the INCLUSIVE trial (n = 295), fixed-combination irbesartan/HCTZ brought greater than 50% of patients previously uncontrolled on HCTZ alone to their systolic BP goals, and 40% to their systolic/diastolic BP goals (<130/80 mmHg).

This review focuses on the benefits and tolerability of the fixed dose ARB/HCTZ combination of irbesartan/HCTZ.[23]

Pharmacological Properties of Irbesartan and HCTZ

Irbesartan antagonizes the activation of angiotensin II type 1 (AT1) receptors. This results in vasodilation and reduces the secretion of vasoconstrictor mediators, thereby reducing BP. HCTZ is a thiazide diuretic and inhibits Na^+/Cl^- reabsorption from distal convoluted tubules in the kidney. The combined effect of those actions is to reduce BP.

Both irbesartan and HCTZ are in active forms following oral administration and do not require biotransformation. They are efficiently absorbed following oral intake, having an oral bioavailability of 60%–80% (for irbesartan) and 50%–80% (for HCTZ). Peak serum concentrations are measured at 1.5–2 h (for irbesartan) and 1–2.5 h (for HCTZ) after oral intake. Food intake has no effect on the bioavailability of either molecule. Irbesartan is mostly excreted unchanged (80%–85%), but is also metabolized in the liver. Irbesartan and its metabolites are eliminated largely in the feces (80%) but also in the urine (20%). Its terminal elimination half-life is 11–15 h, which compares favorably with most other ARBs.[24]

Pharmacokinetic data on the irbesartan/HCTZ fixed-dose combinations are not available, but coadministration of irbesartan and HCTZ has no effect on the pharmacokinetics of either.[25,26] However, a synergistic effect on BP-lowering activity was observed with the addition of irbesartan to HCTZ or vice versa.[19]

Efficacy of Fixed Dose Irbesartan/HCTZ Combinations in Various Subgroups

The favorable effects of irbesartan/HCTZ combination were presented in an early study using a matrix design to evaluate the efficiency and safety profile of different dose combinations of irbesartan (0, 37.5, 100 or 300 mg) plus HCTZ (0, 6.25, 12.5 or 25 mg) on BP.[27] The reduction in DBP by 8 weeks ranged from 3.5 mmHg for placebo, to 5.1–8.3 mmHg for HCTZ monotherapy, 7.1–10.2 mmHg for irbesartan monotherapy, and 8.1–15.0 mmHg for combination therapy, clearly showing a synergistic effect for the addition of irbesartan to HCTZ and vice versa. The ratio of antihypertensive therapy responders at 8 weeks increased from 24% for placebo to 36%–53% for HCTZ monotherapy, 35%–58% for irbesartan monotherapy, and 44%–80% for combination therapy.

The efficacy of fixed-dose irbesartan/HCTZ combination therapy has been showed in several studies with mild, moderate or severe hypertensive patients, summarized in Table 1.

It has been proven that irbesartan/HCTZ with a fixed dose of 150/12.5 mg was more efficacious than other ARB/HCTZ combinations in comparing trials.[21,28] In the Comparative Study of Efficacy of irbesartan/HCTZ with valsartan/HCTZ Using Home BP Monitoring in the Treatment of Mild-to-Moderate Hypertension (COSIMA) study, fixed doses of irbesartan/HCTZ 150/12.5 mg and valsartan/HCTZ 80/12.5 mg were compared.[21] Untreated or uncontrolled mild-to-moderate hypertensive adult patients (n = 800) were enrolled in the study. After a 5-week open-label lead-in

Table 1. Studies demonstrating the efficacy and safety of fixed dose Irbesartan/HCTZ combination therapy.

Study	Patients, n	Treatment duration and dose	BP reduction, mmHg	BP Normalized ratio,%	Adverse event rates,%
Bobrie et al[21]	Failing monotherapy, n: 464	8 weeks; 150/12.5 mg	13.0/9.5 vs 10.6/7.4 for valsartan/HCTZ, $P < 0.001$	50.2 vs 3.2 for valsartan/HCTZ, $P = 0.0003$	–
INCLUSIVE trial[20]	Failing monotherapy, n: 844	18 weeks; titrated to 300/25 mg	21.5/10.4 ($P < 0.001$ vs baseline)	69	Any AE: 27% for 150/12.5 mg; 26% for 300/25 mg, serious AE: 1.0% for both doses
Neutel et al[12]	Severe hypertension, n: 695	5 weeks; titrated to 300/25 mg		34.6 vs 19.2 for irbesartan monotherapy, $P < 0.0001$	Any AE: 30%, discontinuation due to AE: 1.9%, serious AE: 0.2%
Neutel et al[32]	Moderate hypertension, n: 538	8 weeks; titrated to 300/25 mg	27.1/14.6 vs 22.1/11.6 for irbesartan monotherapy, $P < 0.005$	53.4 vs 40.6 for irbesartan monotherapy, $P = 0.0254$	Any AE: 47%, therapy related AE: 14%, discontinuation due to AE: 6.7%, serious AE: 1.8%

Abbreviations: AE, Adverse event; BP, blood pressure; HCTZ, hydrochlorothiazide.

phase in which all patients received 12.5 mg HCTZ once daily, subjects whose BP remained uncontrolled (SBP > 140 mmHg) were randomized (n = 464) to valsartan/HCTZ (80/12.5 mg) or irbesartan/HCTZ (150/12.5 mg) for 8 weeks. Irbesartan/HCTZ showed more decrement in average SBP and DBP as measured by home BP monitoring than valsartan/HCTZ (SBP: −13.0 versus −10.6 mmHg, $P = 0.0094$; DBP: −9.5 versus −7.4 mmHg, $P = 0.0007$). BP normalization rates observed with home BP monitoring (SBP < 135 mmHg and DBP < 85 mmHg) were significantly higher with irbesartan/HCTZ than with valsartan/HCTZ (50.2% versus 33.2%; $P = 0.0003$).

In another study, The irbesartan/HCTZ BP Reductions in Diverse Patient Populations (INCLUSIVE) trial, efficacy of the fixed dose irbesartan/HCTZ combinations were observed.[20] The INCLUSIVE trial was a large scale, prospective, multicenter, open-label, single-arm study in which a total of 844 patients with uncontrolled SBP (140–159 mmHg or 130–159 mmHg for diabetic patients) on monotherapy were enrolled. After screening and a 4- to 5-week placebo administration period, patients received HCTZ 12.5 mg for 2 weeks, followed by fixed-dose irbesartan/HCTZ of 150/12.5 mg for 8 weeks, and then fixed-dose irbesartan/ HCTZ of 300/25 mg for a further 8 weeks. Irbesartan/HCTZ provided significant mean reductions in SBP/DBP from baseline (21.4 ± 13.8 mmHg/10.1 ± 7.8 mmHg, $P < 0.001$) that were comparable to reductions in the all study population (21.5 ± 14.3 mmHg/10.4 ± 8.7 mmHg). Final (18th week) mean SBP and DBP values in the study group were 132.9±13.8 mmHg/81.1±9.7 mmHg. Overall, 77% (95% CI: 74%–80%) of patients reached their SBP goal, 83% (95% CI, 80%–86%) reached their DBP goal, and 69% achieved both their SBP and DBP goals (95% CI, 66%–72%) by week 18 (Fig. 2). Thus, the INCLUSIVE trial has suggested that fixed-dose combination of irbesartan/HCTZ 150/12.5 mg and 300/25 mg provided high efficacy for BP lowering and SBP control in patients with previously uncontrolled hypertension on antihypertensive monotherapy (Table 1).

The post-hoc subgroup analysis of the INCLUSIVE trial demonstrated comparable efficacy and safety with fixed-dose irbesartan/HCTZ in the many subpopulations of patients with hypertension. The study population was composed of patients with diabetes in 30% (n = 254), metabolic syndrome (MS) in 46% (n = 386) and both diabetes and MS in 21% (n = 177). In diabetic subgroup (n = 227), the mean SBP/DBP decrement was −18.2 ± 14.1 mmHg/−8.7 ± 8.2 mmHg, which was statistically significant compared to baseline BP values.[29] Mean SBP/DBP changes in patients with MS (n = 345) were −21.0 ± 14.3 mmHg /−10.4 ± 8.5 mmHg ($P < 0.001$). Overall, 56% (95% CI: 49%–62%) of diabetics and 73% (95% CI: 68%–77%) of MS patients achieved their SBP goal. In addition, 63%

of diabetics and 77% of MS patients achieved their DBP goal, and 40% of diabetics and 61% of MS patients achieved both their SBP and DBP goals. For patients with both diabetes and MS (n = 157), 57% of patients achieved their SBP goal, 59% of patients achieved their DBP goal and 39% of patients achieved both their SBP and DBP goals. Irbesartan/HCTZ fixed-dose combinations lead to achievement of SBP goals in over 50% of the diabetics and nearly 75% of patients with MS in whom SBP was uncontrolled on antihypertensive monotherapy.[29] Because of the increased cardiovascular risk, strict BP control is particularly important for these patients.

In the INCLUSIVE trial, of 844 patients completing placebo treatment, 212 were aged 65 years or older.[30] From baseline to week 18 (n = 184, intent-to-treat population), mean change in SBP was −23.0 ± 13.3 mmHg ($P < 0.001$) and DBP was −10.9 ± 7.7 mmHg ($P < 0.001$). Mean SBP/DBP at the end of study was 134.0 ± 14.7 mmHg/75.1 ± 8.4 mmHg, and SBP, DBP, and SBP/DBP goals were achieved in 73%, 96%, and 72% of patients, respectively. Also, additional analysis of the INCLUSIVE trial data revealed that fixed-dose irbesartan/HCTZ showed more BP reductions in patients with a higher baseline SBP, patients who were female, patients who had diabetes, and patients who were on statin treatment.[31]

Because patients with moderate-to-severe hypertension tend to require ≥2 antihypertensive agents to achieve target BP, there is clear evidence in support of combination therapy from the beginning. Use of fixed-dose irbesartan/HCTZ combination therapy as an initial treatment option in moderate-to-severe hypertensive patients depends on the risk/benefit ratio. The efficacy of initial fixed dose irbesartan/HCTZ combinations in patients with moderate-to-severe hypertension has been evaluated in 2 large-scale multicenter trials, namely the RAPiHD (Rapid Achievement of BP Goals with Irbesartan/HCTZ Fixed Dose Combo) moderate and RAPiHD severe trials. The results of these trials showed that fixed-dose irbesartan/HCTZ treatment achieved more rapid BP reduction than irbesartan or HCTZ monotherapy in patients with moderate to severe hypertension.[12,32,33] Furthermore, for every 100 patients treated with combination therapy, at least 26 fewer weeks of exposure to severe hypertension was experienced than with monotherapy ($P = 0.004$).

A post-hoc pooled analysis of data from both this study and the randomized study in patients with severe hypertension found that the need for initial combination therapy increased with increasing baseline BP and lower BP goals across a range of BP levels spanning moderate and severe hypertension (Fig. 1).

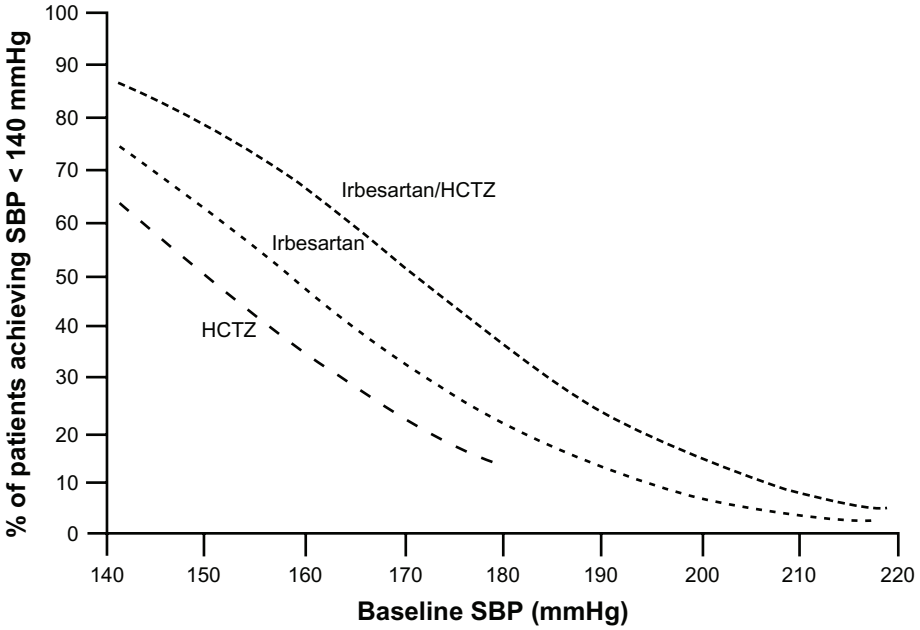

Figure 1. Probability of achieving a SBP < 140 mmHg at weeks 7/8 across a range of baseline SBPs following treatment with Irbesartan/HCTZ, irbesartan and HCTZ.
Note: Results from the RAPiHD study.[33]

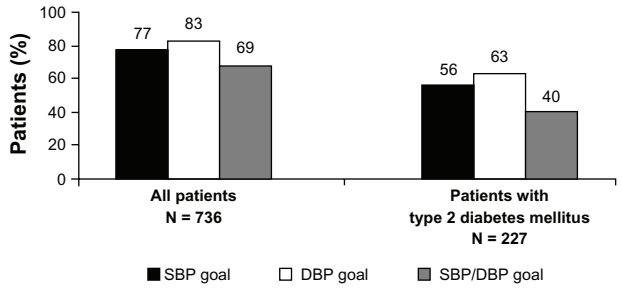

Figure 2. Normalization rates after treatment with Irbesartan/HCTZ: the Irbesartan/HCTZ blood pressure reductions in diverse patient populations (INCLUSIVE) trial.[20]

Safety and Tolerability of Irbesartan/HCTZ Combination

Several clinical trials with HCTZ and irbesartan revealed that both of the agents were welltolerated. Further studies have shown that the combination of irbesartan/HCTZ had no incremental effect on the incidence of drug-related adverse events. The safety profile of the fixed dose irbesartan/HCTZ combination in several major clinical studies is demonstrated in Table 1.

All safety data regarding the use of fixed-dose irbesartan/HCTZ combination treatment revealed that such a ARB/HCTZ combination for hypertensive patients is well tolerated, with adverse events being transient and mostly mild or moderate severity. Also, there is no evidence for an increment in the incidence of adverse events as the dose is uptitrated, with the exception of hypotension. However, in general the incidence of adverse events related to fixed-dose irbesartan/HCTZ combination treatment is low. When used as a monotherapy, HCTZ causes a dose-related hypokalemia side effect. However, this side effect is less expressed with the irbesartan/HCTZ combination, and combination with irbesartan 300 mg provides the greatest reversing effects for the hypokalemia due to HCTZ. Although HCTZ 25 mg monotherapy may cause serum uric acid increment, combination with irbesartan reverses this effect.[27] Thus, there was no significant electrolyte imbalance in clinical trials with fixed-dose irbesartan/HCTZ combination treatment.

The use of fixed-dose irbesartan/HCTZ combination therapy is effective to reduce BP in patients with antihypertensive monotherapy failure, and as an initial treatment in patients with moderate/severe hypertension who mostly require at least two medications to provide BP control. Also, fixed-dose irbesartan/HCTZ combination therapy is welltolerated, and relates to higher patient compliance. So, such a change in hypertension therapy should lead to higher rates of BP control, and lower rates of cardiovascular morbidity and mortality.

Author Contributions

Conceived and designed the experiments: UC, GK. Analyzed the data: UC, GK. Wrote the first draft of the manuscript: UC, GK. Contributed to the writing of the manuscript: UC, GK. Agree with manuscript results and conclusions: GK. Jointly developed the structure and arguments for the paper: UC. Made critical revisions and approved final version: GK. All authors reviewed and approved of the final manuscript.

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Competing Interests

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