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Role of the Renin-Angiotensin-Aldosterone System and Its Pharmacological Inhibitors in Cardiovascular Diseases: Complex and Critical Issues

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Abstract Hypertension is one of the major risk factor able to promote development and progression of several cardiovascular diseases, including left ventricular hypertrophy and dysfunction, myocardial infarction, stroke, and congestive heart failure. Also, it is one of the major driven of high cardiovascular risk profile in patients with metabolic complications, including obesity, metabolic syndrome and diabetes, as well as in those with renal disease. Thus, effective control of hypertension is a key factor for any preventing strategy aimed at reducing the burden of hypertension-related cardiovascular diseases in the clinical practice. Among various regulatory and contra-regulatory systems involved in the pathogenesis of cardiovascular and renal diseases, renin-angiotensin system (RAS) plays a major role. However, despite the identification of renin and the availability of various assays for measuring its plasma activity, the specific pathophysiological role of RAS has not yet fully characterized. In the last years, however, several notions on the RAS have been improved by the results of large, randomized clinical trials, performed in different clinical settings and in different populations treated with RAS inhibiting drugs, including angiotensin converting enzyme (ACE) inhibitors and antagonists of the AT1 receptor for angiotensin II (ARBs). These findings suggest that the RAS should be considered to have a central role in the pathogenesis of different cardiovascular diseases, for both therapeutic and preventive purposes, without having to measure its level of activation in each patient. The present document will discuss the most critical issues of the pathogenesis of different cardiovascular diseases with a specific focus on RAS blocking agents, including ACE inhibitors and ARBs, in the light of the most recent evidence supporting the use of these drugs in the clinical management of hypertension and hypertension-related cardiovascular diseases.

Keywords Renin-angiotensin system · Angiotensin converting enzyme inhibitors · Angiotensin receptor blockers · Hypertension · Myocardial infarction · Stroke · Heart failure · Renal disease · Cardiovascular diseases

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1 Introduction

Arterial hypertension is a condition of great clinical relevance and scientific interest, given its large prevalence and the high social importance of its complications. Despite the large number of clinical studies performed on this area, there are still many unclear points regarding its pathogenesis, diagnosis and, mostly, therapeutic approach.

Among various regulatory and contra-regulatory systems involved in the pathogenesis of hypertension, renin-angiotensin system (RAS) plays a major role. Despite the identification of renin and the availability of various assays for measuring its plasma activity, the specific role of RAS in the pathogenesis of different cardiovascular diseases has

not yet fully characterized. In particular, the lack of an effective evaluation of the tissue RAS probably represents the most relevant factor limiting the prevention of the onset of a clear relationship between increased RAS activity and the development or progression of different pathological conditions. However, the availability of drugs able to interfere with the RAS at various levels led to a better understanding of the pathophysiological role of this system, bringing it to the forefront in clinical practice.

Large, randomized clinical trials, performed in different clinical settings and in different populations treated with RAS inhibiting drugs, including angiotensin converting enzyme (ACE) inhibitors and antagonists of the AT1 receptor for angiotensin II (ARBs), provided relevant data. For example, pathological activation of tissue RAS in the heart is probably responsible for the initial stages of the hypertension-related heart disease, such as diastolic dysfunction, even in the absence of left ventricular (LV) hypertrophy, which is the first expression of hypertension-induced cardiac organ damage. Abnormal RAS activation can also explain at least, in part, the fact that regression of cardiac organ damage, namely LV hypertrophy, does not occur simply by lowering blood pressure (BP) levels. In fact, the only evidence of regression of these structural and functional abnormalities was observed in hypertensive patients without LV hypertrophy treated with ARBs, whereas similar BP reductions obtained with an ACE inhibitor did not improve LV diastolic function. In addition, it is well known that hypertensive heart disease is characterized less by myocyte hypertrophy than by increased tissue collagen deposition, which probably results from the abnormal RAS activation that stimulates collagen synthesis and inhibits collagen breakdown, thereby increasing the proportion of collagen in the connective tissue. It does, therefore, seem conceivable that hypertension activates tissue RAS, which first leads to the development of LV diastolic dysfunction and then triggers the progression to LV hypertrophy. Subsequently, systemic RAS activation mediates the progression from these conditions towards LV systolic dysfunction and congestive heart failure.

More recently, the pathophysiological notions on the RAS have been improved by the results of large, randomized clinical trials, which contributed to better define the role of renin in the clinical practice as a mechanism of transducing both structural and functional damage abnormalities in the presence of vascular atherosclerosis and hypertension. These findings suggest that the RAS should be considered to have a central role in the pathogenesis of different cardiovascular diseases, for both therapeutic and preventive purposes, without having to measure its level of activation in each patient.

2 Hypertension, Heart Failure, and Ischaemic Heart Disease: A Cardiovascular Continuum

Hypertension is a pathological condition characterized by a multifactorial pathogenesis. Its development is usually related to genetic predisposition, but also influenced by diet, stress and other environmental factors. Hypertension has been defined as a systolic BP greater than 140 mmHg and/or a diastolic BP greater than 90 mmHg [1]. The prevalence of this condition in the general population is about 30–45 % and increases with age. Hypertension is the most relevant risk factor for the development of cardiovascular diseases, including ischemic heart disease and congestive heart failure, and it is usually associated with other cardiovascular risk factors [1]. Therefore, the recommended strategy in order to obtain a satisfactory BP control, even in presence of additional cardiovascular risk factors, is represented by a larger use of combination therapies of different drug classes [1, 2]. One of the major concerns is to identification of a given therapeutic strategy that can be accepted by the patient in order to obtain good compliance to prescribed medications and effective BP control. This aspect of treatment is essential not only to obtain clinical response in hypertensive patients, but also to prevent the onset of overt cardiovascular diseases in patients who are asymptomatic. In fact, cardiovascular diseases, in particular those associated with hypertension and atherosclerotic disease, have reached pandemic proportions; they are responsible for 42 % of deaths in European women under the age of 75 years old and 38 % of deaths in males [3].

Hypertension is a major contributor for development and progression of coronary artery disease. Stable coronary artery disease is characterized by episodes of hypoperfusion and reversible myocardial dysfunction, due to ischaemia at rest or during physical exercise, stress or even in the absence of a recognizable stimulus. Clinical manifestations of coronary artery disease are the result of obstruction of the epicardial arteries by atherosclerotic plaques, microvascular dysfunction and/or dysfunction due to a past myocardial infarct or ischaemic heart disease. The recommended treatments at the time of diagnosing coronary artery disease are beta-blockers, calcium-channel blockers and ACE inhibitors or ARBs [4, 5].

Coronary artery disease is responsible for over half the cases of heart failure [6]. This is a clinical syndrome caused by cardiac structural abnormalities with evident functional consequences. About 1–2 % of the adult population in industrialised countries suffers from heart failure and the prevalence exceeding 10 % among people over 70 years old [7]. LV ejection fraction is the main parameter used to interpret the severity of symptoms and describe the

functional impairment in heart failure. RAS and sympathetic nervous system are the key neuro-humoral systems activated in the pathogenesis of heart failure. On the basis of the general pathophysiological profile, the recommended treatments at the time of diagnosing heart failure are diuretics (symptomatic drugs), but above all beta-blockers, ACE inhibitors or ARBs [8].

3 Treatment of Hypertension, Heart Failure and Ischaemic Heart Disease

According to the guidelines, the most important drugs used in treatment of hypertension are ACE inhibitors, ARBs, beta-blockers, calcium antagonists and diuretics [1]. Among these, the most widely used drugs in treatment of heart failure are diuretics (administered to control the symptoms caused by fluid retention), ACE inhibitors (indicated for all stages of heart failure), ARBs (mainly used in patients who develop adverse reactions to ACE inhibitors), beta-blockers (administered to reduce cardiac work and improve LV function) and digoxin. Finally, the drugs mainly used in treatment of ischaemic heart disease are ACE inhibitors (sometimes ARBs), beta-blockers, calcium antagonists, nitrates and antiplatelet agents. Thus, drugs that modulate RAS play an important role in all these pathologies because this system is central to the pathophysiology of these cardiovascular diseases.

3.1 Role of the RAS: Pathophysiological and Pharmacological Aspects

Renin was already indicated to be a fundamental regulator of BP at the end of the 19th century and is still now object of significant research in both pre-clinical and clinical fields. Renin is a glycoprotein which is synthesised, accumulated and secreted by myoepithelial cells of the juxtaglomerular apparatus of the nephron, originating initially from pre-prorenin from which a peptide is removed, to be transformed into prorenin [9].

Prorenin not only has its own enzymatic activity, by binding to its own, specific receptor, but that it also exerts biological effects independently of its enzymatic activity, resulting in cellular hypertrophy and fibrosis [10]. A further consideration on prorenin is related to the potential role of this enzyme as marker of microvascular complications in diabetes. Prorenin blood levels are increased in patients with type 1 and 2 diabetes mellitus with a greater tendency to develop microalbuminuria and could, therefore, predict the progression of renal microvascular damage [9].

The enzymatic action of renin is to convert angiotensinogen to angiotensin I. This latter is the substrate for ACE (Fig. 1). The conversion of angiotensin I to angiotensin II, catalysed by ACE, is not the only known pathway for the biosynthesis of angiotensin II. It is currently hypothesised that there is an alternative pathway, involving an aminopeptidase, which transforms angiotensin I into des-aspartate-angiotensin I; this latter is converted by ACE into angiotensin II [11]. In addition, other non-ACE enzymes can take part in the transformation of angiotensin I into angiotensin II; the most important non-ACE enzymes are the chymases of the cardiovascular apparatus, the chemostatic angiotensin II generating enzyme (CAGE) enzyme system and various endopeptidases that can produce not only angiotensin II, but also other angiotensin fragments such as angiotensin III and IV [12]. As far as concerns the activity of angiotensin fragments, it has been seen that angiotensin IV, formed from angiotensin III through the action of aminopeptidase M, has strong effects on memory and cognition. The central and peripheral effects of angiotensin IV are mediated by specific receptors identified as membrane insulin-responsive aminopeptidases (IRAP), also known as AT4 receptors. When angiotensin IV binds to its receptors, it inhibits the catalytic activity of the IRAP and enables the accumulation of various neuropeptides related to reinforcing memory. Other effects of angiotensin IV binding to its own receptors include renal vasodilatation, natriuresis and extracellular matrix remodelling [13].

The main product generated by ACE, and also by alternative pathways, is angiotensin II, which regulates cardiovascular homeostasis by modulating its own effects through binding to specific receptors. Nowadays, four angiotensin II receptors have been identified (Fig. 2). The AT1 receptor is involved in the main pathophysiological actions of angiotensin [14]. Activation of the AT2 receptor causes opposite effects on the vascular system compared those mediated by the AT1 receptor. The non-AT1/non-AT2 receptor was previously known as AT3 receptor. Its activation leads to the production of NO and is responsible for neuronal development. Finally, the AT4 plays a role in regulating blood flow, inhibiting the reabsorption of sodium, in memory processes and in vasodilatation [15].

Angiotensin II is not the only product that is generated from angiotensin I; this latter can also be metabolised to angiotensin 1–7 through the effect of the human ACE 2. This enzyme is a carboxypeptidase consisting of 805 aminoacids and has a short signal sequence. The preferential substrate of ACE 2 is angiotensin II, to which it binds with an affinity about 400-times higher than its affinity for angiotensin I, thus leading to the formation of angiotensin 1–7. ACE 2 can also catalyse the conversion of angiotensin I into angiotensin 1–9, which is subsequently converted to angiotensin 1–7 by ACE. Similarly, plasma endopeptidases can convert angiotensin I into angiotensin 1–7. The physiological significance of ACE 2 is still
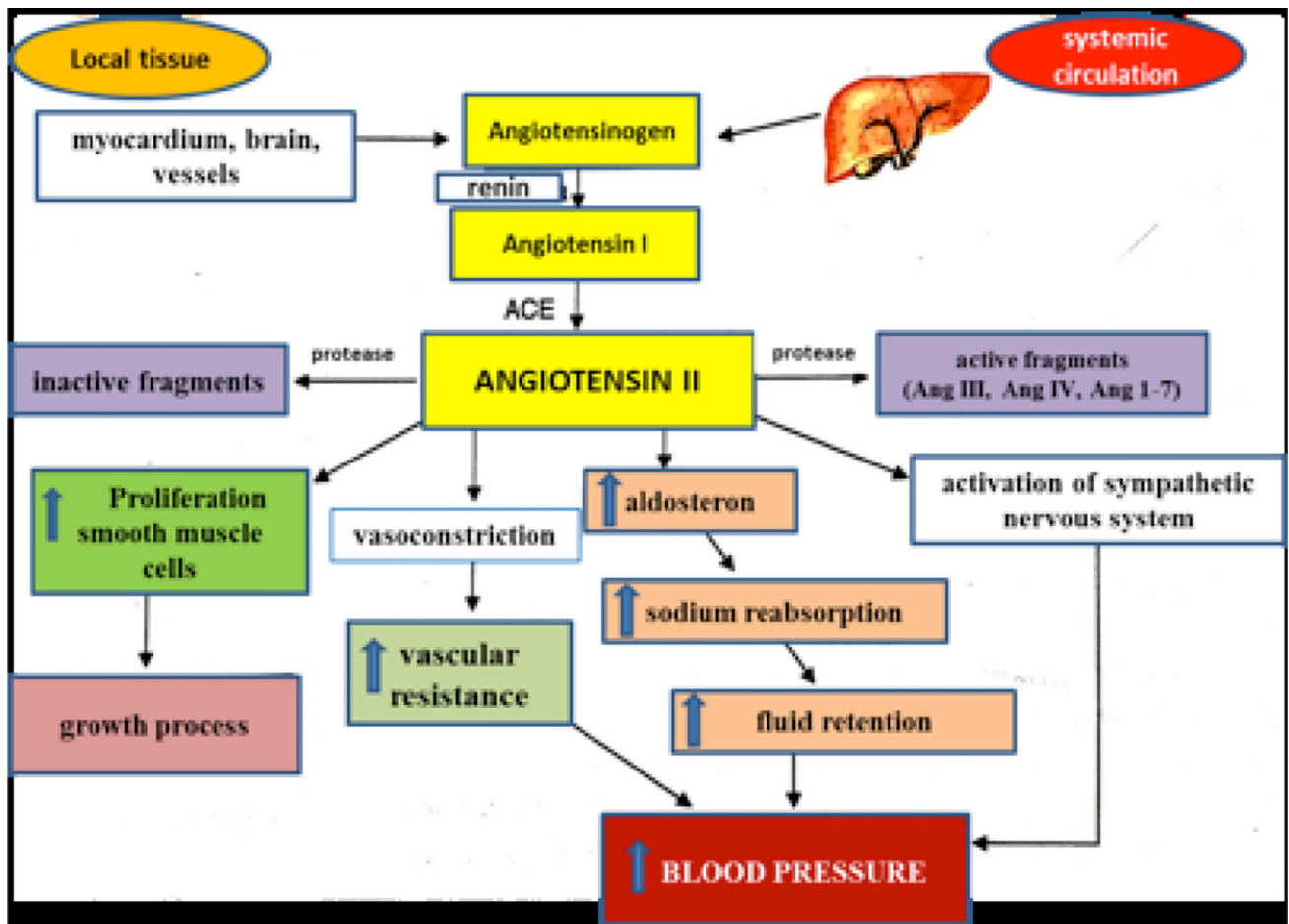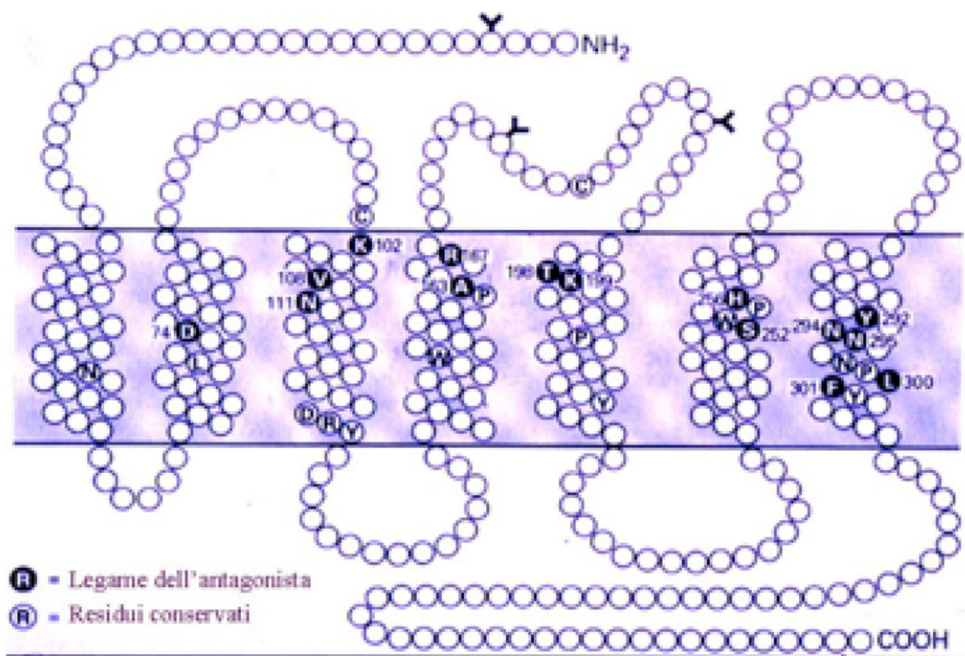
Fig. 1 Schematic representation of the renin-angiotensin system. Modified from Reference [13]

Fig. 2 Schematic representation of the angiotensin II AT1-subtype receptor. Modified from Reference [13]

unclear. It may act as counter-regulatory mechanisms opposing the effects of ACE. Indeed, ACE 2 regulates the levels of angiotensin II and limits its effects by converting it to angiotensin 1–7.

Angiotensin 1–7 has pleiotropic effects, just like angiotensin II, and can influence the functions of many organs and systems. Its effects are mediated by a specific receptor, Mas-1. The proto-oncogene *Mas* encodes this orphan receptor, which has a protein G-mediated mechanism of transduction. By binding to this receptor, angiotensin 1–7 induces vasodilatation, natriuresis and diuresis. It is, therefore, considered that the ACE 2-Angiotensin 1–7-Mas-1 axis acts to counterbalance the vasoconstriction and hydrosalinic retention mediated by the classical ACE-angiotensin I-angiotensin II-aldosterone axis [16, 17].

Recent evidence demonstrated that angiotensin 1–7 could be also produced by the action of neprilysin. This is a ubiquitously distributed, zinc-dependent, type II membrane metalloprotease. Its expression is highest in the kidneys, but is also widely present in cardiovascular and other tissues. The most important biological function of neprilysin is hydrolysis of atrial natriuretic peptides; however, this enzyme has numerous other substrates, including substance P, kinins, opioid peptides, amyloid β protein, enkephalins, and gastrin as well as angiotensin I and II [18]. It has been demonstrated that the role of neprilysin within the RAS is to convert angiotensin I into angiotensin 1–7 and to hydrolyse angiotensin II [19].

From a clinical point of view, the most widely used classes of drugs act mainly at four levels: (1) inhibition of renin release (β-blockers, α_2-adrenergic stimulators); (2) inhibition of ACE, which converts angiotensin I into angiotensin II (ACE inhibitors); (3) antagonism of the AT1 receptors of angiotensin II (ARBs); (4) inhibition of renin (direct inhibitors of renin).

3.2 ACE Inhibitors

3.2.1 Pharmacological Aspects

ACE inhibitors are currently the most widely used agents for the treatment of hypertension, heart failure and ischaemic heart disease. Based on their chemical structure, the ACE inhibitors can be divided into three groups (Table 1): (1) ACE inhibitors containing a sulphydryl group (alacepril, altiopril, captopril, spirapril and zofenopril); (2) ACE inhibitors containing a carboxylate group (benazepril, cilazapril, delapril, enalapril, lisinopril, perindopril, quinapril, ramipril, trandolapril and moexipril); (3) ACE inhibitors containing a phosphonate group (fosinopril).

The presence of a sulphydryl group confers potential benefits against ischaemic insults and atherosclerosis. On

Table 1 Classification of different ACE inhibitors on the basis of their chemical structure

Sulphydryl group	Carboxylate group	Phosphonate group
Alecepril	Benazepril	Fosinopril
Altiopril	Cilazapril	
Captopril	Delapril	
Spirapril	Enalapril	
Zofenopril	Lisinopril	
	Perindopril	
	Quinapril	
	Ramipril	
	Trandolapril	
	Moexipril	

the other hand, it is thought that the sulphydryl group may contribute to specific toxicity profiles, such as dysgeusia, skin rashes and proteinuria [20].

This class of drugs acts on ACE by binding to the Zn^{2+} contained in the enzyme, in this way inhibiting the enzyme and blocking the conversion of angiotensin I into angiotensin II. The antihypertensive activity of the ACE inhibitors is the result of various effects. First of all, the inhibition of the effects of angiotensin II at both systemic and tissue levels, with vasodilatation in various districts, together with a reduction in plasma aldosterone, which translates into increased natriuresis and diuresis. Bradykinin is also involved in the antihypertensive action of the ACE inhibitors. Since ACE is identical to kininase II (responsible for the breakdown of bradykinin), the inhibition of this enzyme leads to an increase in the circulating levels of bradykinin, which induces peripheral vasodilatation. Furthermore, this peptide stimulates the secretion of prostaglandins (PGE_2, PGI_2), which contribute to the vasodilating action. Finally, the ACE inhibitors have an inhibitory effect on the release of antidiuretic hormone and reduce both central and peripheral sympathetic nervous system activity.

The vasodilating effect of ACE inhibitors plays a key role in the treatment of LV dysfunction, with or without symptoms of heart failure [21, 22]. In fact, these drugs induce both dilatation of the arteriolar vessels, with a consequent reduction in pre-load, and venous dilatation that diminishes systolic wall stress and causes an overall reduction in the LV end-diastolic volume. A further effect of ACE inhibitors in various experimental models is to prevent endothelial damage and the formation of atherosclerotic plaques [23]. Furthermore, ACE inhibitors have antimitogenic effects in the heart by inhibiting the action of angiotensin II on cardiac AT1 receptors. Thereby they can reduce LV hypertrophy [24].

Finally, ACE inhibitors are also able to slow the progression of chronic kidney disease, due to their beneficial effects on the kidney. The increase in pressure in the renal capillaries is responsible for the glomerular dysfunction in numerous renal disorders, including diabetic nephropathy. ACE inhibitors are able to lower glomerular capillary pressure by reducing systemic BP and by selective dilatation of the efferent arterioles. Furthermore, since angiotensin II is also implicated in the proliferation of mesangial cells and matrix production, ACE inhibitors have been shown to be effective in inhibiting the growth of these cells, thereby improving renal function and preventing the progression of microalbuminuria to overt proteinuria [25, 26].

3.2.2 Pharmacokinetics

Main pharmacokinetic properties of ACE inhibitors are reported in Table 2.

3.2.3 Clinical Aspects

Given their pharmacokinetic and pharmacodynamics characteristics, all ACE inhibitors are indicated for the treatment of hypertension (Table 3) [1]. With the exceptions of moexipril, spirapril, trandolapril and zofenopril, all ACE inhibitors are also indicated for treatment of heart failure [8]. Captopril, lisinopril, ramipril, trandolapril and zofenopril are also indicated for the treatment of acute myocardial infarction [4, 5]. Compared to other drugs of the same class, perindopril has also been registered for the treatment of stable coronary artery disease, because it demonstrated to reduce the risk of cardiac events in patients with a history of myocardial infarction and/or

revascularization. There are other additional clinical indications for some selected drugs within this class. Ramipril is indicated for global cardiovascular risk reduction. Captopril, lisinopril and ramipril are indicated in diabetic nephropathy. Furthermore, ramipril is indicated for the treatment of non-diabetic glomerular nephropathy.

3.2.4 OsMed Data on Drug Use

According to *Osservatorio sull'impiego dei Medicinali* (OsMed) data [27], in Italy during the first nine months of 2014, in line with the trend observed during the last few years, drugs used for the cardiovascular system were in the first place with regards to consumption, with 468 defined daily doses (DDD) every 1000 inhabitants. Among these, the most prescribed drugs were ACE inhibitors (120.5 DDD/1000 inhabitants). Ramipril is the most used active principle in class A of the Italian National Health System-subsidised drugs, with 59.9 DDD/1000 inhabitants, followed by enalapril with 12 DDD/1000 inhabitants. Ramipril also ranked first among the 30 active principles for which expenditure is highest, while combination therapy with perindopril and amlodipine was at the top of the 30 active principles for which Health System-subsidised expenditure differed most from 2013, with an increase of 39.8 %.

3.3 ARBs

3.3.1 Pharmacological Aspects

ARBs are used for the treatment of hypertension, heart failure and ischaemic heart disease [1, 4, 5, 8]. They predominantly act by blocking AT1 receptors for angiotensin

Table 2 Pharmacokinetic properties of different ACE inhibitors

Molecules	T_{max} (h)	Half-life (h)	Protein binding (%)	Elimination	Interaction with food
Captopril	0.5–1.5	1.7	30	Renal	30–40 % reduction in absorption
Cilazapril	1	1.5–3	Not available	Renal	None
Delapril	1.2	1.2	>95	Renal	None
Enalapril	1	11	<50	Renal	None
Fosinopril	3	5.7	>95	Renal, hepatobiliary	None
Lisinopril	7	12.6	10	Renal	None
Moexipril	1	1–2	<50	Renal	None
Perindopril	8	3–5	20	Renal	None
Quinapril	0.5–1.5	2–3	97	Renal	None
Ramipril	1.5–3	3–10	56–73	Renal, hepatobiliary	None
Spirapril	0.5	0.5	89	Renal, hepatobiliary	None
Trandolapril	0.5	1	80	Renal, hepatobiliary	None
Zofenopril	1	5.5	88	Renal, hepatobiliary	None

Table 3 Clinical indications for the use of ACE inhibitors

Molecules	Clinical conditions					
	Hypertension	Heart failure	Acute myocardial infarction	Diabetic kidney disease	Non-diabetic kidney disease	Cardiovascular risk reduction
Captopril	Yes	Yes	Yes	Yes	No	No
Cilazapril	Yes	Yes	No	No	No	No
Delapril	Yes	Yes	No	No	No	No
Enalapril	YES	Yes	No	No	No	No
Fosinopril	Yes	Yes	No	No	No	No
Lisinopril	Yes	Yes	Yes	Yes	No	No
Moexipril	Yes	No	No	No	No	No
Perindopril	Yes	Yes	–	–	–	Stable coronary artery disease: patients with a history of myocardial infarction and/or revascularisation
Quinapril	Yes	Yes	No	No	No	No
Ramipril	Yes	Yes	Yes	Yes	Yes	Yes
Spirapril	Yes	No	No	No	No	No
Trandolapril	Yes	No	Yes	No	No	No
Zofenopril	Yes	No	Yes	No	No	No

II. The currently available compounds can be differentiated chemically into biphenylmethyl derivatives (azilsartan medoxomil, candesartan cilexetil, irbesartan, losartan, olmesartan medoxomil, telmisartan and valsartan) and thienylmethylacrylic derivatives (eprosartan). ARBs can also be differentiated from a molecular point of view on the basis of their affinity for AT1 receptors and the type of antagonism of these receptors. In decreasing order of affinity for the AT1 receptor, ARBs are: candesartan = olmesartan = azilsartan > irbesartan = eprosartan > telmisartan = valsartan = EXP 3174 (active metabolite of losartan) > losartan [28]. This pharmacodynamic difference has important clinical consequences. With regard to the antihypertensive activity of these drugs, comparative clinical studies have confirmed that the antihypertensive efficacy of losartan is less than that of the other ARBs [29, 30].

ARBs induce intense vasodilatation, reducing both pre-load and afterload, thus decreasing systolic wall stress and LV end-diastolic volume. Selective inhibition of the AT1 receptor has a series of clinical advantages. First of all there is also inhibition of the effects of angiotensin II, developed through non-ACE dependent pathways. Furthermore, free angiotensin II, which finds the AT1 receptors occupied, can exert its effects on the AT2 receptors, which mediate vasodilatation and improvement of vascular and cardiac function; ARBs preserve the activity of the AT4-angiotensin IV system and the synthesis of angiotensin 1-7, both mechanisms involved in vasodilatation. Since ACE is not inhibited, there isn't an increase of bradykinin concentration; this determines a decrease of dry cough, typical side effect of ACE inhibitors and, consequently a possibly better adherence to therapy by patients. Finally, ARBs can exercise beneficial effects at the systemic level, independently of their binding to the AT1 receptor; they have, in fact, been shown to be able to activate the peroxisome proliferator-activated receptor (PPAR-gamma) and can also induce the release of adiponectin from adipocytes. These effects cause an increase in the sensitivity to insulin, reduce the levels of circulating lipids and promote anti-inflammatory activity [31].

3.3.2 Pharmacokinetics

Main pharmacokinetic properties of ARBs are reported in Table 4.

3.3.3 Clinical Aspects

All the drugs belonging to the class of ARBs have been approved for the treatment of hypertension (Table 5). Losartan and valsartan are also indicated for treatment of heart failure. Valsartan is also indicated for the treatment of adult patients with clinically stable symptomatic heart failure or asymptomatic LV dysfunction following a recent myocardial infarction (within the preceding 12 h–10 days). Furthermore, losartan, irbesartan and telmisartan are approved for the prevention of diabetic nephropathy in patients with type 2 diabetes mellitus. Finally,

Table 4 Pharmacokinetic properties of different ARBs

Molecules	T_{max} (h)	Half-life (h)	Volume of distribution (L)	Protein binding (%)	Elimination (%)	Interaction with food
Azilsartan	1.5	11	16	99	55 % fecal, 42 % urine	No
Candesartan	3–4	9	9	99	67 % fecal, 33 % urine	No
Eprosartan	1–2	5–8	308	98	90 % fecal, 7 % urine	No
Irbesartan	1.5–2	11–15	53–93	90	80 % fecal, 20 % urine	No
Losartan	3–4	6–9	13	99	58 % fecal, 35 % urine	No
Olmesartan	2	10–15	16–29	99	60 % hepatobiliary, 40 % renal	No
Telmisartan	0.5–2	16–23	500	98	99 % fecal, 1 % urine	No
Valsartan	3–4	9	17	94–97	83 % fecal, 13 % urine	Interaction with lipids

Table 5 Clinical indications for the use of ARBs

Molecules	Clinical conditions				
	Hypertension	Cardiovascular prevention	Heart failure	Diabetic kidney disease	Acute myocardial infarction
Azilsartan	Yes	No	No	No	No
Candesartan	Yes	No	Yes		No
Eprosartan	Yes	No			No
Irbesartan	Yes			Treatment of kidney disease in hypertensive patients with type 2 diabetes mellitus as part of pharmacological LV antihypertensive treatment	No
Losartan	Yes	Reduction of risk of major cardiovascular events and stroke in adult hypertensive patients with LV hypertrophy documented by ECG	Yes	Treatment of kidney disease in adult patients with hypertension and type 2 diabetes mellitus with proteinuria ≥0.5 g/die in the context of antihypertensive therapy	No
Olmesartan	Yes	No	No	No	No
Telmisartan	Yes	History of coronary artery disease, stroke or peripheral artery disease or type 2 diabetes mellitus with documented damage to target organs		Yes	No
Valsartan	Yes		Yes		Yes

losartan is also approved for prevention of cerebrovascular events.

3.3.4 OsMed Data on Drug Use

According to OsMed data [27], from January to September 2014, ARBs are the second most frequently used drugs (98.1 DDD/1000 inhabitants). Valsartan, alone or in combination, is the leading ARB, with 14.3 DDD/1000 inhabitants, followed by telmisartan (9.3), irbesartan (9.2) and olmesartan (6.9).

4 ACE Inhibitors and ARBs

4.1 Clinical Indications

4.1.1 Hypertension

ACE inhibitors and ARBs have often been gather together for their ability to exert therapeutic effect on BP Although the medical literature is rich in indirect comparisons between these two classes of drugs, there are still only very few direct, randomised clinical trials.

4.1.2 Ischemic Heart Disease

Some meta-analyses [32, 33] suggested that the ARBs are less effective than ACE inhibitors in preventing acute myocardial infarction and all-cause mortality. This effect could be due to the lack of an additional mechanism of action on bradykinin and to the unfavourable impact of the increased amount of angiotensin II produced in response to blocking the AT1 receptor (even if this could act, in part, on AT2 receptors). However, the hypothesis raised by these meta-analyses [32, 33] were not confirmed by the results of several other inclusive and independent meta-analyses [34–37] and, mostly, by one large, randomized, head-to-head clinical trial, the ONgoing Telmisartan Alone and in Combination With Ramipril Global Endpoint Trial (ONTARGET) [38]. This trial directly compared the clinical efficacy, safety and tolerability of an ACE inhibitor (ramipril 5–10 mg) with an ARB (telmisartan 40–80 mg) and this latter resulted equivalent to the former one with regard to incidence of major cardiovascular events, stroke and all-cause mortality [38].

4.1.3 Heart Failure

ACE inhibitors and ARBs are recommended by international guidelines for patients with heart failure, in view of their favourable effects on cardiovascular mortality observed in the Cooperative New Scandinavian Enalapril Survival Study (CONSENSUS) [39, 40], Studies Of Left Ventricular Dysfunction (SOLVD)-Treatment [41], Survival and Ventricular Enlargement (SAVE) [42], Candesartan in Heart failure-Assessment of Reduction in Mortality and morbidity (CHARM) [43], Valsartan Heart Failure Trial (VaL-HeFT) [44], and Evaluation of Losartan in the Elderly Study (ELITE) I-II trials [45, 46]. In addition, the VALsartan in Acute myocardial iNfarction Trial (VALIANT) [47] and SOLVD-Prevention [48] trials evaluated the efficacy of both classes of drugs in patients with asymptomatic LV dysfunction associated with post-ischemic heart disease. On the basis of these findings, in patients with asymptomatic or symptomatic ventricular dysfunction (heart failure), ACE inhibitors remained the first choice drug. In this setting, however, ARBs have demonstrated a similar efficacy compared to ACE inhibitors, thereby excluding any further evaluations to establish greater or lesser efficacy.

4.1.4 Stroke

RAS inhibitors have a variable effect on stroke prevention. An all-inclusive meta-analysis involving more than 180 studies and 500,000 patients (31) showed that the ARBs were more effective than the other classes in reducing ischaemic stroke, probably because of the results of the Losartan Intervention For Endpoint reduction in hypertension study (LIFE) study [49], while the ACE inhibitors remain the drugs of first choice for the treatment of ischaemic heart disease and myocardial infarction.

4.1.5 Kidney Disease

BP control is fundamental in patients with kidney disease in order to slow the progression towards renal failure. The use of RAS inhibitors reduces BP levels (including intraglomerular pressure) and proteinuria and the progression towards chronic kidney disease. Both classes of drugs, including ACE inhibitors and ARBs, have been recently demonstrated to be effective in preventing the onset of microalbuminuria [50, 51], thus confirming the primary protective role of RAS blockade in patients with potential or overt kidney disease.

4.1.6 Atrial Fibrillation

The RAS seems to play a key role in the electrical and structural remodelling that underlies atrial fibrillation and probably in limiting the oxidative stress (and consequent activation of the renin-angiotensin system), which is currently implicated in the development of arrhythmias. Treatment with ACE inhibitors or ARBs has been found to be equally effective in reducing atrial fibrillation in patients with heart failure (ACE inhibitors OR: 0.64; 95 % CI 19–50 %; p = 0.0003; ARBs OR: 0.64; 95 % CI 22–48 %; p < 0.0001) [52].

4.1.7 Diabetes Mellitus

The metabolic abnormalities associated with diabetes mellitus, even in the initial stages, activate the RAS and increase levels of angiotensin II and aldosterone. Thus, RAS inhibitors may contribute in decreasing the production of pro-inflammatory mediators and oxidative stress and increase the sensitivity of tissues to insulin. ACE inhibitors promote an increased sensitivity to insulin in skeletal muscles, reduce the concentration of angiotensin II and increase that of bradykinin. Furthermore, they improve the microcirculation in hyperglycaemic patients, lowering the risk of microvascular complications that are often associated with diabetes. Some ARBs (telmisartan and, to a lesser degree, irbesartan), have demonstrated to act as PPAR-gamma agonists, improving sensitivity to insulin and reduce oxidative stress, beyond their BP lowering activities.

4.2 Adherence to Therapy

The factors responsible for the lack of BP control in clinical practice include a high rate of treatment discontinuation, due to poor adherence to antihypertensive therapy. This poor adherence is conditioned by numerous factors, such as the type of antihypertensive drugs, the concomitant use of other therapies, the patient's clinical condition and sometimes also the conditions and place in which the patient lives [53]. Even a switch from one compound to another, both for ACE inhibitors and for ARBs, can negatively affect adherence to therapy. According to data from studies by Mancia et al. [54, 55], adherence to therapy is better with ARBs than with ACE inhibitors (Hazard Ratio [HR], 1.33; 95 % Confidence Intervals [CI] 1.13–1.57), although still sub-optimal. Furthermore, within the classes of ACE inhibitors and ARBs there are differences in treatment interruption [56]. Among the ACE inhibitors, captopril and moexipril are the drugs with the highest rates of suspension, while ramipril, zofenopril and fosinopril are those with the lowest rates. Among the ARBs, the rate of treatment interruption is highest for losartan and lowest for olmesartan.

4.3 Adverse Reactions and Safety

ACE inhibitors are generally well-tolerated drugs. The most frequent adverse effects are cough, hyperkalaemia and first-dose hypotension. Cough is characteristically non-productive and has been attributed to accumulation of bradykinin, substance P and prostaglandins in the lungs. Hyperkalaemia is a direct consequence of the reduction of aldosterone and is more marked the worse the renal impairment. Other adverse effects include morbilloform or maculopapular skin rashes, with or without pruritus, dysgeusia, neutropenia (generally reversible and tends to disappear within 3 weeks of treatment suspension) and hepatic toxicity [57, 58]. A very small percentage (0.1–0.2 %) of subjects can develop angioedema, which is manifested by rapid swelling of the nose, lips, tongue and glottis, with or without laryngeal oedema. The angioedema resolves within a few hours of interrupting ACE inhibitor treatment; however, the patient's airways must be protected and, if necessary, the patient must be given adrenaline, antihistamines and glucocorticoids [59].

Given their selectivity of action, ARBs were initially introduced onto the market as drugs with a potentially lower risk of causing the typical adverse reactions to ACE inhibitors. Actually these drugs can cause symptomatic hypotension, particularly in patients already taking high doses of diuretics, and may exacerbate the effect of other BP-lowering drugs when taken concomitantly. Other documented reactions are headache, dizziness, back pain and gastrointestinal disorders. Furthermore, these drugs may be responsible for increased levels of serum potassium in patients with kidney disease or taking potassium-sparing diuretics.

Finally, both ACE inhibitors and ARBs are absolutely contraindicated in pregnancy. In the first months they can be teratogenic, in later months they can cause problems to the foetus and oligohydramnios [60].

4.4 Are There Differences Between the Various ACE Inhibitors and ARBs?

Comparisons between the various ACE inhibitors indicate that they are remarkably similar in their capacity to lower BP. In a comparison of 14 active principles, the estimated decrease in BP was between −6/−4 and −9/−5 mmHg (40). Similarly, a comparison of ARBs showed estimated decreases of BP levels in the range from −6/−3 to −10/−7 mmHg.

As far as concerns ARBs, three aspects should be considered: (1) different ARBs not only have different efficacy, but also different durations of action; (2) efficacy is not always the same between the different compounds if administered during the day or the night; (3) efficacy in the last 4 h, (the period furthest from the last dose) seems to be dependent on the type of ARB rather than on its dose. This could be because the influence of dose on antihypertensive efficacy is less relevant than the specific pharmacological characteristics of the individual active principles. Furthermore, the differences seem to be more evident for diastolic BP.

Tables 6 and 7 summarise the main efficacy and safety characteristics of ACE inhibitors and ARBs.

5 Appropriateness of the Use of RAS Inhibitors

Nowadays, it is no longer justifiable to consider only antihypertensive treatment because less than 20 % of patients have isolated hypertension, while more than 75 % of the hypertensive population have at least one associated risk factor (on average 2 or 3). Furthermore, one of the still unresolved problems is that of subjective tolerance, which seems, overall, to be good for RAS inhibitors although better for the ARBs than for the ACE inhibitors. Nowadays the RAS inhibitors are used mainly for all states of hypertension associated with any form of heart disease, whether ischaemic or LV dysfunction of variable severity. Appropriateness of use also involves the identification of specific compounds, since simple "equivalence" based on a prevailing mechanism of action cannot be automatically assumed to translate into the same levels of efficacy. The appropriateness of use of RAS inhibitors also depends on

Table 6 Efficacy and safety of the different ACE inhibitors according to various clinical trials

Molecules	Efficacy in controlling BP	Efficacy on mortality and morbidity	Tolerability
Benazepril	Dose 20–80 mg/die SBP reduction −8.70 (95 % CI −11.43, −5.97) mmHg DBP reduction −4.92 (95 % CI −6.47, −3.36) mmHg	ACCOMPLISH study (2008) reduction of cardiovascular events in high-risk hypertensive patients in combination with a calcium-antagonist or diuretic	Headache 6.2 % Dizziness 3.6 % Cough 1.2 % Angioedema 0.5 %
Captopril	Dose 37.5 mg/die SBP reduction −9.68 (95 % CI −11.73, −7.63) mmHg DBP reduction −5.43 (95 % CI −6.47, −4.40) mmHg	ISIS 4 study (1995) immediately post-infarct: mortality reduced by 7 % (p = 0.02) CCS-1 study (1995) immediately post-infarct: non-significant reduction in mortality at 4 weeks (p = 0.300) SAVE study (1992) post-infarct with heart failure: mortality reduced by 19 % (p = 0.019)	Headache 0.5–2 % Dizziness 0.5–2 % Cough 0.5–2 % Angioedema 0.001 %
Enalapril	Dose 20 mg/die SBP reduction −8.66 (95 % CI −10.48, −6.84) mmHg DBP reduction −4.80 (95 % CI −5.81, −3.79) mmHg	CONSENSUS study in heart failure (1987): 6-month mortality reduction of 40 % (p = 0.002); 1-year mortality reduction of 31 % (p = 0.001). CONSENSUS-II study (19912): immediately post-infarct: no significant effect on mortality SOLVD Treatment study (1991) in heart failure and ejection fraction ≤35 % (1991): mortality reduced by 16 % (p = 0.0036) at dose of 2.5–20 mg b.i.d. SOLVD Prevention study (1992) in patients with asymptomatic LV dysfunction not being treated (ejection fraction ≤35 %): 29 % reduction (p < 0.001) of cardiovascular deaths or onset of evident heart failure at dose of 2.5–10 mg b.i.d. V-HeFT II study in heart failure (1991): reduction in 2-year mortality of 28 % (p = 0.02)	Headache 3 % Dizziness 4.3 % Cough 2.2 % Angioedema 0.2 %
Fosinopril	Dose 20 mg/die SBP reduction −7.62 (95 % CI −11.07, −4.17) mmHg DBP reduction −5.00 (95 % CI −6.94, −3.05) mmHg	FEST study in heart failure (1995): reduction in worsening heart failure (8 vs. 20 %; p = 0.002), without modifying mortality FAMIS study (1997) in post-infarct patients: 30 % reduction of mortality and heart failure (p = 0.05)	Headache >1 % Dizziness 1.6 % Cough 2.2 % Angioedema 0.2–1 %
Lisinopril	Dose 10–80 mg/die SBP reduction −8.00 (95 % CI −10.14, −5.85) mmHg DBP reduction −4.76 (95 % CI −5.92, −3.60) mmHg	GISSI 3 study in post-infarct patients (1997): reduction in 6-week mortality of 12 % (p < 0.05); reduction of 6-month mortality 6 % (p = 0.03) ATLAS study (1999) in heart failure: 12 % reduction in mortality or hospitalisation with high dose compared to low dose (p < 0.002) ALLHAT study (2002) in hypertensive patients: efficacy the same as that of amlodipine in reducing cardiovascular deaths and development of non-fatal myocardial infarction	Headache 5.3 % Dizziness 2.5 % Cough 3.5 % Angioedema 0.1 %
Moexipril	Dose 15 mg/die SBP reduction −8.45 (95 % CI −11.99, −4.91) mmHg DBP reduction −4.38 (95 % CI −6.29, −2.46) mmHg	No evidence	Headache >1 % Dizziness 4.3 % Cough 6.1 % Angioedema <0.5 %

Table 6 continued

Molecules	Efficacy in controlling BP	Efficacy on mortality and morbidity	Tolerability
Perindopril	Dose 4–16 mg/die SBP reduction −7.09 (95 % CI −9.56, −4.61) mmHg DBP reduction −5.02 (95 % CI −6.22, −3.82) mmHg	PROGRESS study in secondary stroke protection (2001): stroke risk reduction 28 % (p < 0.0001) EUROPA study (2003) in patients with coronary artery disease: 20 % reduction of the risk of cardiovascular events (p = 0.0003) PREAMI study (2006) in elderly patients with prior infarction: 78 % reduction of the risk of cardiovascular events (p < 0.001) ADVANCE study (2007) in combination with indapamide in patients with type 2 diabetes: 9 % reduction of the risk of major micro- and macro-vascular events (p = 0.04) and 18 % reduction of cardiovascular deaths 18 % (p = 0.03.) HYVET study (2008) in combination with indapamide in hypertensive patients aged ≥80 years: 30 % reduction in fatal and non-fatal stroke (p = 0.06)	Headache 23.8 % Dizziness 8.2 % Cough 12 % Angioedema 0.1 %
Quinapril	Dose 20 mg/die SBP reduction −7.05 (95 % CI −11.26, −2.84) mmHg DBP reduction −3.35 (95 % CI −5.98, −0.72) mmHg	QUIET study (2001) in patients with coronary arte disease: similar incidence of ischaemic events as in placebo group	Headache 5.6 % Dizziness 3.9 % Cough 2 % Angioedema 0.1 %
Ramipril	Dose 5–10 mg/die SBP reduction −6.29 (95 % CI −9.26, −3.32) mmHg DBP reduction −4.14 (95 % CI −5.81, −2.48) mmHg	HOPE study (2000) of secondary prevention in subjects at high cardiovascular risk (2001): 16 % mortality reduction (p = 0.005) AIRE study (1993) in post-myocardial infarction and heart failure patients: 27 % reduction in mortality (p = 0.002) AIREX study (1997) (extension of AIRE) confirms the benefit in the long-term (3-year follow-up)	Headache 5.4 % Dizziness 2.2 % Cough 12 % Angioedema 0.3 %
Trandolapril	Dose 1–16 mg/die SBP reduction −7.31 (95 % CI −8.85, −5.77) mmHg DBP reduction −4.42 (95 % CI −5.24, −3.60) mmHg	TRACE study (1995) in post-infarct patients: 25–30 % reduction in mortality, sudden death and progression of heart failure (p < 0.05) PEACE study (2004) in patients with coronary artery disease and normal or slightly impaired ventricular function: 4 % non-significant reduction in cardiovascular events (p = 0.43)	Headache >1 % Dizziness 1.3 % Cough 1.9 % Angioedema 0.13 %
Zofenopril	Dose 30–60 mg/die SBP reduction −18 mmHg DBP reduction −14 mmHg	SMILE Pilot study (1991) designed for a safety analysis of early treatment of acute myocardial infarction SMILE study (1995) in post-myocardial infarction patients: 34 % reduction of death or heart failure at 6 months (p = 0.018) SMILE-2 study (2003) in post-myocardial infarction patients: less hypotension with zofenopril SMILE-3 study (2007) in post-myocardial infarction patients: greater efficacy of zofenopril than placebo on post-ischaemic events (p = 0.001) SMILE-4 study (2012) in post-myocardial infarction patients with LV dysfunction: 30 % greater reduction of cardiovascular events (p = 0.028) with zofenopril + ASA compared to the rate with ramipril + ASA	Headache, dizziness, cough in the same percentages as other ACE inhibitors

SBP systolic blood pressure, *DBP* diastolic blood pressure, *CI* confidence interval

Table 7 Efficacy and safety of the different ARBs according to various clinical trials

Molecules	Efficacy in controlling BP	Efficacy on mortality and morbidity	Tolerability
Candesartan	Dose 4–32 mg/die SBP reduction −8.93 (95 % CI −11.37, −6.50) mmHg DBP reduction −5.59 (95 % CI −6.95, −4.22) mmHg	CHARM study (2003) in patients with heart failure: 23 % reduction in cardiovascular deaths and hospitalisation for cardiac arrest (p < 0.001) ACCESS study (2003) in patients with stroke: 60 % risk reduction of mortality (p = 0.07) and 47.6 % reduction of vascular events (p = 0.026) SCOPE study (2003) in the elderly: 27.8 % reduction in the risk of non-fatal stroke (p = 0.04) 23.6 % reduction of all strokes (p = 0.056)	Dizziness 4 % Oedema <1 % Upper respiratory tract infections 6 %
Eprosartan	Dose 600–1200 mg/die SBP reduction −6.79 (95 % CI −9.35,−4.22) mmHg DBP reduction mmHg −5.12 (95 % CI −6.64, −3.60)	MOSES study (2005) in stroke patients: risk reduction of combined cardiovascular events of 21 % (p = 0.014) and of cerebrovascular events of 25 % (p = 0.03) compared to a calcium-antagonist	Dizziness ≥1 % Oedema <1 % Upper respiratory tract infections 8 %
Irbesartan	Dose 75–300 mg/die SBP reduction −7.91 (95 % CI −9.16, −6.67) mmHg DBP reduction mmHg −5.09 (95 % CI −5.82, −4.36)	I-PRESERVE study (2010) in heart failure with preserved LV function: no effect on mortality. IDNT study (2001) in hypertensive patients with type 2 diabetes and nephropathy: reduction of primary end-point (doubling of baseline serum creatinine concentration; development of end-stage kidney disease; all-cause mortality) of 20 % vs placebo (p = 0.02) and of 23 % vs amlodipine (p = 0.006)	Dizziness ≥1 % Oedema ≥1 % Upper respiratory tract infections NR
Losartan	Dose 50–150 mg/die SBP reduction −6.64 (95 % CI −7.59, −5.68) mmHg DBP reduction −3.59 (95 % CI −4.17, −3.00) mmHg	ELITE study (1997) in the elderly with heart failure: 46 % reduction in mortality compared with captopril (p = 0.035) ELITE II study (2000) in the elderly with heart failure: similar efficacy to that of captopril LIFE study (2002) in hypertensive patients with ECG-diagnosed LV hypertrophy: 25 % risk reduction of stroke compared to atenolol (p = 0.001) OPTIMAAL study (2002) in patients with post-infarct heart failure or LV dysfunction: captopril better than losartan on overall mortality; losartan better tolerated and less frequently interrupted RENAAL study (2001) in hypertensive patients with type 2 diabetes and nephropathy: 16 % reduction in primary end-point (doubling of baseline serum creatinine concentration; development of end-stage kidney disease; all-cause mortality) (p = 0.02)	Dizziness 3 % Oedema ≥1 % Upper respiratory tract infections 8 %
Olmesartan	Dose 20–40 mg/die SBP reduction −10.39 (95 % CI −13.36,−7.42) mmHg DBP reduction −7.31 (95 % CI −8.92, −4.40) mmHg	Study by Lin [Hypertension, 2014] and Walker [Pharmacoepidemiology and drug safety, 2014]: mortality reduced in hypertensive patients with olmesartan in a similar way to other ARBs ROADMAP study (2001) in diabetic patients: 23 % reduction of primary end-point (time to onset of microalbuminuria) (p = 0.01); slight increase in fatal cardiovascular events (0.7 %) vs placebo (0.1 %)	Dizziness 1 % Oedema reported Upper respiratory tract infections NR
Telmisartan	Dose 20–160 mg/die SBP reduction 8.38 (95 % CI −9.69,−7.07) mmHg DBP reduction −6.69 (95 % CI −7.74, −5.64) mmHg	PROFESS study (2008) in patients with stroke: does not significantly reduce the risk of recurrent stroke or other cardiovascular events TRANSCEND study (2008) in patients with preceding cardiovascular disease intolerant to ACE-inhibitors: does not reduce the risk of cardiovascular complications significantly ONTARGET study (2008) in patients with preceding cardiovascular disease: telmisartan equivalent to ramipril and to the combination of the two in the prevention of cardiovascular events	Dizziness 1 % Oedema >0.3 % Upper respiratory tract infections 7 %

Table 7 continued

Molecules	Efficacy in controlling BP	Efficacy on mortality and morbidity	Tolerability
Valsartan	Dose 80–320 mg/die SBP reduction −7.10 (95 % CI −8.30, −5.90) mmHg DBP reduction −4.34 (95 % CI −4.96, −3.72) mmHg	JIKEI study (2007) in patients at high cardiovascular risk: cardiovascular mortality risk reduction of 39 % (p = 0.0002) VaL-HeFT study (2001) in heart failure: 13 % reduction of mortality and morbidity (p = 0.009) VALIANT study (2003) in patients with post-infarct dysfunction: valsartan effective as captopril VALUE study (2004) in patients at high cardiovascular risk: no difference in mortality and morbidity with respect to amlodipine	Dizziness >1 % Oedema >1 % Upper respiratory tract infections >1 %

SBP systolic blood pressure, *DBP* diastolic blood pressure, *CI* confidence interval

some management aspects, including the patient's preference (nowadays determinant for every drug), the need to ensure temporal stability of successful treatments, periodic estimates of the clinical result and subjective tolerability and the level of loyalty of the patient with regards to a specific product that has been demonstrated, in that case, to be effective. Quantitative and qualitative changes in treatment should be taken into consideration in patients with unsatisfactory or partial results and after making sure that the principles of therapeutic adequacy (type of patient, doses and methods of administration) have been respected.

6 Conclusions

The following conclusions can be drawn from the data discussed in this paper. First of all, all RAS inhibitors are similarly effective in lowering BP levels. However, they have differences with regard to pharmacological characteristics (pharmacokinetics and pharmacodynamics) and efficacy in the treatment of different cardiovascular co-morbidities often associated with disorders such as systemic hypertension (for example, acute myocardial infarction, chronic heart failure, diabetes mellitus, stroke and kidney disease with or without proteinuria). For these reasons, when choosing the most appropriate RAS inhibitor, it is essential to consider both the clinical characteristics of the patient and, in particular, the presence of co-morbid conditions, and the pharmacological characteristics of the different compounds with the aim of choosing the drug able to ensure the greatest short and long-term efficacy in terms of cardiovascular prevention.

Once the expected therapeutic objectives have been reached, the on-going effective treatment should be continued to consolidate the results in the long-term. A key aspect of this strategy is to promote adherence to treatment which is a concrete aim that can be met easily with RAS inhibitors because of their very good tolerability, provided that the choice focuses on: (a) adequacy of the drug with respect to the patient, (b) intrinsic tolerability of the different compounds, and (c) continuity of effective therapeutic choices.

Although the RAS has been very well studied, recent research revealed that there are still many aspects to clarify and, in particular, more mediators to take into consideration, also in terms of developing new compounds that can act on this system. At the moment the most important drugs that modulate the renin angiotensin system, ACE-inhibitors and ARBs, are effective in systemic hypertension, heart failure and ischaemic heart disease, as demonstrated by experimental findings and many clinical data. These drugs have excellent tolerability as shown by the fact that they are the most frequently prescribed drugs for the indicated disorders. These drugs have pharmacokinetic and pharmacodynamics differences, and so each doctor, general practitioner and/or specialist, plays a central role when choosing the most appropriate drugs, taking into account any co-morbidities that may be present.

Appendix

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