

# Role of ARBs in the Blood Hypertension Therapy and Prevention of Cardiovascular Events

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**Abstract:** Hypertension has a worldwide high incidence in the general population and undoubtedly it is the most important risk factor for cardiovascular morbidity and mortality, in industrialized countries. In this Review we investigated the role of angiotensin II receptor antagonists (ARBs) therapy in the treatment of essential hypertension. We selected in the PubMed and in a list of selected sources the most significant clinical trials and meta-analysis carried out from 1999 to now, to assess, in adult patients populations, ARBs' efficacy, safety and tolerability profile, in comparison with the efficacy of the other common antihypertensive drugs, with particular regard to both the prevention of disabling consequences of hypertension (like cerebrovascular events, coronary events and heart failure) and the influence of an adequate anti-hypertensive therapy on comorbidities which strongly influence the outcome of hypertensive patients (like atherosclerosis, kidney damage, type II diabetes mellitus and arrhythmias).

We also evaluated, in a detailed pharmacological and pharmaco-economic analysis, the basilar differences between ACE-inhibitors and ARBs in the control of the RAA system, and we assessed the possible benefits of their associated use, according to the new evidences concerning the treatment of arterial hypertension.

**Key Words:** Hypertension, ARBs, ACE inhibitors, heart failure, renin angiotensin aldosterone system.

## 1. INTRODUCTION – ARTERIAL HYPERTENSION AS MAIN FACTOR IN DETERMINING GLOBAL CARDIOVASCULAR RISK

Cardiovascular diseases are the most common cause of morbidity and mortality in industrialized countries [1]. The development of these diseases is correlated with many different risk factors: some of them are not modifiable, like age, sex and genetic predisposition, while others are modifiable with convenient therapeutic measures.

Of these, hypertension is the most common and it represents, in the world, the main cause of death even if all pathologies are considered, including the not cardiovascular ones [2].

In fact, a hypertensive patient, in comparison with a normotensive one, presents a higher risk from 2 to 4 of events like coronary heart diseases, brain ictus, peripheral arteriopathy and heart failure [3-4].

In particular the risk of mortality redoubles for each increase of 10 and 20 mmHg in diastolic and systolic pressure, respectively [4]. In spite of this negative, universally admitted primacy, the number of hypertensive patients who undergoes antihypertensive therapy is still small [5]. Regarding this inadequate treatment, it seems that insufficient control of blood pressure is responsible for 60% of brain ictus and about 50% of coronary ischemic events, that is nearly 7.1 millions of dead people and 64.3 millions of serious disabilities per year [6].

In patients with treated hypertension, a higher ambulatory systolic or diastolic blood pressure predicts cardiovascular events even after adjustment for classic risk factors including office measurements of blood pressure [7].

Thus, an adequate pharmacological therapy is the first step to efficaciously reduce cardiovascular events [8] in hypertensive patients.

## 2. TARGETS OF ANTIHYPERTENSIVE THERAPY

Achieving this favourable effect depends on getting the right therapeutic target yet, that current European guide lines recommend to be 140/90 mmHg and 130/80 mmHg for diabetic, nephropatic and coronaropatic patients [9].

To reach this aim, the same guide lines suggest as equivalent in the control of blood pressure, six different therapeutic classes, which include diuretics, beta-blockers, calcium antagonists, Inhibitors of Enzyme Converting Angiotensin (ACE-inhibitors), angiotensin II receptor antagonists (ARBs) and alpha-blockers; but about the last ones, controlled clinical trials on reduction of events are not available.

Even though their effectiveness in terms of hemodynamic effects is equivalent, the same guide lines admit that some particular pharmacological classes are more efficacious than others for particular events or subgroups of patients. It is the case of ARBs, which show themselves more active than beta-blockers and the usual therapy in patients with left ventricular hypertrophy and in the old.

About hypertensive old patients with left ventricular hypertrophy, the LIFE Study [10] has demonstrated that,

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with the same blood pressure reduction, Losartan reduces risk of fatal and non fatal brain ictus more than beta-blocker. Besides, in the MOSES [11] Study carried out among hypertensive patients with a previous ictus, Eprosartan showed, for the same pressure reduction, a significant cut of 21% in total mortality and total cardiovascular and cerebrovascular events in comparison with the calcium antagonist Nitrendipine. The SCOPE Study also reported a significant decrement of non fatal ictus in an arm of hypertensive old people treated with Candesartan, but, in this case, this evidence was associated with a major reduction in blood pressure than the groups treated with placebo or conventional therapy [12]. Moreover, in the ACCESS Study the same drug, administered for seven days within 36 hours after an ictus causing motor deficiency, reduced cumulative death rate in the following 12 months and vascular events rate in spite of very low and not significant effects on blood pressure [13].

The European Guidelines also pointed out that ARBs are more efficacious than beta-blockers in inducing regression of left ventricular hypertrophy, that is, an independent predictive factor of cardiovascular morbidity and mortality. This datum has been also confirmed by specific metanalysis, which showed as ARBs, thanks to their specific mechanism of action, can better induce regression of left ventricular hypertrophy than diuretics, calcium antagonists and ACE-inhibitors, which for this reason cannot be assimilated to ARBs [14].

In the CATCH Study, in which two different groups of hypertensive patients with left ventricular hypertrophy have been compared, the first treated with Candesartan and the second with Enalapril, after 48 weeks, blood pressure reduction being the same, left ventricular mass (LVM) reduced itself respectively of 10,9% and 8,4%, with a major tendency to reduction of concentric hypertrophy in the ARBs group [15].

However, in spite of ARBs' superiority in reducing fibrosis and left ventricular hypertrophy, the VALIDD Study could not significantly demonstrate that they are also more efficacious than other classes of antihypertensive in preventing diastolic dysfunction, which could represent the pathophysiological link between hypertension and clear heart failure [16].

### 3. PHARMACOLOGICAL CONTROL OF RENIN ANGIOTENSIN SYSTEM: DIFFERENCES BETWEEN ARBS AND ACE-INHIBITORS

This particular effectiveness of ARBs depends on the important role of renin angiotensin aldosterone system (RAAS) in the appearance and development of damage that hypertension causes on target organs. This explains the large, worldwide use of drugs able to interfere with this system.

Today two pharmacological classes are available, ACE-inhibitors and ARBs, which are different in their mechanisms of action and effects, and so they are considered independently by all international guide lines.

A new class of drugs blocking directly the renin receptor is in phase of advanced clinical experimentation, and the most representative of them is Aliskiren [17].

Pharmacologically, the basilar differences between ACE-inhibitors and ARBs in inhibiting RAAS can be so summed up:

- the block ACE-inhibitors induced is not specific, incomplete and not selective
  - ✓ *not specific* because it also influences, as well as RAAS, the kinin system, with possible collateral effects linked to accumulation of active bradikinin.
  - ✓ *incomplete* because it is exclusively addressed to the rate of angiotensin II produced by the metabolic way of the angiotensin conversion enzyme, but it does not influence the production of the final effector by many other enzymatic activities able to convert angiotensin I in angiotensin II; so, during a treatment with ACE-inhibitors, after an initial reduction, angiotensin II concentrations gradually return to the baseline levels. This phenomenon has been defined as "angiotensin II escape" and it can potentially reduce benefits during a long term therapy with ACE-inhibitors.
  - ✓ *not selective* because angiotensin II produced by other metabolic ways can normally interact with both receptor subtypes, angiotensin II receptor type 1 or AT1 (modulating a vasoconstriction endothelin-1, PGH2 and TXA2 mediated and endothelial damage Reactive Oxidative Species mediated) and angiotensin II receptor type 2 or AT2 (modulating vasodilatation by releasing Nitric Oxide and anti-proliferative effects).
- On the contrary, the block ARBs induced on RAAS is specific, more complete and more selective
  - ✓ *specific* because the interaction with receptor guarantees an action aimed at RAAS, without direct interactions with other regulation systems
  - ✓ *complete* because the receptorial antagonism blocks angiotensin action independently from the metabolic way of its production, protracting demodulation of the system
  - ✓ *selective* because these drugs interact electively with angiotensin II receptor subtype 1, leaving AT2 free of binding AT II and potentially mediating favourable effects. So, ARBs selective action allows associating positive effects of inhibiting the AT1 receptors and indirectly stimulating the AT2 ones.

Since there is a demonstrated relationship between early stages of atherosclerosis, blood hypertension and high levels of inflammation markers – C-reactive protein in particular [18-19] – it is likely that a good pharmacological control of RAAS has a protective effect on endothelial structure, function and homeostasis [20]. Nowadays, lots of studies show as Olmesartan [21] seems able to reduce the main inflammation markers, such as CRP, TNF-alpha, IL-6, MCP and fibrinogen (EUTOPIA trial [22]), lipid deposition and trans-differentiation of endothelial cells into myofibroblasts in mice [23], wall-to-lumen ratio in small resistance arteries of hypertensive subjects after one year of treatment (VIOS study [23]), the intima-media thickness (IMT) of the carotid

arteries and the volume of atherosclerotic plaques in hypertensive patients (MORE study [24]).

Therefore, even if ARBs and ACE-inhibitors interact with the same regulation system, actually they are considered two different pharmacological classes for their mechanism of action, for the clinical effects and their effectiveness and tolerability.

The last results significantly better for ARBs, which nowadays represent the best tolerated class of antihypertensive drugs.

In fact ARBs tolerability has two distinctive characteristics: it is not dose-dependent and it can be totally superimposed on the placebo one.

The difference between ARBs and ACE-inhibitors is universally recognized to the point that the associated use of these two pharmacological classes has been proposed, verified and officially approved. It is evident that, if the two classes were equivalent, their association would be nonsense, especially considering that it has been just codified in many complex conditions, on clinical, epidemiologic and ethic levels.

For example, adding an ARB to the conventional treatment in steady heart failure produces significant clinical advantages.

This therapeutic hypothesis, based on the double modulation of RAAS by ACE-inhibitor plus ARB, has been tested the first time in the Val-HeFT Study [25], published in 2001. In this trial the addition of Valsartan to the baseline treatment of hypertension induced an important reduction in frequency of end-points, including both mortality and morbidity; among morbidities, the most important event was certainly represented by hospitalization for reheightening of heart failure, that influences more than other events the quality of patients' life and costs for their assistance. The relative risk of re-hospitalization has been reduced of 27%.

As for the social and economic consequences of heart failure, this disease causes 100.000 dead people on a national scale per year, and it is the first reason of mortality in Italy and in absolute the main cost for hospitalization.

Every day over 500 individuals with heart failure are admitted to hospital – with an increase of 40% in the last five years – and at least a third part of these die within a year. With almost 200.000 admissions for year, heart failure is the second reason for hospitalization after birth and its respective Diagnosis-Related Group (DRG) is the most expensive, over 520 million of euro per year, equivalent to 2% of National Health Service total costs for admission to hospital.

Therefore, nowadays heart failure, among chronic diseases, has a very strong impact on survival, quality of patients' life and national cost absorption [26].

The protective effect induced by Valsartan on patients already treated with ACE-inhibitors shows that the difference between these classes is not only pharmacological, but also clinical.

In the JIKEY Heart Study, an interesting trial carried out with 3081 Japanese patients affected by previous cardiovascular illnesses, the addition of Valsartan to conventional therapeutic protocols not only of hypertension, but also

coronary heart disease, heart failure and combination of these disorders, improves significantly prognosis, in terms of cardiovascular mortality and morbidity. These considerable benefits cannot be exclusively explained by a better control of blood pressure, but they suggest that the clinical validity of ARBs is wider and more complex than other antihypertensive groups taken separately in consideration [27].

To confirm what said above, it is possible to mention the RESOLVD Study, in which the association Candesartan – Enalapril showed favourable effects on the neuro-hormonal profile (significant reduction of plasma levels of aldosterone and brain natriuretic peptide), on the tendency to left ventricular remodelling and on ventricular volumes (prevention of telesystolic and telediastolic volumes increase, potentially induced by these drugs separately) [28].

This observation has been further confirmed by the CHARM Study [29], performed with Candesartan and published in 2003. This complex experimental trial, besides showing the effectiveness of an ARB in patients suffering from chronic heart failure and the utility of associating ARBs and ACE-inhibitors, also demonstrated that the same association is useful and sure in patients treated with other drugs for heart failure, including beta-blockers, too.

Recently, the CHARM investigators have also revealed that, of 6379 patients without atrial fibrillation at baseline ECG, during a medium follow up of 37,7 months, 177 patients in the Candesartan arm and 215 in the placebo one [30] developed atrial fibrillation respectively.

Even other trials, carried out among hypertensive individuals without heart failure and with or without left ventricular hypertrophy, based on the use of an ARB or an ACE-inhibitor, have proved their capability of preventing the onset of atrial fibrillation [31].

Antihypertensive treatments are efficacious in preventing this arrhythmia by reducing blood pressure, but RAAS blockers seem especially to be able to reduce its incidence by reducing left atrium dilatation, conduction velocity and probably for intrinsic antiarrhythmic properties [32].

Another important element is the reduction of new cases of diabetes mellitus during the follow up [33]. The systematic review of literature between 1966 and 2006 allowed to identify 22 studies and 143,153 not diabetic patients in all at the moment of randomization and to infer that ARBs are the most effective antihypertensive class in diabetes prevention, followed by ACE-inhibitors and calcium-antagonists.

These results gain particular value considering that cardiovascular risk of the hypertensive diabetic patient is considerably higher than the hypertensive not diabetic one [34-35].

About this matter, recently the ONTARGET Investigators have compared Ramipril, Telmisartan and both in 25,577 patients with high risk diabetes or coronary, peripheral and cerebrovascular disease, without heart failure [36]. In this study they could not show a statistical superiority of ARBs as compared with ACE-inhibitors, but it was clear their non-inferiority [37] in preventing the primary outcomes (death from cardiovascular causes, myocardial infarction, stroke or hospitalization for heart failure) and the secondary ones (new heart failure, diabetes mellitus, atrial fibrillation,

dementia or cognitive decline, nephropathy and revascularization procedures). The treatment with Telmisartan was furthermore associated with fewer episodes of angioedema and cough, but this benefit was partially offset by higher rates of hypotensive symptoms, excluding syncope. Moreover, the combination therapy, target to full doses, despite reduced systolic blood pressure of 2-3 mmHg, was associated with more adverse events – like hypotension, syncope, renal dysfunction requiring dialysis and hyperkalemia – than single treatments. For this result the ONTARGET Study is in contrast with the CHARM: whether this difference is due to the condition studied (heart failure) or the type or regimen of ACE inhibition is uncertain [37].

Assuming that ARBs and ACE-inhibitors are two different pharmacological classes, even the Agenzia Italiana del Farmaco (AIFA) - an Italian state organ promoting new knowledge about drugs - has approved and financed some spontaneous researches, still in progress, to verify for example if the combination of an ARB and an ACE-inhibitor in patients with type II diabetes and clear kidney damage can more efficaciously prevent progression towards end stage renal disease.

In fact, this datum is already evident in a meta-analysis ensued from 16 clinical trials, selected in MEDLINE from 1969 to June 2007 and referred to over 200 patients coming from many different high risk populations [38].

This hypothesis originates from important clinical studies performed with Irbesartan (IRMA-2 Study [39]) and Losartan (COOPERATE Study [40]), which demonstrated a clear, important protective effect of ARBs in preventing progression of kidney damage in type II diabetic patients, while ACE-inhibitors do not show a sure effectiveness.

Nowadays the CALM trial with Candesartan and Lisinopril shows, in type II diabetics, that their combined therapy produces a major reduction of blood pressure and albumin/creatinine ratio than relative monotherapies [41].

In the DETAIL Study, indeed, the Authors did not register significant differences in glomerular impairment, considered as a primary end-point, between an arm of diabetic patients treated with Telmisartan and an other one treated with Enalapril [42].

An important reference about this theme is in 2007 Canadian Hypertension Education Program, which identifies in the progression of kidney failure the second clinically relevant predictor of mortality and morbidity in the hypertensive patient, obviously after the degree of blood pressure reduction [43].

This has an economic counterpart too: renal insufficiency can make it necessary the dialysis - with an annual count of 2.600 euro for patient [44] – hospitalization – with a count of 1.500 euro (DRG 317, Testo Unico di Compensazione) – and, in the last stages, kidney transplantation – with an economic impact of over 40.000 euro for case (DRG 302, Testo Unico di Compensazione).

#### 4. ARBs AND OPEN QUESTIONS ABOUT THE TREATMENT OF ARTERIAL HYPERTENSION

The real clinical problem in the treatment of blood hypertension is that, in spite of the availability of many different

antihypertensive classes, the therapeutic target is still far, as reaching optimal pressure values.

Thus the primary economic problem is not which class of antihypertensive drugs to choose, but the risk of not reaching the attended pressure target.

This fact has a double counterpart: clinical and economic. Clinically, the patient is marginally protected from cardiovascular events, both in terms of mortality and morbidity, including all severe permanent disabilities; actually, it has been demonstrated as a more aggressive therapeutic approach, which aims to reach its pressure target fully, can significantly reduce the incidence of major cardiovascular events, in particular brain ictus and its severe disabling consequences [45-46].

Economically, an unsuccessful prevention of events exposes to an enormous cost for treatment of disabilities and permanent damages (chronic heart failure, outcomes of brain ictus, limbs amputation).

The main reasons of an unsuccessful achievement of pressure targets are two: the first is that, even nowadays, not all hypertensive patients are treated; the second is that only a minority of treated patients achieves pressure targets: actually, the percentage of treated hypertensive patients who achieve pressure values < 140/90 mmHg varies, in industrialized realities, from 6% in United Kingdom to 24% in France and Germany [47].

As regards Italy, the PAMELA study has showed a little better situation, with a percentage of well-controlled patients of 28% [48] among all the treated ones – a quote still judged insufficient.

The unsuccessful achievement of pressure targets cannot be explained by the ineffectiveness of antihypertensive drugs today available, but as a result of many different factors. Among these, the compliance with therapy by patient and its continuity, which are largely influenced, as well as by motivational aspects, by the type of prescribed therapy. In this sense two important factors must be taken into account: drug tolerability and the complexity of therapeutic program.

Actually, if all different classes of antihypertensive drugs can be considered equiactive, their tolerability is universally recognized as significantly different. In particular, all reviews showed that ARBs are the best tolerable class of antihypertensive drugs, so far. This better tolerability clinically expresses itself with a higher compliance - over 60% [49] – that is a percentage two times higher than that of diuretics, which many people suggest as the first step in the antihypertensive treatment, although almost 70% individuals is not compliant with them.

So it is evident that choosing little tolerated drugs, such as diuretics, contributes as a determinant factor to an unsuccessful compliance of patients with therapy and, at the end, to the reaching of pressure targets only in a little percentage of patients.

Just for the above reasons, it is important to remember that ARBs tolerability is the only one than can be totally superimposed on the placebo one – with a percentage of suspension for adverse events of almost 2% [50] - and that ARBs tolerability is not dose-dependent too: even with

higher doses they show a tolerability profile that can be superimposed both on lower doses and on the placebo one.

These remarks are confirmed by some studies, in which Valsartan results better tolerated than the other classes of antihypertensive drugs, including ACE-inhibitors that are not equal to ARBs for this aspect, either.

In particular, a systematic review of 61 clinical studies comparing these two pharmacological classes showed that ACE-inhibitors are associated with a higher number of collateral effects – especially persistent cough linked to accumulation of active bradikinin – that inevitably limit the prosecution of the antihypertensive therapy, while ARBs, being better tolerated, assure major stability and continuity of the treatment [51].

Just starting from these problems of compliance and continuity of therapy, a group of Swiss investigators tested a vaccine based on a virus-like particle – CYT006-AngQb – that targets AT II [52].

They compared 3 arms, each of 24 individuals: the one underwent subcutaneous injections of 100 µg vaccine, the other of 300 µg and the third was the placebo-arm.

The 300 µg dose reduced blood pressure of almost 9 mmHg in patients with mild-to-moderate hypertension especially in the early morning, and this protective effect went on for 4 months; so it is possible that 3 or 4 boosters can increase compliance and continuity of antihypertensive therapy, even if lots of limitations must be considered: the vaccine cannot be adjusted, as a pharmacological therapy, to variable pressure levels and emergency conditions in which RAAS intervenes (haemorrhage, trauma, dehydration); it is unknown if the block of AT II induced by the vaccine is partial or total; finally, it is possible that a long term immunization causes adverse effects more severe than those observed during experimentation and common to many other vaccines.

Nowadays ARBs, among tested and sure treatments, certainly represent the best class of antihypertensive for many reasons, and their large prescription by Doctors of General Medicine (DGM) indirectly confirms this datum: actually DGM usually choose drugs which can be better managed, effectiveness being the same, because among reasons that induce DGM to change an antihypertensive therapy, the most common is just the onset of adverse events [53].

A forced prescription of drugs less expensive but also less tolerated by patients makes it not an efficacious sanitary expense and, finally, this increases assistance costs for the not prevented cardiovascular events. Actually, a best compliance with treatments is linked to a cut of medical and pharmaceutical costs [54-55], and risk of hospitalization [56].

Therefore, a real rationalization of antihypertensive therapy costs must point firstly to achieve the therapeutic target, thanks to the continuity of treatment. This is possible favouring the use of pharmacological classes and active molecules that scientific researches can prove as really efficacious and capable of increasing the patient's compliance with therapy in clinical practice.

From this point of view, today ARBs are the antihypertensive class provided with the largest scientific documentations about their effectiveness, even in comparison with

ACE-inhibitors, whose literature, even though historically very important, often refers to past and smaller clinical trials.

The high value of scientific documentation about ARBs has encouraged their increasing diffusion, all around the world. On this subject, in Europe the relative ratio between ARBs and ACE-inhibitors is variable and in Italy the percentage of therapies with ARBs is one of the lowest, being significantly inferior to that of the United Kingdom, France and Spain.

In the light of pharmacological evaluations, clinical evidences and pharmaco-economic considerations exposed so far, it is evident that the two classes modulating the RAAS differ each other and so a quantitative link of their mutual use has justification neither on the scientific level, nor on the clinical one. Therefore, limitations on freedom of choice between one class or the other or both associated could become the negation of a patient's primary right, that is, to obtain a therapeutic benefit otherwise not obtainable. This right is indeed respected in other European countries.

Thus, sanitary operators should maintain a free prescriptive choice between the two classes, following for single patients the international "clinical evidences" and the guide lines issued by national and international scientific Societies.

## ABBREVIATIONS AND ACRONYMS

ARBs	= Angiotensin II receptor antagonists
ACE-inhibitors	= Inhibitors of enzyme converting angiotensin
RAAS	= Renin angiotensin aldosterone system
LVM	= Left ventricular mass
IMT	= Intima-media thickness
DGM	= Doctors of general medicine
CRP	= C-reactive protein
TNF-alpha	= Tumor Necrosis Factor
IL-6	= Interleukin 6
MCP	= Monocytes chemotactic protein
DRG	= Diagnosis-related group
AIFA	= Agenzia italiana del farmaco

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