Irbesartan: a review of its use alone and in combination with hydrochlorothiazide

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Blood pressure is one of the most important and frequent risk factors for cardiovascular disease morbidity and mortality; however, it is largely uncontrolled in the population. Inhibition of the renin–angiotensin–aldosterone system provides beneficial effects in the hypertensive population. Association of low-dosed diuretics in drug combinations with renin–angiotensin–aldosterone system-blocking agents allows maximum benefit from potassium depletion and control of the compensatory increase in renin secretion, thus increasing the efficacy and safety of the renin–angiotensin–aldosterone system blockers. Irbesartan is a potent and selective angiotensin II subtype 1 receptor antagonist indicated for use in patients with hypertension, including those with Type 2 diabetes mellitus and nephropathy. Once-daily irbesartan administration provides 24-h control of blood pressure. In patients with mild-to-moderate hypertension, irbesartan was as effective as enalapril, atenolol and amlodipine, and more effective than losartan and valsartan (but not olmesartan), in terms of absolute reduction in blood pressure and response rate. Irbesartan also induced regression of left ventricular hypertrophy. Moreover, irbesartan 300 mg/day exerted a significant renoprotective effect in hypertensive Type 2 diabetics. The relative risk of doubling of serum creatinine was significantly lower with irbesartan than with amlodipine or placebo. It was also found to be effective in nondiabetic nephropaties. Furthermore, irbesartan has peroxisome proliferator-activated receptor agonistic effects in *in vitro* studies and also demonstrated beneficial effects on inflammatory markers of atherosclerosis and endothelial function. The overall incidence of adverse events is similar to that of placebo. A fixed-dose combination of hydrochlorothiazide and irbesartan show additive antihypertensive effects in a dose-dependent manner up to hydrochlorothiazide 25 mg and irbesartan 300 mg, with high tolerability in diverse patient groups. Effects of combination on end-organ protection must be evaluated by broad-spectrum studies. Ongoing trials with irbesartan and its combination with diuretics may provide necessary data to interpret the value of this association among others.

Keywords: angiotensin receptor antagonists, combination therapies, hydrochlorothiazide, hypertension, irbesartan, thiazide

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Hypertension is one of the most important and prevalent causes of mortality and morbidity worldwide, and its treatment is important to prevent risks of developing myocardial infarction, heart failure, stroke and chronic renal failure [1,2]. According to WHO reports, high suboptimal blood pressure (BP) levels, even though only suboptimal, are responsible for 62% of cerebrovascular disease and 49% of ischemic heart disease [2].

Although BP control is improving, in 1999–2000 only 53% of hypertensive patients receiving medical treatment reached the BP levels recommended by the seventh report of the Joint National Committee on prevention, detection, evaluation and treatment of high BP (JNC VII) [1].

One solution for the problem of poor BP control is the use of combination therapies, usually including a low-dose diuretic, also suggested as initial therapy for stage 2 hypertensive patients (systolic BP [SBP] ≥160 mmHg or diastolic BP [DBP] ≥100 mmHg) [2]. The rationale of combination therapy in antihypertensive treatment is mainly to enhance the BP-reducing effect of antihypertensive drugs. Combinations may also serve to counteract counter-regulatory mechanisms that are triggered whenever pharmacological intervention is started and limit the efficacy of the therapy. For example, in the combinations with diuretics, compensatory rise in renin secretion induced by sodium depletion may be the prominent cause of persistent high BP. Simultaneous blockade of the renin–angiotensin–aldosteron system (RAAS) with either an angiotensin-converting enzyme (ACE) inhibitor or an angiotensin (AT)1 receptor blocker breaks this vicious cycle and allows maximum benefit from sodium depletion. Thus, fixed combinations of diuretic and ACE inhibitor or AT1 receptor

blocker antihypertensives became increasingly used, both as second- and first-line therapy in hypertension [3].

ACE inhibitors have been successfully tested in the treatment of various forms of hypertension, congestive heart failure and nephropathies. ACE has some other physiological actions that are not related to the RAAS, including the degradation of bradykinin and substance P. The inhibition of these actions by ACE inhibitors may account for some of the known adverse effects of these drugs, such as dry cough [4]. Thus, in recent years, renin inhibitors and AT receptor antagonists were targeted for development as more specific inhibitors of the RAAS.

AT II antagonists are effective in the last steps of the RAAS cascade and they selectively inhibit the binding of AT II to AT1 receptor. AT1 receptors mediate the vasoconstriction, sodium retention, endothelin secretion, vasopressin and aldosterone release, suppression of renin secretion and activation of the sympathetic nervous system [5,6].

AT1 receptor antagonism improves vascular functions in humans [7]. Accordingly, animal studies have demonstrated that AT1 receptor blockers attenuate the development of atherosclerosis in different experimental models of animal dyslipidemia, and these effects have been achieved without significantly altering BP or plasma cholesterol levels [8–10]. There are also increasing data that AT II creates an imbalance between the levels of tissue plasminogen activator (t-PA) and plasminogen activator inhibitor type 1 (PAI-1), favoring the development of adverse thromboembolic cardiovascular events [11]. Moreover, AT II, via AT1 receptors, activates intracellular signaling pathways that promote atherogenesis through inflammation, endothelial dysfunction and increased autocrine growth factor release and LDL oxidation [12–15]. By AT1 receptor stimulation, AT II also contributes to cardiac hypertrophy development and might have positive chronotrophic effects. Thus, blockade of AT II by direct AT1 receptor blockade can prevent atherosclerosis development and cardiac hypertrophy, and improve procoagulative conditions [16]. Clinical trials also show potentially important correlations between AT receptor antagonist use and reduction in new-onset diabetes [17].

The combination of AT II receptor antagonists with diuretics increase efficacy and reduce adverse effects [18], decreasing resistance to diuretic action due to increased renin in the circulation [16]. Fixed-dose combinations also simplify treatment regimens and are likely to improve patient compliance [18].

Irbesartan is a potent, noncompetitive, long-acting, AT II AT1 receptor blocker marketed both alone and in association with a fixed dose of hydrochlorothiazide (HCTZ) [6]. This combination reduces BP significantly in patients inadequately controlled by irbesartan or HCTZ alone [19,20].

The addition of irbesartan had positive effects on HCTZ-induced biochemical abnormalities. In matrix studies, irbesartan appeared to blunt hypokalemia associated with HCTZ, and uric acid and total cholesterol levels were lower with combination than with HCTZ monotherapy. The HCTZ-associated increases in serum triglycerides were not increased by irbesartan [21]. Finally, the irbesartan–HCTZ combination has positive effects of AT receptor blocker on undesired effects of diuretic, provides advantages of AT II blockade, decreases resistance because of activated RAAS, simplifies the treatment regimen and provides better BP control. Moreover, HCTZ may increase organ-protective benefits of the AT receptor antagonist by providing better BP control in this combination.

Introduction to Irbesartan & HCTZ

Chemistry

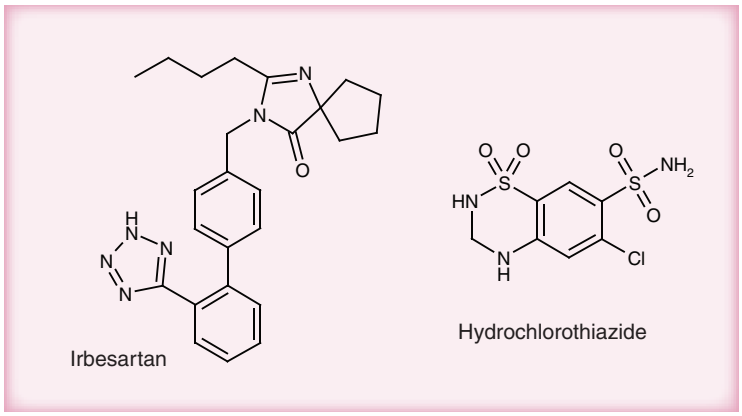
Irbesartan is an AT II (AT1 receptor subtype) antagonist with a lipophylic, nonpeptide chemical structure. It is a white crystalline powder and is chemically described as 2-butyl-3-[p-(o-1H-tetrazol-5-ylphenyl)benzyl]-1,3-diazaspiro[4,4]non-1-en-4-one, with empirical formula $C_{25}H_{28}N_6O$ (**Figure 1**). Irbesartan is slightly soluble in alcohol and methylene chloride and practically insoluble in water [22].

HCTZ is a diuretic and antihypertensive drug. It is the 3,4-dihydro derivative of chlorothiazide. Its chemical name is 6-chloro-3,4-dihydro-2*H*-1,2,4-benzothiadiazine-7-sulfonamide 1, 1-dioxide, with empirical formula $C_7H_8ClN_3O_4S_2$ (**Figure 1**). It is also a white crystalline powder and slightly soluble in water, but is freely soluble in sodium hydroxide solution [201].

Pharmacodynamics

AT II is a primary vasoactive hormone involved in the RAAS and is a potent vasoconstrictor formed from AT I by a reaction catalyzed by ACE, kininase II. AT II stimulates aldosterone synthesis and secretion by adrenal cortex, cardiac contraction, renal reabsorption of sodium, sympathetic nervous system activity and smooth muscle cell

Figure 1. Irbesartan and hydrochlorothiazide.



growth [22]. Irbesartan blocks the vasoconstrictor and aldosterone-secreting effects of AT II by selectively binding to AT1 AT II receptor [4].

Irbesartan shows long-acting inhibitor effects on pressor response to exogenous AT II when used in normotensive subjects [23–25]. This inhibitor effect is dose-dependent and 100% inhibition is provided after 2–4 h of drug administration. 24 h after the drug administration, DBP responses to AT II were decreased from 30 to 70%, compared with the baseline [25].

In randomized studies on healthy subjects and hypertensive patients with and without renal dysfunction, irbesartan increases plasma renin activity and AT II levels in a dose-dependent manner. In hypertensive patients, AT II receptor inhibition with chronic irbesartan administration causes a 1.5- to twofold increase in AT II plasma concentration and a two- to threefold increase in plasma renin levels [25–27].

Irbesartan shows insurmountable antagonism for AT1 receptors: it has no agonistic activity nor affinity for AT2 receptors [22,28].

Irbesartan, losartan and valsartan were compared regarding their AT1 receptor blocking effect in two randomized, double-blind studies on normal subjects. Single or multiple oral doses of irbesartan 150 mg/day, valsartan 80 mg/day and losartan 50 mg/day were administered [23,24]. Response to exogenous AT II as DBP inhibition was higher after 4, 24 and 30 h in one study, and also after 36 h in the other. Both studies showed a stronger receptor blockade by irbesartan.

In healthy subjects, irbesartan 50 mg provides significant increase in renal blood flow and has no significant effect on glomerular filtration rate [26,27]. Irbesartan may also have anti-inflammatory effects on the vascular endothelium [29].

In hypertensive patients, chronic irbesartan (up to 300 mg) use had no effect on glomerular filtration rate, renal plasma flow or filtration fraction. In multiple-dose studies in hypertensive patients, there were no clinically important effects on lipid and glucose metabolism. During chronic oral administration, no effect on serum uric acid concentration nor uricosuric effect were demonstrated [26,27].

HCTZ is a thiazide diuretic affecting the renal tubular mechanisms of electrolyte resorption, directly increasing renal tubular excretion of sodium by inhibiting thiazide-sensitive NaCl cotransporter (SLC12A3) in the distal convoluted tubule [30]. After oral administration of HCTZ, diuresis begins within 2 h, peaks at approximately 4 h and lasts approximately 6–12 h.

Indirectly, the diuretic action of HCTZ reduces plasma volume with a consequent increases in plasma renin activity, aldosterone secretion and urinary potassium loss, and decreases in serum potassium. The RAAS link is mediated by AT II, thus coadministration of AT II receptor antagonist tends to reverse the potassium loss associated with the use of these diuretics [201].

The combination of AT1 receptor antagonists with thiazides, and in particular irbesartan with HCTZ, has been studied in different trials [21,31,32]. Diuretic treatment alone activates the RAAS, so that its combination with RAAS blockers provides a convenient condition for antihypertensive action of RAAS blockers. In fact, the combination of AT1 receptor antagonists and HCTZ produces incremental increases in magnitude of the mean BP reduction compared with monotherapy [21,32–34]. Such combinations also attenuate potassium loss, usually associated with HCTZ therapy.

Pharmacokinetics & metabolism

Irbesartan has interesting pharmacokinetic properties that are described in **Table 1**.

Its bioavailability is not affected by foods and it is well absorbed [36]. When taken by healthy subjects as a single dose, irbesartan 150 mg has peak plasma concentration (C_{max}) of 1.9 mg/l; time to reach C_{max} (T_{max}) of 1.5 h; area under curve in time versus plasma concentration curve (AUC) of 9.7 mg/h/l; bioavailability of 61%; elimination half-life ($t_{½}$) of 16 h; and a renal clearance of 0.18 l/h. For 300 mg irbesartan, the C_{max} is 2.9 mg/l; the T_{max} is 1.5 h; AUC is 20 mg/h/l; and the $t_{½}$ is 14 h [37].

Irbesartan is metabolized via glucuronide conjugation and oxidation [38,39]. Following oral or intravenous administration of ^{14}C-labeled irbesartan, more than 80% of the circulating plasma radioactivity is attributed to unchanged irbesartan. The primary circulating metabolite is the inactive irbesartan glucuronide conjugate. The remaining oxidative metabolites do not add appreciably to irbesartan pharmacological activity [40].

Peak plasma concentrations are reached after 1.5–2 h of oral administration [41].

Irbesartan and its metabolites are excreted by both biliary and renal routes. Following either oral or intravenous administration of ^{14}C-labeled irbesartan, approximately 20% of radioactivity is recovered in the urine, and the remainder is recovered in the feces as irbesartan or irbesartan glucuronide [40].

In vitro studies of irbesartan oxidation by cytochrome P450 (CYP) isoenzymes indicated irbesartan was oxidized primarily by CYP2C9, and metabolism by CYP3A4 was negligible. Irbesartan was neither metabolized by, nor does it substantially induce or inhibit, isoenzymes commonly associated with drug metabolism (CYP1A1, CYP1A2, CYP2A6, CYP2B6, CYP2D6 and CYP2E1). There was no induction or inhibition of 3A4 [39].

Whereas losartan and candesartan require active metabolites to be active, irbesartan does not need biotransformation for pharmacological activity [42–44].

Irbesartan is 90% bound to serum proteins and the average volume of distribution is 53–93 l in healthy males [45,46]. Total plasma and renal clearances are in the range of 157–176 ml/min (9–11 l/h) and 3 ml/min (0.18 l/h), respectively [41].

Studies in animals indicate that radiolabeled irbesartan crosses the blood–brain barrier and placenta weakly. Moreover, irbesartan is excreted in the milk of lactating rats [46]. Irbesartan pharmacokinetics has not been investigated in detail in children. In the study by Sakarcan and colleagues, the pharmacokinetics of irbesartan were comparable groups aged 6–12 years and 13–16 years and a 2-mg/kg once-daily dose in hypertensive pediatric patients was found comparable with that of adults receiving a 2 mg/kg once-daily dose [47]. When the elimination half-life of the drug is compared between healthy young (aged 18–40 years) and healthy elderly (aged 65–80 years) patients, no significant difference was found. Thus, dose adjustment is not needed for the elderly population. Although somewhat higher plasma concentrations of irbesartan were observed in females, this is not significant and there is no need for gender-related dose adjustment [48].

The pharmacokinetics of orally administered irbesartan are not affected in mild-to-moderate liver failure [49], heart failure [50], mild-to-moderate renal failure or in dialysis patients [51].

Irbesartan has no relevant interactions with other drugs. Since it is metabolized by the CYP2C9 isoform, the other drugs that are the substrates or inhibitors of this cytochrome have been investigated: nifedipine [52], warfarin [53], simvastatin [54] and tolbutamide [55] have no significant interaction. HCTZ [56], magnesium- and aluminum-containing antacids [57] also have no effect on irbesartan pharmacokinetics.

Fluconazole, which is a potent inhibitor of CYP2C9, increases irbesartan AUC by 63% and C_{max} by 19%; however, when used together, the

Table 1. Main pharmacokinetic parameters of irbesartan and other angiontensin II receptor antagonists.

Parameter	Irbesartan	Candesartan	Eprosartan	Losartan	Olmesartan	Telmisartan	Valsartan
Usual dosage range (mg)	150–300	8–32	400–800	25–200	20–40	20–80	80–320
Dosing frequency	qd	qd/b.i.d.	qd/b.i.d.	qd/b.i.d.	qd	qd	qd
Terminal half-life (h)	11–15	9	5–9	3	13	24	13
Volume of distribution (l)	53–93	91	308	34	17	500	17
Renal elimination (%)	Unknown	26	7	4	35–50	0.5–0.9	35–50
Bioavailability (%)	60–80	15	13	29–43	26	30–60	10–35
Effect of food on bioavailability	no	no	↑C_{max}/AUC	↓C_{max}	min	min	↓C_{max}/AUC
Cytochrome P450 interaction	2C9	min	no	2C9 and 3A4	min	no	no

b.i.d.: Twice daily; C_{max}: Maximum concentration; qd: Once daily.

time needed to reach C_{max} for irbesartan does not change [58]. Therefore, irbesartan administration has no effect on digoxin pharmacokinetics [59].

Irbesartan absorption is not affected by food intake. In liver or kidney diseases, dose adjustment is not necessary; however, in hemodialysis patients and in patients aged over 75 years, treatment may be initiated at 75 mg/day [60].

HCTZ is not metabolized but eliminated by the kidney, at least 61% of the oral dose is eliminated unchanged within 24 h and it shows additive effects or potentiation of other antihypertensive drugs. It also potentiates the orthostatic hypotension effect of alcohol, barbiturates or narcotics. When used together, dose adjustment of antidiabetic drugs may be required according to the plasma glucose levels of the patient, since thiazide diuretics may lead to slight impairment of metabolic control and resistance to insulin action [61]. Absorption of HCTZ is decreased in the presence of exchange resins. HCTZ intensifies the hypokalemic effects of corticosteroids. Diuretic agents reduce the renal clearance of lithium and increase the risk of lithium toxicity [201]. HCTZ also crosses the placenta but not the blood–brain barrier, and is excreted in breast milk [201].

Clinical efficacy

Irbesartan can be used in hypertension, nephropathies and heart failure. Its combination with HCTZ is primarily indicated for moderate-to-severe hypertension, but it could also be useful for other irbesartan indications. Therefore, it is possible to evaluate the clinical efficacy under two main titles: BP-lowering efficacy and end-organ protection.

BP-lowering efficacy of irbesartan alone & in combination with HCTZ

Reeves and colleagues tested irbesartan at 1–900 mg/day doses for 9–12 weeks in 2955 hypertensive patients. Among them, 56% of the patients responded to therapy with a 150 mg/day dose and the antihypertensive effect increased with increased doses until 300 mg/day, and the response reached a plateau after 300 mg/day doses [62].

In another study, compared with placebo, 8 weeks treatment with irbesartan 50 mg/day or higher doses determined a significant decrease in BP but, with doses of 100, 200 and 300 mg/day, this response was already significantly higher after only 2 weeks. The plasma irbesartan concentration and BP decrease were proportional [63].

Fogari and colleagues demonstrated, in 215 patients, that irbesartan with multiple or a single 150 mg/day dose caused a significant decrease in systolic and DBP by having 24-h ambulatory BP (ABP) monitoring [63].

In mild-to-moderately hypertensive patients, irbesartan 150 mg/day monotherapy provides BP control in 56% of patients and, with doses up to 300 mg/day, this rate increase up to 66% [22].

Comparing the antihypertensive effect of irbesartan with other antihypertensive drugs, it appears to be as effective as enalapril [64,65] and atenolol [66]. When compared with other AT receptor blocker drugs, irbesartan has higher efficacy than valsartan [67] and losartan [68] in decreasing DBP. Irbesartan also has similar antihypertensive efficacy when compared with fosinopril [69].

Although, in another study, irbesartan 150 mg showed comparable efficacy with amlodipine 5 mg in the treatment of patients with seated DBP of 95–110 mmHg [70]. Comparison with doxazocin revealed that irbesartan has significantly better antihypertensive efficacy but doxazosin had more beneficial effects on metabolic parameters [71].

HCTZ and irbesartan show additive antihypertensive effect in a dose-dependent manner up to HCTZ 25 mg and irbesartan 300 mg [21]. In fact, compared with placebo, irbesartan 300 mg alone determined a systolic and DBP decrease of -14.9 and -10.2 mmHg, respectively; when associated to HCTZ 6.25 mg, decreases of -17.2 and -13.2 mmHg were observed; when associated to HCTZ 12.5 mg, decreases of -15.9 and -15.0 mmHg were observed; when associated to HCTZ 25 mg, decreases of -23.1 and -14.4 mmHg were observed. These data have been confirmed in different clinical trials [72–74].

The irbesartan–HCTZ combination (irbesartan 75–300 mg/day and HCTZ 12.5–25 mg/day) also provides an adequate control on 24-h BP level in up to 83% of patients in studies with 24-h ABP monitoring [75,76]. Combination therapy was also tested in patients with Type 2 diabetes and metabolic syndrome in subgroup analysis in the IrbesartaN/hydrochlorothiazide BP reductionS In diVErse patient populations (INCLUSIVE) trial. Treatment was well tolerated and achieved SBP goals (<140 mmHg; <130 mmHg for Type 2 diabetic patients) in 56% (95% confidence interval [CI]: 49–62%) of Type 2 diabetic and 73% (95% CI: 68–77%) of metabolic syndrome patients [77]. In the INCLUSIVE trial, efficacy and safety of

irbesartan–HCTZ fixed combinations were determined in 1005 adult patients of diverse population with uncontrolled BP while using antihypertensive monotherapy. Target BP levels were achieved in 77% (95% CI: 74–80%) of the patients for systolic (<140 mmHg; <130 mmHg for patients with Type 2 diabetes mellitus), 83% (95% CI: 80–86%) for diastolic (<90 mmHg; <80 mmHg for patients with Type 2 diabetes mellitus) and 69% (95% CI: 66–72%) for both BP levels. A total of 69% of patients enrolled in this study reached both systolic and DBP goals with irbesartan–HCTZ combination therapy, ademonstrating that such a combination therapy may be a convenient treatment option in patients with uncontrolled BP levels with monotherapy, and it also simplifies treatment [78]. In addition, when racial differences were evaluated in the same study between Caucasian, African–American and Hispanic/Latino patients, by week 18, 70% of Caucasian, 66% of African–American and 65% of Hispanic/Latino patients achieved both systolic and DBP goals. All treatments appeared well tolerated without major adverse effects and without significant difference between races [79].

In The COmpative Study of efficacy of Irbesartan/HCTZ with valsartan/HCTZ using home BP Monitoring in the treAtment of the mild-to-moderate hypertension (COSIMA) study, home BP monitorizations of 800 patients was evaluated, and fixed-dose combinations of irbesartan–HCTZ (150/12.5 mg) versus valsartan–HCTZ (80/12.5 mg) were compared. A superior BP-lowering efficacy of the irbesartan–HCTZ combination was observed [80].

When monitoring ABP of patients treated with losartan–HCTZ (50/12.5 mg) and irbesartan–HCTZ (150/12.5 mg), irbesartan–HCTZ combination resulted in greater reductions in ABP, especially in diastolic and mean ambulatory SBP measurements [81].

The newest AT II receptor antagonist, olmesartan, showed a significantly greater reduction in DBP when compared with irbesartan, losartan potassium and valsartan, and comparable reductions in DBP when they were all used in combination with HCTZ [82]. The percentage of patients achieving the combined SBP/DBP goal rate of <140/90 mmHg was found to be highest with olmesartan medoxomil (32.4%) compared with recommended starting doses of losartan potassium (16.1%), valsartan (14.5%) or irbesartan (25.9%) [83]. When 12-week ABP monitoring goal rates were evaluated, comparing olmesartan medoxomil 20 mg/day, losartan potassium 50 mg/day, valsartan 80 mg/day and irbesartan 150 mg/day, effects on mean change from baseline in ABP and ABP goal rates after 8 weeks of treatment were numerically better, but not statistically significant, for olmesartan medoxomil than for irbesartan [84].

End-organ protective effects

Efficacy on left ventricular hypertrophy & electrical stability of ventricle

Left ventricular hypertrophy is a well-known risk factor for cardiovascular mortality and morbidity [85,86]. In one study studying the effects of enalapril and irbesartan on left ventricular mass in 40 hypertensive subjects, both drugs were found to be effective in decreasing left ventricular mass significantly ($p < 0.05$), although this effect was more significant in the irbesartan group [87].

When compared with amlodipine 5–10 mg/day, irbesartan 150–300 mg/day use for 6 months causes a significantly more relevant decrease in left ventricular mass index, without decreasing the BP ($p < 0.0001$) [88].

Also, in other studies with atenolol and irbesartan, irbesartan provided a significantly more relevant decrease in left ventricular mass. Starting with mean left ventricular mass index 154 and 144 g/m^2 in irbesartan and atenolol groups, respectively, the difference became statistically significant after 48 weeks (17 and 10% decrease, $p = 0.024$) with similar decline in BP levels [89].

In the Swedish Irbesartan Left Ventricular Hypertrophy Investigation Versus Atenolol (SILVHIA) study, the effect of irbesartan and atenolol on QT dispersion and left ventricular mass after 24 weeks of drug use was studied [90]. Left ventricular mass decrease was -27 ± 28 versus 15 ± 24 g/m^2 in irbesartan and atenolol groups with similar BP decrease levels ($p = 0.021$). Also in the same study, QT dispersion decreased from 56 ± 24 to 45 ± 20 ms, the corrected QT dispersion (QT_c) decreased from 57 ± 24 to 44 ± 19 ms ($p < 0.001$). This decrease was significantly lower in the atenolol group ($p = 0.011$).

Effects on chronic heart failure

Tonkon and colleagues tested 12 weeks irbesartan treatment in addition to conventional combination treatments with ACE inhibitors on chronic heart failure patients and, significantly better ejection fraction and exercise tolerance with the addition of irbesartan to therapy [91]. In another study with 134 heart failure patients, lisinopril (titrated to 20 mg) and irbesartan

(titrated to 150 mg) were found to have the same efficacy on exercise tolerance and left ventricular ejection fraction [92].

Nephroprotective effects & use in patients with diabetic nephropathy

Microalbuminuria is defined as an independent cardiovascular disease risk factor in the VII JNC report and as an end-organ damage in ESH-ECC guidelines [2,93]. Microalbuminuria or proteinuria is related with a poor prognosis in hypertensive patients and the National Kidney Foundation advises to decrease proteinuria and control BP in its Proteinuria, Albuminuria Risk Assessment, Detection and Elimination (PARADE) task force [94].

Hypertension is an important risk factor for renal damage, especially in diabetic patients [95]. In Type 1 diabetic patients with albuminuria, ACE inhibitors were found to be effective in renoprotection [96].

In Type 2 diabetic patients, there are four major studies showing renoprotective effects of AT1 antagonists. In the MicroAlbuminuria Reduction with VALsartan (MARVAL) and Reduction of End points in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL) trials, valsartan and losartan were studied, respectively [97,98].

Studies in rats with streptozocin-induced diabetes have clearly demonstrated that irbesartan exerts a renoprotective effect, reducing proteinuria and albuminuria and preventing renal hyperfiltration. The irbesartan renoprotective effect may be related to its inhibition of renal hypertrophy and expression of growth factors, such as transforming growth factor-β_1 and connective tissue growth factor [99]. In this animal model, irbesartan significantly inhibited the increase in kidney weight, kidney weight:body weight ratio as a profile of kidney hypertrophy, renal tissue protein contents, glomerular area and glomerular volume [100]. Moreover, long-term diabetes in spontaneously hypertensive rats is also associated with a reduction in gene and protein expression of nephrin, which is an important protein in the slit diaphragm of the glomerular–podocyte barrier within the kidney. These changes in nephrin levels were completely prevented by irbesartan treatment [101]. In clinical studies carried out on Type 2 diabetic patients, irbesartan demonstrates beneficial effects on albumin excretion independent of its antihypertensive effects [102].

The renoprotective effects of irbesartan were evaluated in Program for Irbesartan Mortality and Morbidity Evaluation (PRIME) with two studies: IRbesartan in patients with Type 2 diabetes and MicroAlbuminuria (IRMA-2) and Irbesartan Diabetic Nephropathy Trial (IDNT) [103,104].

In the IRMA-2 study, 590 Type 2 diabetic, hypertensive and microalbuminuric patients were included. The aim of the study was to show whether irbesartan prevented or slowed nephropathy in these patients. In the 24-month follow-up period, irbesartan 150 and 300 mg/day were compared with placebo. Proteinuria development risk was significantly lower in both irbesartan groups. With irbesartan 300 mg/day, microalbuminuria also significantly decreased and a relevant quota of patients became normoalbuminuric (34% with 150 mg/day irbesartan vs 21% in placebo group; $p = 0.006$). This renoprotective effect was independent from the BP-lowering effect [103].

In the IDNT study, 1715 hypertensive Type 2 diabetic patients with nephropathy were followed-up for 2.6 years and irbesartan 300 mg/day and amlodipine 10 mg/day were compared. Development of end-stage renal disease, doubling of the creatinine values and overall mortality were primary end points. These primary end points were significantly less in the irbesartan group (23% with irbesartan, 20% in amlodipine; $p = 0.006$ and 0.02, respectively). Serum creatinine increase was 37% less in the irbesartan group when compared with amlodipine and 33% less when compared with placebo ($p < 0.001$ and $= 0.003$, respectively). Overall mortality and cardiovascular mortality rates were similar. Again, the effect of irbesartan on nephropathy development was independent of the BP-lowering effect [104].

According to IRMA-2, when we treat ten Type 2 diabetic hypertensive and microalbuminuric patients with irbesartan 300 mg/day, we prevent development of obvious nephropathy in one. And, according to IDNT data, when we treat 15 Type 2 diabetic hypertensive and proteinuric patients for 3 years, we prevent end-stage renal disease and doubling of creatinine values in one [105].

Thus, with the IRMA-2 and IDNT studies, irbesartan was found to be effective on both microalbuminuric and nephropathic Type 2 diabetic hypertensive patients.

Beyond beneficial effects in diabetic nephropathy, irbesartan may also have nephroprotective effects in nondiabetic kidney diseases. In a study by De Rosa and colleagues in 52 patients with hypertensive nephropathy, the BP-reducing effect of irbesartan was accompanied by a significant

reduction in proteinuria. Irbesartan was well tolerated and hyperkalemia requiring cessation of therapy was observed in only one patient [106].

In nondiabetic renal disease, dual blockade of the RAAS provides better control of proteinuria [107]. High-dose lisinopril (up to 40 mg/day) and irbesartan–HCTZ combination (300/12.5 mg/day) efficacy and safety were also evaluated in a small group of nondiabetic proteinuric patients [108]. This combination resulted in higher reductions in proteinuria but hyperkalemia, dizziness, increase in serum creatinine and cough were observed in five out of eight patients.

Irbesartan in combination with fosinopril is more effective in reducing proteinuria in patients with nondiabetic nephropathy than each drug alone, and the additive antiproteinuric effect of this combination is independent of changes in BP or creatinine clearance [109].

Irbesartan also significantly reduces arterial BP and proteinuria with good safety and tolerability in children with chronic kidney disease: its antiproteinuric effect appears to be better than that observed with amlodipine [110,111].

Other potentially important molecular actions

Multiple clinical trials show a consistent reduction in development of new diabetes during antihypertensive treatment with ACE inhibitors or AT II receptor antagonists [112,113]. Their mechanisms on insulin resistance is still not totally explained, although there is an intriguing hypothesis for the effects with AT II receptor antagonists involving off-target effects on the peroxisome proliferator-activated receptor (PPAR) nuclear hormone receptor system. The PPAR-γ agonists do not only improve insulin resistance in patients but also exert a broad spectrum of antiatherogenic effects *in vitro* and in animal models of atherosclerosis [114]. Telmisartan and irbesartan are identified as two AT receptor antagonists with selective PPAR modulator activity [115]. Notably, the effects observed with telmisartan and irbesartan were shown to be independent of AT II receptor antagonism in an AT1 receptor-deficient PC12W cell model; telmisartan and irbesartan enhanced transcriptional PPAR-γ activity by approximately twofold in this model (for irbesartan 3.4 ± 0.9-fold, for telmisartan 2.6 ± 0.6-fold stimulation), compared with 5.1 ± 1.1-fold stimulation by the PPAR-γ ligand pioglitazone [116]. However, among sartans, until now, telmisartan was only found to substantially activate PPAR-γ at plasma concentrations typically achieved with therapeutic dosages in different experimental models [117].

In an interesting study by Schieffer and colleagues, effects of irbesartan and enalapril were compared in a group of patients with coronary artery disease and hypertension for their effects on inflammation markers and platelet aggregation [118]. The study demonstrated that RAAS blockade by both ACE inhibition and AT1 receptor blockade enhance serum levels of interleukin (IL)-10, which has anti-atherogenic effects and they reduce matrix metalloproteinase (MMP)-9 protein/activity in patients with angiographically documented coronary artery disease. But only AT1 receptor blockade by irbesartan reduced circulating levels of IL-6 and high-sensitivity C-reactive protein (hsCRP), which are known markers of inflammation in atherosclerotic patients, and thromboxane (Tx)A2-induced platelet aggregation. The authors suggested that AT1 receptor blockade exerted more complete blockade of AT II proinflammatory and procoagulatory effects at the AT1 receptor level when compared with ACE inhibitors and showed stronger systemic antiinflammatory and anti-aggregatory effects. By blockade of AT II, irbesartan can also reduce serum markers of oxidative stress and improve endothelial function. In adolescents and young adults with early signs of diabetic angiopathy, treatment with irbesartan restored catalase and glutathione peroxidase activities and reduced markers of oxidative stress (serum malondialdehyde, fluorescent products of lipid peroxidation, monocyte chemoattractant protein-1 and 8-isoprostanes prostaglandin $F_{2\alpha}$) [119]. In another study carried out on patients with metabolic syndrome, the effects of irbesartan 150 mg/day, an over-the-counter nutritional supplement and antioxidant lipoic acid (300 mg/day) and their combination were compared in endothelial dysfunction, which was evaluated by brachial artery reactivity testing technique. Also, fasting plasma levels of IL-6, PAI-1, as markers of inflammation, and 8-isoprostane as a marker of oxidative stress, were detected. The combination of irbesartan and lipoic acid revealed better improvement on endothelial function than each preparation alone and both caused reductions in proinflammatory markers [120]. This study extends the anti-inflammatory and antioxidant effects of irbesartan to patients with metabolic syndrome and also demonstrates that irbesartan improves endothelial function in these patients.

Recently, in the EPAS (Endothelial protection, AT1 blockade and cholesterol-dependent oxidative stress) trial, 60 patients with stable coronary artery disease were randomized to pravastatin 40 mg/day, irbesartan 150 mg/day and a combination of these two drugs, or a control group, 4 weeks before coronary artery bypass grafting surgery. The examination of their internal mammary artery rings showed that irbesartan and pravastatin, both separately and in combination, improved endothelial function and increased the ratio of expression of vasoprotective genes to proatherogenic ones [121].

Safety & tolerability

Simon and colleagues analyzed the tolerability data of nine double-blind, randomized, placebo-controlled studies, with a total of 2606 patients. Placebo and irbesartan 900 mg/day or lower doses had similar undesirable effects (21 and 20%, respectively) [122]. Headache was found to be the only adverse effect reported by a significantly ($p = 0.005$) lower percentage of irbesartan patients (12%) compared with the placebo group (17%). In this study, 417 patients had taken 600–900 mg/day (higher than maximum daily doses), but the side effect rates were similar to 150–300 mg/day doses. The only undesirable effect was musculoskeletal trauma with irbesartan (1.9%) compared with placebo (0.5%). Other side effects and undesirable events were similar (fatigue, diarrhea, cough, heartburn, dyspepsia, tachycardia and anxiety) in both groups [122]. However, in another study including 1006 patients, the undesirable event rate was 20% with irbesartan and treatment was stopped because of this in 6% of patients [123]. In the study by Pool and colleagues, the most common side effects were headache (irbesartan group 12.7% vs placebo 15.8%), upper respiratory infection (irbesartan 9.0% vs placebo 5.1%), musculoskeletal pain (irbesartan 6.6% vs placebo 6.3%) and dizziness (irbesartan 4.4% vs placebo 5.1%) [21].

In postmarketing follow-up, most of the undesirable events were mild and the most frequent were dizziness (1.9%) and headache (1.8%) [124]. With irbesartan therapy, cough incidence is significantly lower than with enalapril therapy [125,126]. Also, irbesartan–HCTZ combination has side effects similar to placebo [72–74].

In the IDNT study, irbesartan therapy had a lower undesirable effect rate when compared with placebo and amlodipine ($p = 0.002$) [104]. Also in the IRMA-2 study, irbesartan treatment was associated with a lower undesirable effect rate than placebo [103]. In both studies, the amount of patients leaving treatment because of hyperkalemia were higher than placebo (0.4%) and amlodipine (0.5%) groups (1.9% for both studies, $p = 0.01$).

In another study with hypertensive chronic renal failure patients, irbesartan tolerability and safety was evaluated and hyperkalemia (>6 mEq/l) requiring drug withdrawal occurred in only one patient [106].

Prior to irbesartan treatment, volume or salt depletion (e.g., in patients treated vigorously with diuretics or in patients on dialysis) should be corrected. Otherwise, symptomatic hypotension may occur [202].

Irbesartan is contraindicated in pregnancy. When pregnant rats were treated with irbesartan, increased incidences of renal pelvic cavitation, hydroureter and/or absence of renal papilla were observed. In pregnant rabbits, irbesartan was associated with maternal mortality and abortion [202].

HCTZ may have adverse effects, especially on the fluid–electrolyte balance and lipid and glucose metabolism. These include extracellular fluid volume depletion, associated orthostatic hypotension and prerenal azothemia. It may cause hypokalemia owing to potassium secretion secondary to enhanced tubular fluid flow and aldosterone secretion induced by diuretic administration [127].

Irbesartan–HCTZ exposure in 975 patients was followed for 325 days, and a total of 82 patients (7.5%) discontinued the study as a result of adverse effects [128]. The most frequent causes were fatigue (0.8%), rash (0.5%), atrial rhythm disturbances (0.4%), dizziness (0.4%) and increased liver enzymes (0.4%). Among them, 41 (50%) were found to be unrelated to medication. During open-label therapy, out of 1095 patients, 794 (72%) reported one or more adverse events. The most common adverse events were musculoskeletal pain (13.1%), upper respiratory infection (12.5%), headache (10.3%) and fatique (7.5%). Orthostatic dizziness was reported in 3.2% of patients [128]. Clinically important laboratory abnormalities were rare during therapy. In all, 11 patients (1%) discontinued due to laboratory adverse events. The most common laboratory abnormality was increased liver enzymes or bilirubin (0.4%). Elevated creatinin kinase, glucose, potassium and triglycerides each led to discontinuation of one patient. Thus, long-term therapy with this combination was found to be safe.

Regulatory affairs

Irbesartan therapy is approved in essential hypertension and in nephropathy treatment of Type 2 diabetic and hypertensive patients. Irbesartan can be used as monotherapy or in combination with other antihypertensive drugs. Treatment is usually started with 150 mg/day and, according to follow-up, it may be increased up to 300 mg/day. In hypertensive Type 2 diabetic patients, the recommended dose is 300 mg/day for nephropathy treatment [60,104].

Ongoing studies

AT II AT1 receptor blockers have been widely tested on heart failure (in patients who also have preserved left ventricular systolic function) and post-infarction left ventricular dysfunction (VAL-HEFT, VALIANT and CHARM-PRESERVED), diabetic renal disease (PRIME and RENAAL) and stroke prevention in hypertensive patients with atrial fibrillation (in a LIFE substudy) [98,103,104,129–132].

Atrial fibrillation is an important and frequent, long-lasting cardiac rhythm disorder and increases cardiovascular mortality and morbidity [133]. There is a 3–6-fold increase in stroke risk in atrial fibrillation [134]. Usually, stroke risk is highest in the first few months after diagnosis [135]. In cohort studies, more than half of the patients with atrial fibrillation had hypertension and, in 15%, hypertension was the cause of atrial fibrillation [136]. Hypertension itself also increases the stroke risk in this patient group [137]. Left ventricular hypertrophy causes a 3–3.8-fold increase in atrial fibrillation risk [137]. In hypertension, atrial premature beats increase: this increase is more prominent when there is also left ventricular hypertrophy [92]. In hypertension, atrial conduction is affected and atrial refractoriness decreased [138].

Madrid and colleagues compared amiodarone monotherapy with amiodarone and irbesartan combination in cardioverted patients because of persistent atrial fibrillation and reported that the drug combination significantly decreased atrial fibrillation recurrence [139]. Also, in the SILVHIA study, irbesartan caused prominent improvement on ventricular repolarization parameters when compared with atenolol [90].

On the basis of these data, the Atrial Fibrillation Clopidogrel Trial With Irbesartan for Prevention of Vascular Events (ACTIVE) study has been planned. In this trial, aspirin–clopidogrel combination, aspirin monotherapy and standard oral anticoagulant treatment will be compared in atrial fibrillation patients. This study has ACTIVE W (warfarin vs aspirin plus clopidogrel; n = 6500), ACTIVE A (aspirin vs aspirin plus clopidogrel; n = 7500) arms and in the ACTIVE I group the patients from both other groups will also receive placebo or irbesartan (n = 10000 patients planned). Patients from the ACTIVE W or ACTIVE A group with systolic BP of 110 mmHg or higher will be included to ACTIVE I group. Primary end points are stroke, extracranial embolism, myocardial infarction and vascular death. Secondary end points are bleeding (for ACTIVE A and W), total mortality, hospitalization due to stroke and heart failure (for ACTIVE I) [60].

Another planned study on irbesartan involves diastolic heart failure patients. In the Framingham Heart Study, 51% of patients with heart failure had ejection fraction over 50% [140]. A third of the heart failure patients had normal or nearly normal left ventricular functions and, in another third, both systolic and diastolic functions were decreased [141,142]. Malmqvist and colleagues showed that irbesartan had positive effects on left ventricular hypertrophy and electrophysiology [89,90]. The Irbesartan in Heart Failure With Preserved Systolic Function (I-PRESERVE) study has planned a multicentre, double-blind, placebo-controlled study with 4100 patients who have ejection fraction higher than 45 but have symptomatic heart failure. Patients will be aged over 60 years, with hospitalization due to heart failure in last 6 months, and still with New York Heart Association (NYHA) II–IV heart failure symptoms and electrocardiographic or echocardiographic findings. Primary end points will be overall mortality and cardiovascular morbidity, and secondary end points are cardiovascular deaths, overall mortality, combined cardiovascular targets (cardiovascular death, nonfatal myocardial infarction and nonfatal stroke), combined heart failure targets (heart failure mortality or hospitalization as a result of heart failure), changes in quality of life, changes in NYHA class and changes in blood B-type natriuretic peptide levels [143,144].

Outlook

Ongoing and future large trials will help us to define which kind of patients will more strongly benefit from chronic treatment with

Highlights

- Irbesartan is an angiotensin II (AT1 receptor subtype) antagonist with lipophylic, nonpeptide chemical structure. Hydrochlorothiazide (HCTZ) is a diuretic derivative of chlorothiazide.
- Irbesartan blocks the vasoconstrictor and aldosterone-secreting effects of angiotensin II by selectively binding to AT1 angiotensin II receptor.
- HCTZ blocks the renal tubular mechanisms of electrolyte resorption, directly increasing excretion of sodium.
- Diuretic treatment alone activates the renin–angiotensin–aldosterone system (RAAS), so that its combination with RAAS blockers provides a convenient condition for antihypertensive action of RAAS blockers. Such combination also attenuates the potassium loss, usually associated with HCTZ therapy.
- A single dose of irbesartan 150 mg has a C_{max} of 1.9 mg/l; t_{max} of 1.5 h; AUC of 9.7 mg.h/l; a bioavailability of 61% (not influenced by food intake); half-life of 16 h; and a renal clearance of 0.18 l/h.
- Irbesartan is metabolized via glucuronide conjugation and oxidation. The primary circulating metabolite is the inactive irbesartan glucuronide conjugate. The remaining oxidative metabolites do not add appreciably to irbesartan pharmacological activity.
- Since irbesartan is metabolized by cytochrome P450 (CYP)2C9, it has no relevant interaction with other drugs.
- Irbesartan is 90% bound to serum proteins and its average volume of distribution is 53–93 l. Total plasma and renal clearances are in the range of 157–176 ml/min (9–11 l/h) and 3 ml/min (0.18 l/h), respectively.
- The pharmacokinetic of orally administered irbesartan is not affected in mild-to-moderate liver failure, heart failure, mild-to-moderate renal failure and also in dialysis patients.
- HCTZ is not metabolized but is eliminated rapidly by the kidney. At least 61% of the oral dose is eliminated unchanged within 24 h.
- Irbesartan 150–300 mg/day are the doses with proven efficacy for the treatment of mild-to-moderate hypertension and also has end-organ protective effects, such as nephroprotective actions, use in chronic heart failure and other potential molecular actions.
- The irbeartan antihypertensive effect is usually demonstrated after 2 weeks of treatment.
- Monotherapy with irbesartan 150–300 mg/day led to blood pressure normalization in 56–66% of patients.
- Irbesartan has a blood pressure-lowering effect similar to that of enalapril, atenolol and fosinopril and superior to that of valsartan and losartan (but less than olmesartan).
- Irbesartan–HCTZ fixed-dose combinations achieved blood pressure targets in 77% of patients for systolic, 83% for diastolic and 69% for both blood pressure levels.
- When compared with other fixed-dose sartan–HCTZ combinations, irbesartan–HCTZ showed superior blood pressure-lowering efficacy than valsartan–HCTZ and losartan–HCTZ.
- Irbesartan reduces left ventricular hypertrophy more significantly than amlodipine and atenolol.
- Irbesartan's efficacy as a chronic heart failure treatment is similar and addictive to that of angiotensin-converting enzyme (ACE) inhibitors.
- Renal protection effects of irbesartan have been demonstrated in two large trials: IRbesartan in patients with Type 2 diabetes and MicroAlbuminuria (IRMA-2) and Irbesartan Diabetic Nephropathy Trial (IDNT).
- Irbesartan also has nephroprotective effects in nondiabetic kidney diseases.
- Irbesartan in combination with the ACE inhibitor fosinopril is more effective in reducing proteinuria in nondiabetic nephropathy.
- Irbesartan has peroxisome proliferator-activated receptor (PPAR)-γ modulator activity, but among sartans, only telmisartan was found to activate PPAR-γ at plasma concentrations achieved with the therapeutic doses in experimental models.
- Irbesartan may demonstrate beneficial effects on inflammatory markers on atherosclerosis and endothelial function.
- End-organ protective and potential molecular actions of the combination of irbesartan with HCTZ should be tested by comprehensive studies.
- In clinical trials, the adverse events incidence with irbesartan and irbesartan plus HCTZ is similar to that observed with placebo.
- In postmarketing follow-up, most of the undesirable events were mild and the majority of them were dizziness (1.9%) and headache (1.8%). With irbesartan therapy, cough incidence is significantly lower than enalapril therapy.
- On the basis of animal data, irbesartan is contraindicated in pregnancy.
- In combination therapy, the most frequent cause of discontinuation of drug was fatigue (0.8%) and the most common adverse effect was musculoskeletal pain (13.1%).The most common laboratory abnormality was increased lived enzymes or bilirubin (0.4%), and long-term therapy with this combination was found to be safe.
- The Atrial Fibrillation Clopidogrel Trial With Irbesartan for Prevention of Vascular Events (ACTIVE) study has been planned to compare the preventive efficacy of irbesartan in patients affected by atrial fibrillation and treated with a aspirin–clopidogrel combination, aspirin monotherapy and standard oral anticoagulant treatment.
- The Irbesartan in Heart Failure With Preserved Systolic Function (I-PRESERVE) study has been planned to study the effect of irbesartan in elderly diastolic heart failure patients.
- There is still a need for new data concerning the use of this combination for potential actions on endothelial functions and target-organ protection.

irbesartan eventually associated to HCTZ. In particular, the ACTIVE study investigating the stroke preventive efficacy of irbesartan in arrhythmic patients, and the I-PRESERVE, studying its efficacy in diastolic heart failure patients, may clarify new potential effects of the molecule. Moreover, other research lines are evaluating the efficacy and safety of irbesartan on elderly subjects, patients affected by intracranial aneurysms and for other therapeutic indication, such as migraine attack prophylaxis. Therefore, as for other antihypertensive drugs, we will have to investigate whether irbesartan could have synergistic effect with other drugs affecting BP control and with antihyperlipidaemic agents, namely statins. All these results will presumably be available during the next 5 years. We may need several more years to obtain a clear answer to the question of if it will be possible to foresee irbesartan and its association with HCTZ efficacy on BP control and cardiovascular outcomes in patients with specific polymorphism involved in the clinical answer to antihypertensive patients in the view of a pharmacogenetic approach to hypertension treatment. Beyond all the available data on irbesartan, there is need for more studies on irbesartan alone and also its combination with HCTZ, especially on potential molecular actions concerning endothelial function and target organ protection.

Conclusion

In summary, irbesartan is a well-tolerated and effective antihypertensive drug that can also be used in hypertensive Type 2 diabetic patients in both early and late stages to slow renal disease. As shown from studies with other antihypertensive drugs in this class, new indications in cardiovascular and nephrologic diseases may evolve for irbesartan. Its combination with HCTZ provides better control of BP, decreased adverse effects of each drug and probably better patient adherence. Also, as in monotherapy, this combination may also be effective in indications beyond hypertension, including congestive heart failure, postmyocardial infarction management, diabetic nephropathy and others. However, there is still a need for new data regarding the use of irbesartan and also its combination with diuretics on its potential molecular actions.

Information resources

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