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REVIEW ARTICLE

The Comparative Efficacy and Safety of the Angiotensin Receptor Blockers in the Management of Hypertension and Other Cardiovascular Diseases

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Abstract All national guidelines for the management of hypertension recommend angiotensin receptor blockers (ARBs) as an initial or add-on antihypertensive therapy. The eight available ARBs have variable clinical efficacy when used for control of hypertension. Additive blood pressure-lowering effects have been demonstrated when ARBs are combined with thiazide diuretics or dihydropyridine calcium channel blockers, augmenting hypertension control. Furthermore, therapeutic use of ARBs goes beyond their antihypertensive effects, with evidence-based benefits in heart failure and diabetic renal disease particularly among angiotensin-converting enzyme inhibitor-intolerant patients. On the other hand, combining renin–angiotensin system blocking agents, a formerly common practice among medical subspecialists focusing on the management of hypertension, has ceased, as there is not only no evidence of cardiovascular benefit but also modest evidence of harm, particularly with regard to renal dysfunction. ARBs are very well tolerated as monotherapy, as well as in combination with other antihypertensive medications, which improve adherence to therapy and have become a mainstay in the treatment of stage 1 and stage 2 hypertension.

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Key Points

Angiotensin receptor blockers (ARBs) are effective initial antihypertensive therapies, which both lower blood pressure and have pleomorphic effects.

ARBs have proven benefits in diabetic kidney disease, stroke prevention and heart failure.

The safety and tolerability profiles of ARBs are among the best for antihypertensive drugs, and comparisons of agents within the class are similar.

1 Introduction

Hypertension is a common disorder in adults around the globe and is among the most common attributable causes of mortality [1]. The goal of antihypertensive therapy is to maintain blood pressure (BP) of <140/90 mmHg for most people [2–7]. Recent hypertension guidelines recommend that diuretics, calcium channel blockers (CCBs), angiotensin receptor blockers (ARBs) and angiotensin-converting enzyme (ACE) inhibitors are all appropriate initial antihypertensive therapies for most people. In the USA, it is suggested that African-Americans with hypertension should be started on diuretics or CCBs because of evidence-based clinical efficacy results. In addition, ACE inhibitors or ARBs are advocated for people with stage I–II hypertension and type 1 or 2 diabetes [3].

ARBs have been in clinical use since 1995 and are known to be effective antihypertensive agents with excellent tolerability profiles. ARBs have additive BP-lowering effects when they are combined with thiazide diuretics and

dihydropyridine CCBs, without increasing adverse event rates. Furthermore, ARBs have proven mortality and morbidity effects in heart failure and chronic renal disease, particularly when associated with type 2 diabetes. Concerns were raised surrounding the association of ARBs with development of solid cancers and coronary artery disease. These issues have largely been dismissed by both clinicians and US Food and Drug Administration (FDA) regulators [8–10]. Herein, we review the pharmacology and pharmacokinetics of ARBs. We also present pertinent research trials comparing the antihypertensive effects and cardiovascular benefits of ARBs, including the safety and tolerability issues encountered.

2 Pharmacology of Angiotensin Receptor Blockers

The renin–angiotensin–aldosterone system has been a major target pathway for development of antihypertensive medications. The four classes of medications that are involved in this pathway include ACE inhibitors, angiotensin II receptor blockers (ARBs), aldosterone antagonists and direct renin inhibitors. The interest in this pathway is due to the action of angiotensin II on the vascular system, renal sodium and water handling, and cellular proliferation [11]. Inhibition of ACE only partially inhibits formation of angiotensin II. Angiotensin II activates two types of angiotensin II receptors (ATR): ATR_1 and ATR_2. ATR_1 are abundant in the vessels, brain, heart, kidney, adrenal gland and nerves, while ATR_2 are prominently expressed in the fetus but decrease in number during the postnatal period, where they are only available in small numbers in the adult kidney, adrenal gland, heart, brain, uterus and ovary [12]. Activation of ATR_1 increases inositol triphosphate and various arachidonic acid metabolites, and decreases cyclic adenosine monophosphate. This causes generalized vasoconstriction from contraction of vascular smooth muscle, increases in aldosterone, resulting in increased sodium reabsorption in the proximal tubule, and cell growth in the arteries and heart [11]. Angiotensin II also facilitates catecholamine release from the adrenal medulla and nerve endings, inducing sympathetic nervous system hyperactivity [13]. Thus, antagonizing ATR_1 causes a reduction in both cardiac afterload and preload [11]. The antihypertensive property of ARBs is mainly due to a reduction of peripheral vascular resistance [14]. Angiotensin II is believed to have an important mechanistic role in promoting cardiovascular diseases that is unrelated to its effect on BP. Several animal studies have shown that it causes cardiac hypertrophy even in the absence of elevated BP [15]. Alderman et al. [16] found that individuals with a high renin–sodium profile have a greater risk of myocardial infarction than those with a normal or low profile.

ATR_2 function remains unclear, but its stimulation may inhibit cell growth, cell differentiation and apoptosis, and may cause vasodilation [17]. Animal studies show that ATR_2 stimulation improves cardiac function and prevents cardiac remodelling post-myocardial infarction [18].

The eight ARBs approved for use in the USA and Europe are nonpeptide compounds characterized by having biphenyl, tetrazole, benzimidazole or nonbiphenyl nontetrazole groups (Table 1). Candesartan, olmesartan, irbesartan, losartan and valsartan have a common tetrazolobiphenyl structure; candesartan and telmisartan have a common benzimidazole group; and eprosartan has a nonbiphenyl, nontetrazole chemical structure [19]. With the exception of irbesartan, all active ARBs have a free carboxylic acid group. On the other hand, azilsartan medoxomil is structurally similar to candesartan, except it has 5-oxo-1,2,4-oxadiazole in place of the tetrazole ring.

ARBs have more affinity for ATR_1 than for ATR_2 and can block the activities of angiotensin II on ATR_1 regardless of whether it was created from ACE or other enzymes such as cardiac chymase. ATR_1 binding affinity is not directly correlated with the antihypertensive effect of ARBs. All ARBs are insurmountable antagonists, except for losartan [14, 20]. Higher concentrations of angiotensin II cannot overcome the effect of an insurmountable ARB, but the impact of surmountability of ATR_1 blockade on final health outcomes has not been established [17].

3 Pharmacokinetic Considerations

Table 1 lists the pharmacokinetic characteristics of the eight available ARBs, including the half-life, time to maximum plasma concentration (T_{max}), bioavailability, elimination route, drug interaction and cytochrome P450 (CYP) metabolism [21–29]. All ARBs increase renal reabsorption of lithium, so concomitant use with lithium should be avoided. Their maximum BP effects occur about 3–6 h after administration [14, 19].

Losartan undergoes first-pass metabolism in the liver via the CYP system to form its active metabolite EXP-3174, which is 10–40 times more potent than losartan when given intravenously [14]. Its dose must be decreased by half in patients with severe hepatic impairment [30]. Although food delays its absorption and reduces its maximum plasma concentration (C_{max}), this is not clinically significant [14]. Fluconazole, a CYP2C9 inhibitor, increases the half-life of EXP-3174 but reduces its biological creation from losartan to a greater extent, decreasing its area under the curve (AUC) and C_{max} by 47 and 30 %, respectively. Rifampin, a uridine 5′-diphosphoglucuronosyltransferase glucuronosyl transferase and pan-CYP enzyme inducer, decreases the AUCs of losartan and

Table 1 Pharmacological characteristics of angiotensin receptor blockers (ARBs)

ARB	Half-life (h)	T_{max} (h)	Bioavailability (%)	Route of elimination: renal % (R) biliary/faecal % (B)	Food interaction	Drug interactions[a]	CYP metabolism
Losartan[b]	2	1–1.5	33	35 R; 60 B	Yes[c]	Rifampin, fluconazole	2C9, 3A4
Candesartan cilexetil	9	2–5[d]	42	33 R; 67 B	No	None	2C9 [negligible]
Eprosartan	5–9	1–3	63	7 R; 90 B	Yes[f]	None	No
Irbesartan	11–15	1.3–3	60–80	20 R; 80 B	No		2C9, 3A4 [negligible]
Telmisartan	24	0.5–1	43	<1 R; >97 B	No	Digoxin	No
Valsartan	6	2–4	23 [capsule] 50 [solution]	13 R; 83 B	Yes[e]	None	2C9 [weak]
Olmesartan medoxomil	12–14	1.7–2.5	26	35–50 R; 50–65 B	No	None	No
Azilsartan medoxomil	12	1.5–3	60	42 R; 55 B	No	None	2C9, 2B6 [negligible], 2C8 [negligible]

AUC area under the curve, C_{max} maximum plasma concentration, *CYP* cytochrome P450, T_{max} time to maximum plasma concentration

[a] Coadministration of ARBs with lithium increases lithium toxicity because of increased renal absorption of lithium

[b] Losartan is converted to EXP-3174, with a terminal half-life of 6–9 h and a T_{max} of 4–6 h

[c] Food delays the absorption and lowers the C_{max} of losartan, but the AUCs of it and EXP-3174 are not significantly altered

[d] T_{max} of candesartan, its active metabolite

[e] 40–50 % reduction in bioavailability

[f] High-fat food increases the bioavailability of eprosartan by 80 % and increases its AUC by 55 %, but slows gut absorption

EXP-3174 by 35 and 40 %, respectively. As such, any CYP2C9 enzyme inhibitors or inducers may reduce the effectiveness of losartan, and this must be considered during drug selection [30].

Three ARBs (candesartan cilexetil, olmesartan medoxomil and azilsartan medoxomil) are prodrugs and require activation in the gastrointestinal tract and liver to their active forms (candesartan, olmesartan and azilsartan, respectively) [31–33]. The C_{max} of olmesartan is increased by 14 % in elderly patients, but this is not clinically significant. The mean AUC of olmesartan is also significantly increased in patients with severe renal impairment (creatinine clearance <20 mL/min) and, while caution is advised, dose adjustment is not recommended [32].

Eprosartan, irbesartan, telmisartan and valsartan are not prodrugs and do not require metabolic activation. Irbesartan has one of the highest bioavailabilities among the ARBs. Irbesartan also exhibits a nearly linear dose response, with a plateau at 300 mg [14, 17, 34]. Telmisartan is the longest-acting angiotensin II receptor blocker on the market, with a mean half-life of 24 h. It has a rapid onset of action of about 0.5–1.0 h [14, 35]. Telmisartan coadministration with digoxin increases plasma digoxin levels, which may lead to toxicity secondary to P-glycoprotein blockade [36]. The bioavailability of valsartan is higher in its solution formulation than in capsule form [37].

4 Efficacy of Angiotensin Receptor Blockers

4.1 Blood Pressure Reductions with Angiotensin Receptor Blocker Monotherapy

Table 2 provides a summary of the initial and maximum doses, as well as the dosing intervals, for ARBs [22–29]. Antihypertensive efficacy is assessed by determining mean BP reductions from baseline, derived from the trough (end of dosing period) clinic BP readings or from ambulatory BP measurements. Table 3 lists randomized controlled trials directly assessing inter-agent antihypertensive effectiveness [21, 38–54]. The key findings regarding comparative efficacy in ARB monotherapy trials are highlighted below.

In the CLAIM studies, candesartan cilexetil doses of 16 and 32 mg/day were found to be more potent than losartan doses of 50 and 100 mg/day, respectively [38, 39]. Candesartan 16 mg/day also reduced clinic BP to a greater extent than losartan 100 mg/day [39]. In a trial of olmesartan medoxomil 20 mg/day, ambulatory systolic BP values were lowered more than with valsartan 80 mg/day and losartan 50 mg/day, and similarly to irbesartan 150 mg/day [44].

Forced titration of telmisartan from 40 mg and 80 mg/day has been observed to be more efficacious in reducing BP than losartan 50 mg and 100 mg/day [48]. In a small study evaluating telmisartan 80 mg/day, less BP reduction

Table 2 Doses for hypertension and other indications of angiotensin receptor blockers (ARBs)

ARBs	Starting dose (mg/day)[a]	Maximum dose (mg/day)	Dosing interval	Other approved indications, apart from hypertension
Losartan [22]	50	100	Once daily or twice daily	Diabetic nephropathy when serum creatinine is increased and proteinuria is present in patients with hypertension and type 2 diabetes; stroke reduction in patients with hypertension and left ventricular hypertrophy (non-black only)
Candesartan cilexetil [24]	16[b,c]	32	Once daily or twice daily	Treatment of heart failure (NYHA classes II–IV)
Eprosartan [28]	600	800	Once daily or twice daily	None
Irbesartan [25]	150[b]	300	Once daily	Diabetic nephropathy when serum creatinine is increased and proteinuria is present in patients with hypertension and type 2 diabetes
Telmisartan [27]	40[b]	80	Once daily	Cardiovascular risk reduction in patients unable to take ACE inhibitors
Valsartan [23]	80 or 160[c]	320	Once daily	Treatment of heart failure (NYHA classes II–IV); reduction of cardiovascular mortality in clinically stable patients with left ventricular failure or dysfunction following myocardial infarction
Olmesartan medoxomil [26]	20[b]	40	Once daily	None
Azilsartan medoxomil [29]	40 or 80	80	Once daily	None

ACE angiotensin-converting enzyme, *NYHA* New York Heart Association

[a] Recommended starting monotherapy dose in the absence of dehydration

[b] Lower doses for initial therapy are available for patients with renal dysfunction, including older persons

[c] Lower starting doses are typically initiated for the indication of heart failure (candesartan and valsartan) in twice-daily regimens

was observed than with valsartan 160 mg/day following 12 weeks of therapy [49]. Much larger controlled trials have found that telmisartan 80 mg/day was superior to valsartan 160 mg/day [55]. Furthermore, during the last 6 h of the once-daily dosing periods, telmisartan 80 mg/day lowered both systolic and diastolic BP to a greater extent than valsartan 160 mg/day [50].

Irbesartan 300 mg/day (but not 150 mg/day) has been found to have superior antihypertensive effects to losartan 100 mg/day [51]. Irbesartan 150 mg/day did demonstrate greater BP reductions than valsartan 80 mg/day [52]. Azilsartan medoxomil 40 mg/day was found to be equivalent to olmesartan 40 mg/day but superior to valsartan 320 mg/day, while the antihypertensive effect of azilsartan 80 mg/day was superior to both valsartan 320 mg/day and olmesartan 40 mg/day, using ambulatory systolic BP as the primary efficacy endpoint [21]. Eprosartan at 600 and 1,200 mg/day significantly reduces BP compared with placebo but has not been studied in comparison with other ARBs [56].

4.2 Blood Pressure Reductions with Combination Therapies

Most hypertension guidelines recommend that combination therapy should be used as initial therapy in stage 2 hypertension or in those patients for whom a single agent does not result in hypertension control. Fixed-dose combination (FDC) pills containing ARBs/diuretics and ARBs/amlodipine are increasingly used in the USA. Diuretic administration leads to activation of the renin–angiotensin system, and ARBs blunt this effect, allowing for the maximum benefit from diuretic-induced sodium depletion. This complementary action improves tolerability, since the dose of the components may be lowered [57]. The addition of ARBs also mitigates the negative metabolic effects associated with diuretics, including hypokalaemia, hyperuricaemia and glucose intolerance [58].

Similarly, the combination of ARBs with amlodipine has been shown to be highly effective and well tolerated as FDCs. Dihydropyridine calcium antagonists can cause peripheral oedema secondary to arterial vasodilatation-induced increases in capillary hydrostatic pressure. ARBs normalize capillary hydrostatic pressure by improving venous return to the heart and hence counteract the effect of amlodipine in a large proportion of individuals with oedema. Fogari et al. [59] showed that amlodipine alone causes an increase in ankle–foot volume and pretibial subcutaneous tissue pressure, and the addition of an ARB significantly attenuated these effects.

Table 3 Blood pressure (BP) reductions in randomized controlled trials of angiotensin receptor blockers (ARBs)

Study and year	Duration (weeks)	Titration type	Drug	Dosage (mg)	Sample size (*n*)	Mean baseline BP (mmHg)	Mean BP reduction (mmHg)
Candesartan (CAN) versus other ARBs							
Andersson and Neldam [38]	8	None	Candesartan	8	77	169/102	16[a]/9[a]
			Candesartan	16	80	168/103	17[a]/10[a]
			Losartan	50	74	168/104	15/9
Gradman et al. [40]	8	Optional	Candesartan	16–32	160	153/100	12/11
			Losartan	50–100	169	154/101	10/9
Lacourcière and Asmar [39]	8	Forced	Candesartan	8/16	106	162/101	*13*[a,b]/*9*[a]
			Losartan	50/100	100	161/100	*9*[a]/*7*[a]
Manolis et al. [41]	12	Optional	Candesartan	8–16	462	153/100	16/13
			Losartan	50–100	449	153/100	14/12
Vidt et al. [42]	8	Forced	Candesartan	16/32	306	154/100	13[b]/11[b]
			Losartan	50/100	303	152/100	10/9
Bakris et al. [54]	8	Forced	Candesartan	16/32	319	152/100	13[b]/11[b]
			Losartan	50/100	303	152/100	10/9
Olmesartan (OLM) versus other ARBs							
Oparil et al. [44]	8	None	Olmesartan	20	145	157/104	13[b]/9[b]
			Irbesartan	150	145	156/104	11/7
			Valsartan	80	142	155/104	8/6
			Losartan	50	146	157/104	9/6
Brunner et al. [43]	8	None	Olmesartan	20	312	162/104	21/16
			Candesartan	8	323	162/104	21/15
Giles et al. [45]	12	Forced	Olmesartan	20/40	182	155/103	14/12
			Losartan	50/100	180	155/103	13/12
			Valsartan	80/320	181	154/103	15/12
Telmisartan (TEL) versus other ARBs							
Mallion et al. [47]	6	None	Telmisartan	40	57	162/101	*14*[a]/*9*[a]
			Telmisartan	80	54	164/102	*16*[b]/*10*[b]
			Losartan	50	57	162/100	*10*[a]/*6*
Lee et al. [46]	4	Optional	Telmisartan	40–80	86	154/101	17[b]/9
			Losartan	50–100	90	155/102	14/9
Derosa et al. [33]	54	None	Telmisartan	40	40	143/92	8[a]/8[a]
			Eprosartan	600	39	144/91	7[a]/4[a]
Zhu et al. [48]	8	Optional	Telmisartan	40–80	164	149/99	13[b]/11[b]
			Losartan	50–100	166	165/100	9/9
Calvo et al. [49]	12	None	Telmisartan	80	34	152/89	*11/8*
			Valsartan	160	36	157/92	*19*[b]/*12*[b]
White et al. [50]	8	Forced	Telmisartan	40/80	244	154/99	*12/8*
			Valsartan	80/160	246	153/99	*11/7*
Irbesartan (IRB) versus other ARBs							
Kassler-Taub et al. [51]	8	None	Irbesartan	150	129	155/101	12[a]/10[a]
			Irbesartan	300	134	155/100	16[a,b]/12[a,b]
			Losartan	100	131	153/100	11[a]/9[a]
Mancia et al. [52]	8	None	Irbesartan	150	211	159/101	16[b]/11[b]
			Valsartan	80	215	158/101	10/7
Azilsartan (AZL) versus other ARBs							

Table 3 continued

Study and year	Duration (weeks)	Titration type	Drug	Dosage (mg)	Sample size (*n*)	Mean baseline BP (mmHg)	Mean BP reduction (mmHg)
White et al. [21]	6	None	Azilsartan	40	280	157/93	13[a,b] [versus VAL only]
			Azilsartan	80	285	158/92	15[a,b] [versus both VAL and OLM]
			Valsartan	320	282	157/93	10[a]
			Olmesartan	40	290	158/92	12[a]
Sica et al. [53]	24	Forced	Azilsartan	20/40	327	158/91	15[b]
			Azilsartan	20/80	329	158/92	17[b]
			Valsartan	80/320	328	157/91	12

Italicized mean BP reduction values are mean 24-h ambulatory readings

AZL azilsartan, *CAN* candesartan, *IRB* irbesartan, *OLM* olmesartan, *TEL* telmisartan, *VAL* valsartan

[a] Statistically significant versus placebo

[b] Statistically significant versus ARB comparator

Tables 4 and 5 list randomized controlled trials assessing the efficacy of therapies combining ARBs with diuretics and ARBs with amlodipine versus their component single therapies [60–76]. The key findings regarding comparative efficacy in ARB combination therapy trials are highlighted below.

In the nine trials assessing the impact of adding a thiazide diuretic to an ARB versus the diuretic alone, combination therapy reduced the systolic and diastolic BP values significantly more than diuretic monotherapy (at equivalent doses) after 6–12 weeks [61–68, 76]. In one trial, the addition of 12.5 mg/day of hydrochlorothiazide to candesartan 16 mg/day resulted in BP reductions similar to those seen with candesartan 32 mg/day [60].

There are three approved ARB/amlodipine FDCs: olmesartan/amlodipine, telmisartan/amlodipine and valsartan/amlodipine. Trials have shown that the addition of amlodipine to an ARB resulted in greater BP reductions than each component at similar doses. More patients in the combination therapy groups responded to achieve the target BP, compared with the component monotherapies, and with comparable adverse events [71–74]. Trials performed in South Korea and Japan have also shown beneficial effects of adding amlodipine to losartan and candesartan, but these combinations of losartan/amlodipine and candesartan/amlodipine are not approved in the USA [75, 76].

Management of hypertension in African-Americans, hypertension in patients with chronic kidney disease and isolated systolic hypertension in older people are often challenging [77]. In the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) cohort, about 31.5 % of black men versus 27.2 % of non-black men, and 27.2 % of black women versus 24.5 % of non-black women are taking three or more antihypertensive medications [78]. These more complicated patient populations have led to the development of FDCs with three classes of antihypertensives, comprising a thiazide diuretic, an ARB and a dihydropyridine calcium antagonist. The randomized controlled trials assessing the efficacy of these 'triple' FDCs versus their monotherapeutic components are shown in Table 6 [79, 80].

Calhoun et al. [79] published the first large-scale randomized controlled trial involving patients with stage I–II hypertension (entry BP $\geq$145/100 mmHg), assessing the efficacy of triple therapy with valsartan, amlodipine and hydrochlorothiazide versus dual therapy with its components. The valsartan/amlodipine/hydrochlorothiazide combination resulted in mean BP changes from baseline of 39.7/24.7 mmHg at maximum doses of each component. The triple therapy was statistically superior to the dual therapies ($p < 0.0001$ for triple therapy versus amlodipine/hydrochlorothiazide, amlodipine/valsartan and valsartan/hydrochlorothiazide). At 8 weeks of therapy, 70.8 % of patients receiving the triple therapy achieved control, versus 48.3 % for valsartan/hydrochlorothiazide, 54.1 % for amlodipine/valsartan and 44.8 % for amlodipine/hydrochlorothiazide (all $p < 0.0001$) (Table 6).

The TRINITY trial involved 2,492 randomized patients and showed that triple therapy with olmesartan/amlodipine/hydrochlorothiazide at 40/10/25 mg/day resulted in a 37/22 mmHg reduction in mean BP, compared with 27.5/15, 30/17 and 30/18 mmHg BP reductions with amlodipine/hydrochlorothiazide 10/25 mg/day, olmesartan/hydrochlorothiazide 40/25 mg/day and olmesartan/amlodipine 40/10 mg/day dual therapies, respectively (all $p < 0.001$). After week 12, 69.9 % of patients in the triple

Table 4 Blood pressure (BP) reductions in randomized controlled trials of angiotensin receptor blocker/diuretic combinations versus component monotherapies

Study and year	Duration (weeks)	Drug	Dose (mg)	Sample size (*n*)	Mean baseline BP (mmHg)	Mean BP reduction (mmHg) from baseline [versus comparator dose]
Candesartan (CAN)/HCTZ versus component monotherapy						
Bönner et al. [60]	12	CAN + HCTZ	16 + 12.5	3,337	160/95	29/14
		CAN	32	1,263	162/95	30/14
Eprosartan (EPR)/HCTZ versus component monotherapy						
Sachse et al. [61]	8	EPR + HCTZ	600 + 12.5	152	155/100	12[a]/11[a] [versus EPR 600]
		EPR	600	157	156/99	9/8
Olmesartan (OLM)/HCTZ versus component monotherapy						
Rosenbaum et al. [62][c]	8	OLM + HCTZ	20 + 12.5	262	156/97	7[a]/4 [versus OLM 40]
		OLM + HCTZ	20 + 25	474	153/97	12[a]/8[a] [versus OLM 40]
		OLM + HCTZ	40 + 12.5	263	154/98	9[a]/5[a] [versus OLM 40]
		OLM + HCTZ	40 + 25	607	154/97	14[a]/9[a] [versus OLM 40]
		OLM	40	264	156/97	3/2
Losartan (LOS)/HCTZ versus component monotherapy						
Saruta et al. [63]	8	LOS + HCTZ	50 + 12.5	154	154/101	18[a]/13[a] [versus both LOS 50 and HCTZ 12.5]
		LOS + HCTZ	50 + 6.25	159	155/101	15[a]/10[a] [versus HCTZ 12.5]
		LOS + HCTZ	25 + 6.25	153	155/101	14/10
		LOS	50	157	154/101	10/9
		HCTZ	12.5	162	155/100	12/8
Salerno et al. [64][b]	6	LOS + HCTZ	50/100 + 12.5/25	393	171/113	25[a]/18[a] [versus LOS 100]
		LOS	50/100	192	171/113	14/12
Irbesartan (IRB)/HCTZ versus component monotherapy						
Neutel et al. [65][b]	8	IRB + HCTZ	150/300 + 12.5/25	303	162/98	27[a]/15[a] [versus both IRB 300 and HCTZ 25]
		IRB	150/300	95	161/98	22/12
		HCTZ	12.5/25	95	162/98	16/7
Valsartan (VAL)/HCTZ versus component monotherapy						
Calhoun et al. [66][b]	6	VAL + HCTZ	160/320 + 12.5/25	307	169/112	33[a]/24[a] [versus VAL 320]
		VAL	160/320	301	168/112	24/18
Telmisartan (TEL)/HCTZ versus component monotherapy						
Lacourcière and Martin [67]	8	TEL + HCTZ	40 + 12.5	159	147/96	11[a]/7[a] [versus TEL 40]
		TEL	40	162	147/96	3/4
Lacourcière et al. [68]	8	TEL + HCTZ	80/12.5	246	149/96	13[a]/8[a] [versus TEL 80]
		TEL	80	245	149/97	7/5
Neldam et al. [69]	8	TEL + HCTZ	80/12.5	361	148/95	7/6
		TEL + HCTZ	80/25	352	148/95	10[a]/7[a] [TEL 80 + HCTZ 12.5]
Azilsartan (AZL)/chlorthalidone (CHL) versus component monotherapy						
Sica et al. [70]	8	AZL + CHL	20 + 12.5	156	165/95	34[a]/14[a] [versus both AZL 25 and CHL 12.5]
		AZL + CHL	20 + 25	154	165/96	37[a]/16[a] [versus both AZL 20 and CHL 25]
		AZL + CHL	40 + 12.5	147	165/96	37[a]/16[a] [versus both AZL 40 and CHL 12.5]
		AZL + CHL	40 + 25	156	164/94	40[a]/17[a] [versus both AZL 40 and CHL 25]
		AZL + CHL	80 + 12.5	153	165/94	37[a]/17[a] [versus both AZL 80 and CHL 12.5]

Table 4 continued

Study and year	Duration (weeks)	Drug	Dose (mg)	Sample size (*n*)	Mean baseline BP (mmHg)	Mean BP reduction (mmHg) from baseline [versus comparator dose]
		AZL + CHL	80 + 25	162	164/94	40[a]/19[a] [versus both AZL 80 and CHL 25]
		AZL	20	155	163/95	20/7
		AZL	40	153	164/95	23/9
		AZL	80	162	164/95	24/10
		CHL	12.5	157	164/96	21/7
		CHL	25	159	166/96	27/9

AZL azilsartan, *CAN* candesartan, *CHL* chlorthalidone, *EPR* eprosartan, *HCTZ* hydrochlorothiazide, *IRB* irbesartan, *LOS* losartan, *OLM* olmesartan, *TEL* telmisartan, *VAL* valsartan

[a] Statistically significant versus the equivalent component monotherapy

[b] Forced titration

[c] 24-h ambulatory BP monitoring data; the rest are clinic BP data

therapy group achieved goals of BP <140/90 (or <130/80 mmHg for patients with diabetes or chronic kidney disease), compared with 41.1, 53.4 and 52.9 % of the amlodipine/hydrochlorothiazide, olmesartan/hydrochlorothiazide and olmesartan/amlodipine combination treatment groups, respectively (all $p < 0.001$) [80]. This more effective reduction in BP with triple therapy was not affected by race/ethnicity, body weight or presence of type 2 diabetes mellitus [81–83].

5 Use of Multiple Renin–Angiotensin Blockers

A meta-analysis comprising 38 randomized controlled trials showed no mortality benefit associated with dual ARB and ACE inhibitor therapy, and did reveal an increase in nonfatal adverse events, including hyperkalaemia (potassium level ≥6.0 mmol/L; relative risk [RR] 1.66 [95 % confidence interval (CI) 1.38–1.98], $p < 0.001$), hypotension (RR 1.66 [95 % CI 1.38–1.98], $p < 0.001$) and increased risk of a decline in renal function (creatinine >2.0 mg/dL; RR 1.41 [95 % CI 1.09–1.84], $p = 0.01$) versus ARB or ACE inhibitor therapy alone [84].

The Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET) showed that although the telmisartan/ramipril combination reduced progression of proteinuria in patients with vascular disease (hazard ratio [HR] 0.76 [95 % CI 0.60–0.96], $p = 0.019$ for combination therapy versus ramipril), the incidence of the composite primary renal outcome (dialysis, doubling of creatinine and death; HR 1.09 [95 % CI 1.01–1.18], $p = 0.037$) was actually increased with the combination therapy versus ramipril alone [85].

Similarly, in the Aliskiren Trial in Type 2 Diabetes Using Cardio-Renal Endpoints trial (ALTITUDE), the direct renin inhibitor aliskiren or placebo was added to background ACE inhibitor or ARB therapy. The trial was terminated prematurely because of a lack of benefit and an increase in hyperkalaemia (potassium level ≥6.0 mm/L; 11.2 % in the aliskiren arm versus 7.2 % in the placebo arm, $p < 0.001$) and reported hypotension (12.1 % in the aliskiren arm versus 8.3 % in the placebo arm, $p < 0.001$) [86].

6 Angiotensin Receptor Blockers and Cardiovascular Outcomes in Patients with Hypertension (Table 7)

Data from the INTERHEART (Effect of Potentially Modifiable Risk Factors Associated with Myocardial Infarction) trial showed that hypertension is one of the top risk factors for acute myocardial infarction, with an odds ratio of 2.48 (99 % CI 2.30–2.68). Other risk factors identified in this population study included current smoking, raised apolipoprotein (Apo)-B/ApoA1, history of diabetes and psychosocial factors [87].

In the Losartan Intervention for Endpoint Reduction in Hypertension (LIFE) trial, losartan was found to reduce cardiovascular morbidity and death by 13 %, compared with the beta blocker atenolol ($p = 0.021$), despite similar reductions in BP among hypertensive patients with left ventricular hypertrophy [88]. Losartan also reduced the incidence of fatal and nonfatal stroke by 25 %, compared with atenolol ($p = 0.002$). In contrast, losartan did not reduce cardiovascular mortality or myocardial infarction, compared with atenolol [88]. In the Valsartan Antihypertensive Long-term Use Evaluation (VALUE) trial [89], valsartan did not show an advantage over amlodipine in reducing cardiac mortality and morbidity. However, in VALUE, there was an unexpected difference in BP control, particularly during the first year of the study, with the

Table 5 Blood pressure (BP) reductions in randomized controlled trials of angiotensin receptor blockers and amlodipine in combination versus component monotherapy

Study and year	Duration (weeks)	Drug	Dosage (mg)	Sample size (*n*)	Mean baseline BP (mmHg)	Mean BP reductions from baseline (mmHg) [versus comparator dose]
Olmesartan (OLM)/amlodipine (AML) versus component therapy						
Chrysant et al. [71]	8	OLM + AML	10 + 5	163	166/102	24[a]/14[a] [versus both AML 5 and OLM 10]
		OLM + AML	10 + 10	162	163/101	25[a]/16[a] [versus both AML 10 and OLM 10]
		OLM + AML	20 + 5	161	164/102	24[a]/14[a] [versus both AML 5 and OLM 20]
		OLM + AML	20 + 10	160	164/101	29[a]/17[a] [versus both AML 10 and OLM 20]
		OLM + AML	40 + 5	162	162/101	25[a]/16[a] [versus both AML 5 and OLM 40]
		OLM + AML	40 + 10	162	166/102	30[a]/19[a] [versus both AML 10 and OLM 40]
		OLM	10	161	163/102	12/8
		OLM	20	161	164/102	14/9
		OLM	40	162	163/101	16/10
		AML	5	161	163/102	15/9
		AML	10	163	164/102	20/13
Valsartan (VAL)/amlodipine (AML) versus component therapy						
Philipp et al. [72] study 1	8	VAL + AML	40 + 5	125	153/99	20[a]/15[a] [versus both AML 5 and VAL 40]
		VAL + AML	80 + 5	128	153/99	21[a]/15[a] [versus both AML 5 and VAL 80]
		VAL + AML	160 + 5	127	153/99	20[a]/14[a] [versus both AML 5 and VAL 160]
		VAL + AML	320 + 5	127	153/99	23[a]/16[a] [versus both AML 5 and VAL 320]
		VAL + AML	40 + 2.5	129	153/100	16[a]/11 [versus both AML 2.5 and VAL 40]
		VAL + AML	80 + 2.5	130	152/100	17[a]/13[a] [versus both AML 2.5 and VAL 80]
		VAL + AML	160 + 2.5	127	152/99	17[a]/13[a] [versus both AML 2.5 and VAL 160][e]
		VAL + AML	320 + 2.5	129	152/99	18[a]/14[a] [versus AML 2.5 only]
		VAL	40	127	154/99	12/10
		VAL	80	124	153/99	13/10
		VAL	160	128	152/99	15/11
		VAL	320	128	155/99	16/13
		AML	2.5	126	154/100	12/9
		AML	5	128	153/99	15/12
Philipp et al. [72] study 2	8	VAL + AML	160 + 10	209	157/99	28[a]/18[a] [versus both AML 10 and VAL 160]
		VAL + AML	320 + 10	210	157/99	28[a]/19[a] [versus both AML 10 and VAL 320]
		VAL	160	207	156/99	20/13
		VAL	320	208	158/99	20/13
		AML	10	207	156/99	24/16
Flack et al. [73][b,c]	8	VAL + AML	160/320 + 5/10	286	170/99	33[a]/14[a] [versus AML 10 only]
		AML	5/10	286	171/98	27/11
Telmisartan (TEL)/amlodipine (AML) versus component therapy						
Neutel et al. [74]	8	TEL + AML	80/10	421	185/103	48[a]/19[a] [versus both AML 10 and TEL 80]
		TEL	80	217	186/103	37/14
		AML	10	220	185/103	43/16
Losartan (LOS)/amlodipine (AML) versus component therapy						
Hong et al. [75][d]	8	LOS + AML	100 + 5	70	142/98	13[a]/12[a] [versus LOS 100]
		LOS	100	72	141/97	3/3
Candesartan (CAN)/amlodipine (AML) versus component therapy						

Table 5 continued

Study and year	Duration (weeks)	Drug	Dosage (mg)	Sample size (*n*)	Mean baseline BP (mmHg)	Mean BP reductions from baseline (mmHg) [versus comparator dose]
Rakugi et al. [76]	12	CAN + AML	8 + 5	101	152/95	27[a]/16[a] [versus both AML 5 and CAN 8]
		CAN + AML	8 + 2.5	36	152/96	20/12
		CAN + AML	4 + 5	36	155/97	27/17
		CAN + AML	4 + 2.5	35	153/96	16/10
		CAN	8	100	155/97	14/8
		AML	5	100	153/96	20/11

AML amlodipine, *CAN* candesartan, *LOS* losartan, *OLM* olmesartan, *TEL* telmisartan, *VAL* valsartan

[a] Statistically significant versus component monotherapy

[b] Forced titration

[c] African-American patients

[d] Korean patients

[e] Statistically significant for systolic BP reduction versus AML monotherapy alone and for diastolic BP reduction for both component monotherapies

amlodipine arm resulting in a 17.3/9.9 mmHg versus 15.2/8.2 mmHg reduction in those randomized to valsartan, respectively, $p < 0.0001$). These differences likely contributed to the finding that cardiac events were significantly higher in the valsartan arm (Table 7).

In the Study on Cognition and Prognosis in the Elderly (SCOPE) [90], involving 4,964 participants aged 70–89 years with hypertension, candesartan (versus placebo) did not result in a significant risk reduction in major cardiovascular events, including myocardial infarction and cardiovascular mortality, but nonfatal stroke was reduced by 27.8 % (95 % CI 1.3–47.2, $p = 0.04$).

The Telmisartan Randomised Assessment Study in ACE Intolerant Subjects with Cardiovascular Disease (TRANSCEND) study [91] evaluated high-risk patients intolerant of ACE inhibitors with a prior history of cardiovascular disease or diabetes mellitus without heart failure, with about 70 % of the participants being hypertensive. Patients were randomized to telmisartan or placebo added to standard-of-care therapy (excluding renin–angiotensin blocking therapy). After 56 months of follow-up, telmisartan resulted in fewer major cardiovascular events compared with placebo (15.7 versus 17.0 %), but the result was not statistically significant (HR 0.92 [95 % CI 0.81–1.05], $p = 0.216$).

7 Angiotensin Receptor Blockers in Diabetes and Kidney Disease

ARBs have been used to reduce intraglomerular hypertension in patients with diabetic nephropathy. By reducing the gradient within the glomerulus, the hypothesis is that fibrosis of the nephron will be averted. The Irbesartan in Patients with Type 2 Diabetes and Microalbuminuria (IRMA 2) trial showed that over 1 year in patients with hypertension, type 2 diabetes mellitus and microalbuminuria, fewer participants progressed to macroalbuminuria among patients treated with irbesartan compared with placebo, with hazard ratios (HRs) of 0.30 in the irbesartan 300 mg/day group (95 % CI 0.14–0.61, $p < 0.001$) and 0.61 in the irbesartan 150 mg/day group (95 % CI 0.34–1.08, $p = 0.08$) [92].

The Microalbuminuria Reduction with Valsartan in Patients with Type 2 Diabetes Mellitus trial (MARVAL) compared the antiproteinuric effects of valsartan and amlodipine in patients with type 2 diabetes and microalbuminuria. Both arms targeted a BP of 135/85 mmHg. The urine albumin excretion rate at 24 weeks with valsartan 80 mg/day was 56 % of baseline, compared with 92 % of baseline with amlodipine 5 mg/day ($p < 0.001$). Additionally, more patients reversed to normoalbuminuria with valsartan compared with amlodipine (29.9 versus 14.5 %, $p < 0.001$) [93].

The Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL) trial included patients with type 2 diabetes mellitus with nephropathy. Losartan reduced the incidence of doubling of serum creatinine (risk reduction 25 %, $p = 0.006$), with a 35 % reduction in proteinuria, and reduced the incidence of end-stage renal disease (risk reduction 28 %, $p = 0.002$) versus placebo, but without a mortality benefit. Except for lowering the rate of first hospitalizations for heart failure (risk reduction 32 %, $p = 0.005$), the composite endpoint of morbidity and mortality from cardiovascular causes was similar for losartan therapy and placebo after 3.4 years of therapy [94].

Table 6 Blood pressure (BP) reductions in randomized controlled trials of angiotensin receptor blockers with diuretic and amlodipine triple combinations versus dual therapy

Study and year	Duration (weeks)	Drug	Dosage (mg)	Sample size (*n*)	Mean baseline BP (mmHg)	Mean BP reductions from baseline (mmHg)
Calhoun et al. [79][b]	8	VAL + HCTZ + AML	160 + 12.5 + 5/ 320 + 25 + 10	571	170/106	40[a]/25[a] [versus all dual therapies]
		VAL + HCTZ	160 + 12.5/ 320 + 25	553	170/106	32/20
		VAL + AML	160 + 5/ 320 + 10	558	170/107	34/22
		HCTZ + AML	12.5 + 5/ 25 + 10	554	171/107	32/20
Oparil et al. [80]	12	OLM + HCTZ + AML	40 + 25 + 10	614	168/101	37[a]/22[a] [versus all dual therapies]
		OLM + HCTZ	40 + 25	627	169/101	30/17
		OLM + AML	40 + 10	624	168/101	30/18
		HCTZ + AML	25 + 10	593	169/101	28/15

AML amlodipine, *HCTZ* hydrochlorothiazide, *OLM* olmesartan, *VAL* valsartan

[a] Statistically significant versus dual therapy

[b] Forced titration

In the Irbesartan Diabetic Nephropathy Trial (IDNT) involving hypertensive patients with diabetic nephropathy, the irbesartan arm had a 37 % lower risk of doubling serum creatinine versus the amlodipine arm ($p < 0.001$) and 33 % lower than the placebo group ($p = 0.003$). The rate of development of end-stage renal disease was nominally lower with irbesartan than with amlodipine and placebo, but it did not reach statistical significance ($p = 0.07$) [95].

8 Angiotensin Receptor Blockers in Post-myocardial Infarction and Heart Failure Patients

Angiotensin blockade is a major therapeutic strategy in patients with heart failure, providing a balanced reduction in preload and afterload when reduced systolic function occurs after an ischaemic event or because of nonischaemic cardiomyopathy. In a number of trials, ARBs have been compared with ACE inhibitors in patients with systolic heart failure. In the Losartan Heart Failure Survival Study (ELITE II), losartan 50 mg/day was not found to be superior to captopril 150 mg/day (given in three doses) in reducing all-cause mortality in patients with New York Heart Association (NYHA) class II–IV heart failure and a left ventricular ejection fraction (LVEF) ≤40 %. Of note, approximately 80 % of the patients in ELITE II had ischaemic causes of heart failure, and 50 % were classified as NYHA class II (mild–moderate). There was an average annual mortality rate of 11.7 % in the losartan arm versus 10.4 % in the captopril arm (HR 1.13 [95 % CI 0.95–1.35], $p = 0.16$). In addition, 142 and 115 sudden deaths or resuscitated cardiac arrests were recorded in the losartan and captopril groups, respectively (HR 1.24 [95 % CI 0.97–1.59], $p = 0.08$). Not surprisingly, fewer patients discontinued treatment prematurely because of adverse effects in the losartan group, compared with captopril (9.7 % versus 14.7 %, $p = 0.001$) [96].

The Valsartan in Acute Myocardial Infarction (VALIANT) Study showed that valsartan was as effective as captopril in reducing all-cause mortality among patients with a history of acute myocardial infarction (valsartan group versus captopril; HR 1.00 [97.5 % CI 0.90–1.11], $p = 0.98$), but the combination of captopril plus valsartan did not prove to be superior to the monotherapy regimens [97]. The Optimal Trial in Myocardial Infarction with the Angiotensin II Antagonist Losartan (OPTIMAAL) Study demonstrated that another ARB, losartan, was comparable to captopril in reducing overall mortality in patients with a history of myocardial infarction and heart failure with left ventricular dysfunction (LVEF <35 %; RR 1.13 [95 % CI 0.99–1.28], $p = 0.07$) [98].

The Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity (CHARM) study was actually composed of three trials: CHARM-Alternative (LVEF ≤40 % and ACE intolerant) versus placebo; CHARM-Added (LVEF ≤40 % in patients already on

Table 7 Impact of angiotensin receptor blocker (ARB) therapies on cardiovascular outcomes

Study and year	ARB (mg/day) [*n*]	Comparator (mg/day) [*n*]	Primary outcome	Main results	Comments
Hypertension primary outcome trials					
LIFE [88]	Losartan 100 [4,605]	Atenolol [4,588]	Death, myocardial infarction or stroke	Losartan reduced cardiovascular morbidity and death more than atenolol (RR 0.87, $p = 0.021$)	Similar reductions in BP achieved in two groups with left ventricular hypertrophy
VALUE [89]	Valsartan 160 [7,649]	Amlodipine 10 [7,596]	Cardiovascular mortality and morbidity	No difference between valsartan and amlodipine (HR 1.04, $p = 0.49$)	Amlodipine resulted in greater BP reduction than valsartan, causing potential confounding in high-risk patients
SCOPE [90]	Candesartan 16 [2,477]	Placebo [2,460][a]	Cardiovascular death, nonfatal stroke and nonfatal myocardial infarction	No difference between candesartan and placebo ($p = 0.19$)	Candesartan reduced nonfatal stroke by 27.8 % ($p = 0.04$)
Renal disease					
ONTARGET [85]	Telmisartan 80 [8,541]	Telmisartan/ramipril combination 80/10 [8,502] Ramipril 10 [8,576]	Composite of dialysis, doubling of serum creatinine and death	Composite primary renal outcome was similar between telmisartan (HR 1.00, 95 % CI 0.92–1.09) but increased with combination therapy (HR 1.09, 95 % CI 1.01–1.18, $p = 0.037$)	Patients were aged 55 years or older with established atherosclerotic vascular disease or with diabetes with end-organ damage
IRMA 2 [92]	Irbesartan 150 [195] or irbesartan 300 [194]	Placebo [201][a]	Progression to diabetic nephropathy based on increases in proteinuria	Reduction of progression to diabetic nephropathy (IRB 300 mg HR 0.30, $p < 0.001$; IRB 150 mg HR 0.61, $p = 0.08$)	The effect of irbesartan was independent of its antihypertensive effect
RENAAL [94]	Losartan 100 [751]	Placebo [762][a]	Doubling of baseline serum creatinine, development of ESRD or death from any cause	Losartan reduced the incidence of doubling of serum creatinine (25 % risk reduction, $p = 0.006$) and the incidence of ESRD (28 % risk reduction, $p = 0.002$) versus placebo	Losartan showed no ESRD mortality benefit
IDNT [95]	Irbesartan 300 [579]	Amlodipine 10 [567] Placebo [569][a]	Doubling of serum creatinine, development of ESRD or death from any cause	Irbesartan reduced the incidence of doubling of serum creatinine versus amlodipine (37 % risk reduction, $p < 0.001$) and placebo (33 % risk reduction, $p = 0.003$)	Irbesartan was associated with 23 % lower incidence of ESRD versus placebo and amlodipine (both $p = 0.07$)
Heart failure					
ELITE II [96]	Losartan 50 [1,578]	Captopril 150 [1,574]	All-cause mortality and sudden death or resuscitated arrest	No significant differences in all-cause mortality with average annual mortality of 11.7 % in the losartan arm versus 10.4 % in the captopril arm (HR 1.13, $p = 0.16$)	Losartan was better tolerated than captopril
CHARM-Alternative [100]	Candesartan 32 [1,013]	Placebo [1,015]	Composite of cardiovascular death or hospital admission for CHF	Candesartan reduced cardiovascular death and hospitalization for CHF versus placebo (adjusted HR 0.70, $p < 0.0001$)	ACE inhibitor-intolerant patients

Table 7 continued

Study and year	ARB (mg/day) [*n*]	Comparator (mg/day) [*n*]	Primary outcome	Main results	Comments
CHARM-Added [101]	Candesartan 32 [1,276]	Placebo [1,272][b]	Composite of cardiovascular death or hospital admission for CHF	Candesartan reduced cardiovascular death and hospitalization for CHF versus placebo (unadjusted HR 0.85, $p = 0.011$)	Patients were on background of lisinopril, enalapril, captopril or ramipril; ARB + ACE inhibitor had higher withdrawal rate due to prespecified doubling of creatinine and hyperkalaemia
CHARM-Preserved [102]	Candesartan 32 [1,514]	Placebo [1,509]	Composite of cardiovascular death or hospital admission for CHF	Trend towards reduction in cardiovascular mortality and morbidity versus placebo but not statistically significant (adjusted HR 0.86, $p = 0.051$).	
Val-HeFT [103]	Valsartan 320 [2,511]	Placebo [2,499][b]	Combined endpoint of mortality and morbidity	Valsartan reduced mortality and morbidity versus placebo (RR 0.87, $p = 0.009$)	Valsartan was associated with improvement in NYHA class, LV ejection fraction and quality of life versus placebo
I-PRESERVE [104]	Irbesartan 300 [2,061]	Placebo [2,067]	Composite of death from any cause or hospitalization for a cardiovascular cause (heart failure, myocardial infarction, unstable angina, arrhythmia or stroke)	No difference between the 2 groups (HR 0.95 with irbesartan versus placebo, $p = 0.35$)	Patients with preserved LV function
Post-myocardial infarction					
VALIANT [97]	Valsartan 320 [4,909]	Captopril 150 [4,909] Valsartan 160 + captopril 150 [4,885]	All-cause mortality	No difference between the 3 groups (HR 1.00 with valsartan versus captopril, $p = 0.98$; HR 0.98 with valsartan + captopril versus captopril, $p = 0.73$)	Higher adverse effect rates with combined therapy
OPTIMAAL [98]	Losartan 50 [2,744]	Captopril 150 [2,733]	All-cause mortality	No difference between valsartan and captopril (RR 1.13 [95 % $p = 0.07$)	Losartan was better tolerated than captopril
Stroke prevention					
LIFE [88]	Losartan 100 [4,605]	Atenolol [4,588]	Nonfatal and fatal stroke	Favoured losartan over atenolol, showing a 24.9 % RR reduction versus atenolol ($p = 0.001$)	Similar reduction in BP achieved in two groups with left ventricular hypertrophy
PRoFESS [129]	Telmisartan 80 [10,146]	Placebo	Recurrent stroke	No difference between telmisartan and placebo (HR 0.95, $p = 0.023$)	

ACE angiotensin-converting enzyme, BP blood pressure, *CHARM* Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity, *CHF* congestive heart failure, CI confidence interval, *ELITE II* Losartan Heart Failure Survival Study, ESRD end-stage renal disease, *HR* hazard ratio, *IDNT* Irbesartan Diabetic Nephropathy Trial, *I-PRESERVE* Irbesartan in Heart Failure with Preserved Ejection Fraction, *IRMA 2* Irbesartan in Patients with Type 2 Diabetes and Microalbuminuria, *LIFE* Losartan Intervention for Endpoint Reduction in Hypertension, LV left ventricular, *MARVAL* Microalbuminuria Reduction with Valsartan in Patients with Type 2 Diabetes Mellitus, *NYHA* New York Heart Association, *ONTARGET* Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial, *OPTIMAAL* Optimal Trial in Myocardial Infarction with the Angiotensin II Antagonist Losartan, *PRoFESS* Prevention Regimen for Effectively Avoiding Second Strokes, *RENAAL* Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan, *RR* relative risk, *SCOPE* Study on Cognition and Prognosis in the Elderly, *Val-HeFT* Valsartan Heart Failure Trial, *VALIANT* Valsartan in Acute Myocardial Infarction, *VALUE* Valsartan Antihypertensive Long-Term Use Evaluation

[a] Other antihypertensive medications were allowed

[b] Patients were allowed to use ACE inhibitors and beta blockers

ACE inhibitors); and CHARM-Preserved (LVEF >40 %) and were also placebo controlled [99]. In the CHARM-Alternative study, candesartan was associated with a significant 23 % relative risk reduction in CV death or hospitalization for CHF, with a number needed to treat of about 14 patients [100]. In CHARM-Added, candesartan was associated with a significant 15 % relative risk reduction of CV death or hospital admission with an absolute risk reduction of about 4 % after 41 months of median follow-up. There was a higher permanent discontinuation rate in the candesartan group than in the placebo group (24 versus 18 %, $p = 0.0003$), because of adverse events, including hyperkalaemia and doubling of serum creatinine. [101]. In the CHARM-Preserved trial, there was no significant reduction in cardiovascular mortality and morbidity in patients with preserved left ventricular function receiving candesartan versus placebo after 36.6 months of follow-up [102].

The Valsartan Heart Failure Trial (Val-HeFT) demonstrated beneficial effects of ARBs in heart failure patients, particularly through those participants unable to tolerate ACE inhibitors. Patients with chronic NYHA class II–IV heart failure were randomized to receive valsartan (a target dose of 160 mg twice daily) or placebo. Fewer patients in the valsartan group reached the combined endpoint of mortality and morbidity defined by cardiac arrest with resuscitation, hospitalization for heart failure or administration of intravenous inotropic or vasodilator drugs (RR 0.87 [97.5 % CI 0.77–0.97], $p = 0.009$). There were also significant improvements in NYHA class, ejection fraction and quality of life in the valsartan arm, compared with placebo ($p < 0.01$). In contrast to the findings of CHARM-Added [101], the addition of valsartan to an ACE inhibitor adversely affected mortality ($p = 0.009$) and was associated with a trend towards increases in combined mortality and morbidity ($p = 0.10$) [103].

To date, there is no established specific therapy for heart failure associated with preserved ejection fraction, other than maintaining good BP control and managing volume status. As noted above, in the CHARM-Preserved trial, there was no improvement in the primary outcome with candesartan relative to placebo [102]. A second and larger trial, Irbesartan in Heart Failure with Preserved Ejection Fraction (I-PRESERVE) [104], involved patients at least 60 years of age with NYHA class II–IV heart failure and an LVEF of at least 45 %. Irbesartan 300 mg/day did not reduce mortality or hospitalization for any cardiovascular cause, compared with the control group. The rates of hospitalization due to cardiovascular causes were 70.6 and 74.3 per 1,000 patient-years in the irbesartan and placebo groups, respectively (HR 0.95 [95 % CI 0.85–1.08], $p = 0.44$).

9 Safety and Tolerability of ARBs in Hypertension

9.1 Safety of Angiotensin Receptor Blocker Monotherapies

ARBs have demonstrated excellent safety profiles alone and in combination with other antihypertensive therapies during the past 20 years. The tolerability profiles of ARBs are similar to that of placebo and superior to those of ACE inhibitors. For example, ACE inhibitors increase the risk of cough two- to threefold over placebo and may cause up to 0.1–0.2 % rates of angioedema, which can be life threatening in a minority of cases [105]. Cough and angioedema most likely result from accumulation of bradykinin and substance P, which are both degraded by ACE, and they recur with reintroduction of the ACE inhibitor or use of another ACE inhibitor [106]. In a meta-analysis involving 11 randomized controlled trials evaluating the tolerability of ARBs versus ACE inhibitors, diuretics and placebo, the cough risk of the ARBs was comparable to that of placebo (RR 1.01 [95 % CI 0.74–1.39]) [107]. Among patients intolerant of ACE inhibitors, angioedema was a rare event among ARB users, with an incidence of 0.12 % versus 0.07 % in the placebo arm (RR 1.62 [95 % CI 0.17–15.79]). Compared with placebo, ARB use was associated with a higher risk of renal dysfunction, hypotension and hyperkalaemia [106]. Despite these findings, discontinuation events were similar in patients treated with ARBs, diuretics (RR 1.50 [95 % CI 0.26–8.52]) or placebo (RR 0.99 [95 % CI 0.84–1.17]) [107]. Hence, ARBs have been demonstrated to be one of the better-tolerated antihypertensive class, with improved persistence in the management of hypertension or other comorbidities, and this class is an appropriate option for patients who are intolerant of ACE inhibitors.

The most commonly reported adverse events in randomized controlled trials comparing ARBs with placebo include headache, respiratory infection, dizziness and fatigue. In these analyses, the rates of adverse events with ARBs were comparable to those seen with placebo. Reported discontinuation rates in major ARB trials are low. For example, Andersson and Neldam [38] reported that just 1.5 % patients withdrew from their clinical study because of adverse events. In a study comparing losartan and candesartan performed by Bakris et al. [54], four of the 654 patients (0.6 %) receiving either candesartan or losartan required hospitalization, but none of these events was considered treatment related. Withdrawal from the study was rare and comparable between treatment arms. In a study evaluating the comparative efficacy and safety of olmesartan, valsartan and irbesartan, Oparil et al. [44] reported that seven out of 588 patients (1.2 %) withdrew because of adverse events, including fatigue, malaise and

cough. In a similar trial, Giles et al. [45] reported 16.9, 13.5, 10.3 and 17.9 % total discontinuation rates with olmesartan, losartan, valsartan and placebo, respectively. Fewer than 1 % of randomized patients reported serious adverse events, and all of these events were considered unrelated to the study medication.

In 2012, a gastroenterology group at the Mayo Clinic published a case series involving 22 patients, suggesting an association between olmesartan medoxomil and development of sprue-like enteropathy, based on the clinical presentation, histopathology and temporal relationship to the drug [108]. In July 2013, the FDA issued a warning that olmesartan may cause sprue-like enteropathy, but this warning was later removed from the label of the drug [109]. A case–control study published recently [110] showed no statistically significant association between olmesartan and diarrhoea among patients undergoing upper endoscopy (OR 1.99 [95 % CI 0.79–5.00]) and colonoscopy (OR 0.63 [95 % CI 0.23–1.74]).

In a trial that compared the efficacy and safety of telmisartan, valsartan and placebo, seven out of 207 patients withdrew from the study because of adverse events. Treatment-related adverse event rates were reported as 2.1 % with telmisartan 40 mg, 4.5 % with telmisartan 80 mg, 2.8 % with valsartan 80 mg and 3.5 % with valsartan 160 mg [47].

Discontinuation rates for irbesartan 300 mg (1.4 %) have been reported to be comparable to those seen with placebo (3.4 %) and the lower dose of irbesartan (150 mg; 2.1 %). Again, like other ARBs described above, the overall reported rates of adverse events, including headache, musculoskeletal pain, dizziness and fatigue, were comparable between irbesartan and placebo [51]. No serious adverse events have been considered due to irbesartan (0.5 %) or valsartan (1.4 %) use [52].

9.2 Safety of Angiotensin Receptor Blockers in Combination with Thiazide Diuretics

A number of large safety and efficacy randomized controlled trials of ARB/thiazide diuretic combination therapies have reported adverse events that were mild to moderate in intensity, transient and generally unrelated to the study drug. The different ARB-diuretic combinations have similar safety and tolerability to each other.

9.2.1 Candesartan with Hydrochlorothiazide

Reported adverse events in trials with ARBs in combination with hydrochlorothiazide diuretics are mild to moderate, transient and/or unrelated to treatment. Evaluation of the safety of candesartan/hydrochlorothiazide 16/12.5 mg/day has not shown serious adverse events and, other than one case of hypokalaemia with combination therapy, none were considered treatment related [60]. In a 24-week study of lower doses of this combination (candesartan/hydrochlorothiazide 8/6.25 mg/day), there were no significant changes in plasma glucose, haemoglobin A_{1c}, low-density lipoprotein (LDL), high-density lipoprotein (HDL), creatinine, potassium and uric acid. No serious adverse events and discontinuations due to adverse events were reported [111]. Higher doses of FDC with candesartan/hydrochlorothiazide 32/12.5 or 32/25 mg/day have also been found to be safe and well tolerated. In a large pooled analysis of safety, Mengden et al. [112] reported 49 out of 4,098 patients (1.2 %) having adverse events, seven of which were considered serious (0.2 %).

9.2.2 Eprosartan with Hydrochlorothiazide

The ARB eprosartan was studied by Sachse et al. [61], who reported 65 out of 157 patients (41.4 %) having an adverse event, of which 19 were probably treatment related in the eprosartan monotherapy group (600 mg/day), compared with 69 out of 152 patients (45.4 %), of which 25 were probably treatment related in the eprosartan/hydrochlorothiazide combination group (600/12.5 mg/day).

9.2.3 Olmesartan with Hydrochlorothiazide

In a trial involving olmesartan/hydrochlorothiazide combinations of 40/25, 20/25, 40/12.5 and 20/12.5 mg/day, no differences in adverse events by treatment group thought to be related to drug were reported. About 0.19 % of patients had serious adverse events, and none were reported to be due to the study drug [62]. Fogari et al. [113] reported that 3.9 % of patients in an olmesartan/hydrochlorothiazide 40/12.5 mg/day group had drug-related adverse events, compared with 0.7 % in the olmesartan 40 mg/day monotherapy treatment arm. About 2.3 % and 1.4 % of patients in the combination and monotherapy groups, respectively, discontinued their participation in the study because of adverse events.

9.2.4 Losartan with Hydrochlorothiazide

The percentages of adverse events, both laboratory and clinical, in the trials of losartan/hydrochlorothiazide combination therapy at different doses were comparable to those seen with placebo, except for the incidence of dizziness, which was more common in the combination therapy group [63]. The combination therapy group receiving losartan/hydrochlorothiazide 100/25 mg/day had fewer total clinical adverse events than those receiving losartan monotherapy 150 mg/day (43.3 versus 52.6 %), including a rise in creatinine (0.5 versus 1.1 %). The

reported serious adverse event rates were also greater with monotherapy compared with combination therapy (3.6 versus 1.0 %), but these findings were not statistically significant [64].

9.2.5 Irbesartan with Hydrochlorothiazide

The INCLUSIVE trial [65] had a 3 % rate of serious adverse events, with three occurring in the placebo arm, four in the hydrochlorothiazide monotherapy 12.5 mg/day arm, eight in the irbesartan/hydrochlorothiazide 150/12.5 mg/day arm and seven in the irbesartan/hydrochlorothiazide 200/25 mg/day arm. All were judged as unrelated to the medication, except for one event of hypotension in the irbesartan/hydrochlorothiazide 150/12.5 mg/day arm, which was probably drug related [65]. Lapuerta and Franklin [114] actually reported more adverse events with irbesartan monotherapy than with irbesartan/hydrochlorothiazide combination therapy 300/25 mg/day (36.1 versus 29.9 %). However, hyperkalaemia and hypokalaemia were slightly more common with the combination therapy (0.2 and 0.6 %, respectively) than with monotherapy (0 and 0.4 %, respectively). Hypotension and dizziness were rare in both treatment arms. Severe hypokalaemia (<3 mmol/L) was not observed [114].

9.2.6 Valsartan with Hydrochlorothiazide

With forced titration, dizziness was more frequent with the combination of valsartan/hydrochlorothiazide therapy than with monotherapy (160/320 + 12.5/25 mg) [66]. Otherwise, the safety profile of valsartan/hydrochlorothiazide combination therapy was comparable to that of valsartan monotherapy. Discontinuation rates were greatest with valsartan monotherapy 320 mg/day (7.1 % compared with 3.0 % in the valsartan/hydrochlorothiazide combination group and 2.4 % in the placebo group). During the 54-week extension of the study, treatment-related adverse events were identified in 14.9 % of patients receiving valsartan/hydrochlorothiazide 320/25 mg/day and in 10.5 % of patients receiving valsartan/hydrochlorothiazide 320/12.5 mg/day [115]. In a meta-analysis done by Weir et al., there was an increasing frequency of reported dizziness at increasing component doses of valsartan/hydrochlorothiazide therapy [116]. Finally, hyperuricaemia was reported less often with valsartan/hydrochlorothiazide than with hydrochlorothiazide alone (5.0 versus 8.6 %) [117].

9.2.7 Telmisartan with Hydrochlorothiazide

Lacourcière and Martin [67] reported that telmisartan/hydrochlorothiazide combination therapy had a similar discontinuation rate to telmisartan monotherapy. The incidence of adverse events between these two therapies was also comparable. Although more patients in the combination treatment group complained of dizziness, this finding did not reach statistical significance. Neldam and Edwards [69] reported comparable drug-related adverse event rates with telmisartan/hydrochlorothiazide 80/25 and 80/12.5 mg/day (5.7 versus 5.0 %), resulting in discontinuation rates of 1.7 and 3.0 %, respectively. Two of the serious adverse events were reported as drug related, including atrial flutter in a patient receiving 80/25 mg/day of the combination medication and third-degree atrioventricular block in another patient receiving 80/12.5 mg/day of the combination medication. Hypokalaemia was rare.

9.2.8 Azilsartan with Chlorthalidone

In a pivotal study of this newer ARB with the diuretic chlorthalidone, Sica et al. [70] reported higher rates of increases in creatinine and dizziness with higher doses of the azilsartan/chlorthalidone combination than with chlorthalidone alone. Hypotension was rare, but there were three reported episodes of syncope in the combination treatment group. The reported rises in creatinine were transient, and the values returned to baseline after drug discontinuation.

9.3 Safety of Angiotensin Receptor Blockers in Combination with Amlodipine

A number of large safety and efficacy randomized controlled trials of ARB/amlodipine combination therapies have reported adverse events that were low in frequency, mild to moderate in intensity, transient and typically unrelated to the study drug. The different ARB–amlodipine combinations have similar safety and tolerability to each other.

9.3.1 Olmesartan with Amlodipine

Chrysant et al. [71] reported comparable treatment-related adverse events with the combination of olmesartan/amlodipine and with placebo (19.6–33.1 versus 29.6 %). The frequency of peripheral oedema was lower in patients treated with olmesartan/amlodipine in combination than with amlodipine monotherapy, reaching statistical significance with olmesartan/amlodipine 20/10 mg/day and 40/10 mg/day, compared with amlodipine 10 mg/day ($p = 0.032$ and $p = 0.011$, respectively). Two cases of drug-related hypotension were reported with olmesartan/amlodipine that resulted in discontinuation from the study. No differences in serum chemistry, haematology or urinalysis parameters between treatment groups were observed.

9.3.2 Valsartan with Amlodipine

Flack et al. [73] found that the rates of peripheral oedema with the valsartan/amlodipine combination (12.6 %) were not different from those seen with amlodipine monotherapy (9.5 %; p = NS). In a larger, better powered trial by Philipp et al. [72], there was a significantly higher frequency of peripheral oedema with amlodipine monotherapy than with combination therapy.

9.3.3 Telmisartan with Amlodipine

In a double-blind, randomized trial by Neutel et al. [74], drug-related adverse events were reported in 12.6 % of patients receiving telmisartan/amlodipine 80/10 mg/day, 6.9 % receiving telmisartan 80 mg/day and 16.4 % receiving amlodipine 10 mg/day. The reported serious adverse events were small in number (0.7 versus 0.9 and 0.9 %). The frequency of peripheral oedema was greater with amlodipine monotherapy than with combination therapy (13.2 versus 9.3 %).

9.4 Safety of Angiotensin Receptor Blockers in Combination with Diuretics and Amlodipine (Triple Therapy)

There are two combination therapies with three antihypertensive agents that include an ARB (valsartan and olmesartan), a thiazide diuretic and amlodipine (known as triple therapies). The most common reported adverse events with valsartan/amlodipine/hydrochlorothiazide 320/10/25 mg/day were dizziness, headache and peripheral oedema. Dizziness occurred more commonly with triple therapy and valsartan/hydrochlorothiazide (320/25 mg/day) than with the component monotherapies, the valsartan/amlodipine (320/10 mg/day) combination and the amlodipine/hydrochlorothiazide (10/25 mg/day) combination. Peripheral oedema occurred less frequently with triple therapy (4.5 %) and valsartan/hydrochlorothiazide (0.9 %) than with amlodipine/hydrochlorothiazide (8.9 %) or amlodipine/valsartan (8.5 %) [72].

Olmesartan/amlodipine/hydrochlorothiazide is another triple combination medication approved for the treatment of hypertension. Oparil et al. [80] reported similar rates of dizziness with olmesartan/amlodipine/hydrochlorothiazide 40/10/25 mg/day and olmesartan/hydrochlorothiazide 40/25 mg/day but higher rates than with olmesartan/amlodipine and amlodipine/hydrochlorothiazide at maximum doses (9.9, 10.0, 4.9 and 3.1 %, respectively). Again, peripheral oedema was more frequent in patients receiving the amlodipine-containing regimen than in the other groups. The rates of drug-related adverse events were comparable between triple therapy and dual therapy. Twenty-three out of 574 patients (4.0 %) in the triple therapy group withdrew from the study because of drug-related adverse events. Hypotension occurred more frequently with triple therapy than with olmesartan/hydrochlorothiazide 40/25 mg/day, amlodipine/hydrochlorothiazide 10/25 mg/day and olmesartan/amlodipine 40/10 mg/day (2.1, 0.7, 0.2 and 0 %, respectively). Dizziness and vertigo occurred in 11.3, 10.7, 3.4 and 5.5 % of patients in each study group, respectively. Syncope was rare (<1 %) but was reported more with triple therapy.

10 Safety of Angiotensin Receptor Blockers in Outcome Studies or Analyses

10.1 Angiotensin Receptor Blockers and Myocardial Infarction

After the VALUE trial showed a statistically significant increased incidence of myocardial infarction in the valsartan arm, questions were raised regarding the safety of ARBs. This unexpected relationship of ARBs with MI was termed the 'ARB-MI paradox'. Strauss and Hall [118] published a review article regarding this controversy and suggested that ARBs may be inferior to ACE inhibitors in preventing coronary heart disease. It was hypothesized that this could be a result of activation of ATR_2 due to ATR_1 blockade resulting in cardiac fibrosis and hypertrophy. Other plausible mechanisms included higher levels of plasminogen activator inhibitor-1 and lower levels of bradykinin with ARB use than with ACE inhibitor use.

The results of two multicentre randomized controlled trials—Randomized Olmesartan and Diabetes Microalbuminuria Prevention (ROADMAP) and Olmesartan Reducing Incidence of End Stage Renal Disease in Diabetic Nephropathy (ORIENT)—showed increased cardiac death rates with olmesartan use [119, 120]. The ROADMAP trial, involving 4,447 diabetic patients without overt nephropathy but with one additional cardiovascular risk factor, reported 15 cardiovascular deaths out of 2,232 patients in the olmesartan arm, compared with three deaths out of 2,215 patients in the placebo arm [119]. The ORIENT trial reported ten cardiovascular deaths out of 282 patients in the olmesartan group and three deaths out of 284 patients in the placebo arm [120]. The FDA initially released a statement indicating that the benefit of olmesartan use outweighs the risk but, after an extensive safety review, they found no association between olmesartan and increased cardiovascular risk [121].

A meta-analysis by Cheung et al. [122], which included three major trials (LIFE, SCOPE and VALUE) with 29,375 patients in total, showed that ARBs are associated with an increased risk of myocardial infarction (RR 1.12 [95 % CI

1.01–1.26], $p = 0.041$). On the other hand, another three studies showed a neutral effect [123–125]. However, in the most comprehensive and well-performed meta-analysis, by Bangalore et al. [126], which involved 37 trials with 147,020 patients in total, no evidence of an increased risk of myocardial infarction (an absolute increase of 0.3 %, corresponding to a number needed to harm of ≥333) was determined. In fact, conclusive evidence of a relative risk reduction of stroke, heart failure and new-onset diabetes with ARBs, compared with controls, was the key finding in this large analysis.

Hence, there is no evidence that ARB use increases the risk of myocardial infarction. Clearly, the benefits of ARBs have been demonstrated over the past 25 years in numerous clinical outcome trials.

10.2 Angiotensin Receptor Blockers and Cancer

In 2010, substantial controversy regarding administration of ARBs causing certain solid cancers occurred following a meta-analysis of nine trials, totally approximately 34,000 patients, by Sipahi et al. [8]. This analysis showed an increased risk of new cancers in the ARB group [7.2 versus 6.0 %, RR 1.08 (95 % CI 1.01–1.15), $p = 0.016$] versus control therapy (placebo, ACE inhibitors or beta blockers), with an absolute risk of 1.2 % over an average of 4 years. Most of the patients in this analysis were derived from the ONTARGET and TRANSCEND programmes, which evaluated the ARB telmisartan. The meta-analysis also showed an increase in the relative risk of the occurrence of new lung cancer in the ARB arms (RR 1.25 [95 % CI 1.05–1.49], $p = 0.01$), driven in part by the losartan arm in the LIFE trial, which showed a significantly higher occurrence of new lung cancer compared with atenolol (RR 2.41 [95 % CI 1.23–4.71], $p = 0.01$).

In a much more comprehensive and well-performed meta-analysis on this topic, Bangalore et al. [9] pooled 70 randomized controlled trials involving 324,168 participants with a mean follow-up of 3.5 years. The risk of developing cancer was not found to be different among ARBs (proportion with cancer 2.04 %; OR 1.01 [95 % CI 0.93–1.09]), ACE inhibitors (2.03 %; OR 1.00 [95 % CI 0.91–1.09]), beta blockers (1.97 %; OR 0.97 [95 % CI 0.88–1.07]), CCBs (2.11 %; OR 1.05 [95 % CI 0.96–1.13]) or diuretics (2.02 %; OR 1.00 (95 % CI 0.90–1.11)]. There were also no differences in cancer-related mortality among the four antihypertensive therapy classes compared with placebo [9].

There have been two observational studies [10, 127] that supported the conclusions of the larger meta-analysis performed by Bangalore et al. [9]. Pasternak et al. [10] performed a large cohort study (1998–2006) involving 107,466 new users of ARBs and ACE inhibitors, who were at least 35 years of age, and used Danish registries to compare incidence rates of all cancers, cancer subgroups by anatomic site and cancer mortality. Overall, 3,954 cancer cases were detected among ARBs users, versus 6,214 among ACE inhibitor users (adjusted rate ratio 0.99 [95 % CI 0.95–1.03]). Cancer risk was not increased with increasing ARB exposure. In addition, none of the specific ARBs were associated with a higher incidence of cancer, compared with ACE inhibitor therapy. ARB use was not associated with an increased risk of cancer mortality, compared with ACE inhibitor use (adjusted RR 0.77 [95 % CI 0.72–0.82]) [10]. Another large cohort study involving 377,649 new ARB users at least 18 years of age, from the UK General Practice Research Database, assessed the association between ARBs and cancer risk [127]. After a mean follow-up of 4.6 years, ARB use was not found to increase the overall risk of cancer (adjusted HR 1.03 [95 % CI 0.99–1.06], $p = 0.10$) versus ACE inhibitors. On the other hand, there was an increased risk of breast and prostate cancer, which translated to 0.5–1.1 extra cases, respectively, per 1,000 person-years of follow-up in those with the highest baseline cancer risk. Longer duration of ARB use was also not associated with a higher overall cancer risk [127].

11 Conclusions

ARBs have proven to be a highly effective class of agents for treatment of hypertension and its comorbidities over the past two decades. There are eight ARBs approved for use in the USA for treatment of hypertension (Table 2). As the ARBs were developed during the 1990s, they were accompanied by longer half-lives and, in some cases, greater potency, which translated into enhanced BP reductions and/or durations of action. Therapies combining ARBs with diuretics, calcium antagonists and, most recently, the beta blocker nebivolol [128] have shown better BP reduction in clinical trials than the monotherapy components. While there are theoretical benefits of combining ARBs with ACE inhibitors (e.g. proteinuria reduction), event-driven trials have not shown a benefit and in fact have demonstrated increases in adverse renal events. Hence, there is no clinical rationale for combining ARBs with ACE inhibitors (or direct renin inhibitors) in the management of hypertension. The excellent safety and tolerability profile of the ARB class has improved the adherence to antihypertensive therapy and enhanced our ability to manage hypertension in those patients with sensitivities to other antihypertensive drug classes, including ACE inhibitors.

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