Chapter

Treatment of Essential Hypertension with Emphasis in the Renin-Angiotensin System: How to Prevent Secondary Outcomes without Adding Fuel to the Fire

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Abstract

The effectiveness of angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin II receptor blocker AT-1 (ARBs) in reducing the systemic hypertension (SH) is widely known. However their comparative outcomes resulting from prolonged use remain unknown. The objective of this chapter is to discuss the evidence of prospective randomized double-blind clinical trials; all the events result from prolonged use of ACEIs or ARBs in hypertensive patients. In lowering blood pressure, the use of ACE inhibitors or ARBs reduces, in long-term use, the risk of acute myocardial infarction, stroke, and heart failure. However, the use of ACEIs is effective in an overall quantitative analysis; the total mortality regarding cardiovascular causes an outcome that was not observed with the use of ARBs. This fact is assumed to be related to the higher plasma concentration of bradykinin in the use of ACEIs, a well-known cardiovascular-protective factor.

Keywords: hypertension, outcomes, ACEI, ARB, angiotensin-converting enzyme inhibitor, angiotensin II receptor blocker

1. Introduction

Hypertension is a manifestation in which there is an elevation of blood pressure levels to the point of causing imbalance in homeostasis and, consequently, leading the organism to a debilitated and pathological state with clinical repercussions [1]. Also, systemic arterial hypertension (SAH) is defined as "a multifactorial clinical condition characterized by elevated and sustained levels of blood pressure" [2, 3], considered when it is observed that a value >140 mmHg for systolic blood pressure and/or >90 mmHg for diastolic blood pressure [4].

SAH presents itself as one of the main risk factors for cardiovascular diseases [5], and in a recent study, it was shown as the risk factor with the highest number of citations in studies [6]; its incidence is increasing annually, reaching values of population of approximately 20% of Brazilians [7] or 24.3% [8]. Therefore, the

control and prevention of SAH are fundamental to improve the quality of life and health indicators of the population.

The treatment of this clinical condition is based on three primordial objectives: the decrease in blood pressure levels; the maintenance of the desired levels, in view of the singular conditions of each patient; and adherence of the patient to the treatment as well as its continuity. From these perspectives, the measures in order to achieve this triad are based on two therapeutic pathways: changes in lifestyle and/or the use of drugs. Regarding changes in lifestyle, which also show efficacy in the prevention of hypertensive status, the most important are [9, 10] regular practice of physical activities, abstinence from alcohol, changes in food style prioritizing the decrease in salt intake and the increase in the consumption of fruit and vegetables, cessation of smoking, weight loss, control of psychosocial stress, slow breathing, monitoring, and surveillance by a multidisciplinary team.

Regarding the use of drug therapies, and according to their current availability, there are the following classes of medications [9]: diuretics, adrenergic inhibitors (central alpha-2 agonists, beta-blockers, and alpha-blockers), calcium channel blockers, angiotensin-converting enzyme inhibitors (ACEIs), angiotensin II receptor blockers AT1 (ARBs), and direct vasodilators such as nitrates.

Because they act primarily in one of the most important systems for the development of SAH, the renin-angiotensin-aldosterone system (SRAA) [11], four classes of medications stand out and are effective options in reducing morbidity and mortality due to cardiovascular diseases [12], direct renin inhibitors, ACEIs, ARBs, and aldosterone antagonists. Among these classes, the ACEIs and the ARBs are among the most prescribed options worldwide [11]. Therefore, the study and detailed knowledge of both classes is of fundamental importance.

The control of SAH is performed by the ACEI by blocking the transformation of angiotensin I in angiotensin II in the blood and tissues, while the ARB antagonizes the action of angiotensin II by means of the specific blockade of their AT1 receptors. In addition, studies show that the use of these antihypertensive patients is closely related to the decrease in the progression of renal diseases and in the prevention of heart and/or vascular diseases, such as acute myocardial infarction and stroke [13].

On the other hand, in addition to the aforementioned actions, drugs can act in other places and systems, also causing adverse and deleterious events in the organism. These include dry cough, taste alteration, dizziness, hypersensitivity reactions with rash (rash), angioneurotic edema, hyperkalemia, reduction of glomerular filtration with increased serum levels of urea and creatinine, and fetal complications [11]. Thus, countless events are reported from the use of these drugs, whether they are beneficial or malevolent.

2. ACEI and ARB in the management of hypertension

Assuming that the SRAA is a fundamental regulator of cardiovascular and renal functions, ACEI and ARB have different outcomes in the regulatory systems of the human organism, especially in the cardiovascular system. In recent decades, several clinical studies have confirmed that SRAA suppression reduces cardiovascular mortality and total mortality of patients [14].

Despite this, the protective role of SRAA inhibitors in relation to cardiovascular mortality was questioned by studies such as non-insulin-dependent diabetes, hypertension, microalbuminuria or proteinuria, cardiovascular events, and ramipril study (DIABHYCAR) [15] which showed that the use of ACE inhibitors had no effect on cardiovascular mortality in patients with type 2 diabetes mellitus type 2 (DM2) and albuminuria. Also, studies such as Randomized Olmesartan and Diabetes

Microalbuminuria Prevention (ROADMAP) study [16] ended up demonstrating a high rate of cardiovascular mortality in patients using Olmesartan and DM2.

In this chapter, we seek to synthesize the main prospective, randomized and double-blind clinical trials that report the outcomes resulting from the use of renin-angiotensin system inhibitors in hypertensive patients, and to extend the discussion previously made in an article published by the author [17].

The following outcomes will be analyzed: total mortality (including cardiovascular and other causes of death in this specific population), cardiovascular mortality, acute myocardial infarction, stroke, heart failure, and hospitalization due to heart failure, and an addition of all these outcomes (total outcomes).

3. ACEI × ARB: the state of the art in terms of medical evidence

The use of ACEI or ARB has always been part of the first line of treatment of patients with systemic arterial hypertension, especially in the newly diagnosed or long-term patients. Not uncommon are the revaluation of each medication, due to the inefficacy in reducing pressure values or in the presence of side effects (coughing is a very common effect of ACE inhibitors, leading to the main cause of treatment change) [9].

Thus, even with the notion that the ACEI and the ARB are equally effective in reducing pressure in patients with systemic arterial hypertension, their efficiencies compared and their advantages, disadvantages, and outcomes, related to recent or chronic use, remain unknown or liable to be questioned [11].

Related to the last major clinical trials, such as SOLVD (enalapril in heart failure), HOPE (ramipril in patients with high CVD risk), and EUROPA (perindopril in stable coronary disease) studies, we noticed that the inhibition of the SRAA in specific populations caused a significant reduction in outcomes such as general mortality, mortality from cardiovascular causes, acute myocardial infarction, and STROKE [14].

Even so, the large number of studies performed, comparing the use of ACEI or ARB in reducing outcomes in their patients, was not organized and correlated in a review format with well-established characteristics. Thus, it is perceived that the latest systematic reviews with meta-analyses and clinical trials, related to the topic, can be framed in the following situations:

- Systematic reviews, with meta-analysis, based on clinical trials that studied the outcomes related to the use of ACE inhibitors or ARB without their study population necessarily composed of essential hypertensive patients [15, 16].

- Research that studied the use of ACEI in hypertensive patients secondary to other pathologies, although the focus of the study was the evaluation of the symptomatic treatment of the disease and not the hypertension itself [17].

- Studies that used as a control group another drug, which is not considered as the first line of treatment [18].

- Studies that analyzed hypertensive patients with control groups or with standard first-line treatment, according to the hypertension guidelines used by the research team [19, 20].

This presents itself as one of the most current and systematic revisions of the area. By analyzing 20 clinical trials, involving a number of 158,998 patients, the

authors were able to correlate the outcomes related to the analyzed studies, such as cardiovascular and total mortality. However, the present study did not stratify the influence of a given variable (e.g., which drug has a higher mortality rate per stroke of heart failure?), as well as its selected studies involved various types of control groups when compared to the use of ACEI or ARB [14]. Thus, there was an increase, in the last instance, of the individual heterogeneity of each patient according to their medication and particular health condition.

Another meta-analysis of Ho et al. [19] encompassed 10 clinical studies that used ACEI or ARB with its outcomes stratified in cardiovascular mortality, myocardial infarction, stroke, and overall mortality. However, it involved studies in which the population was not hypertensive in some cases, such as the Comparison of Amlodipine vs. Enalapril to Limit Occurrences of Thrombosis (CAMELOT) study, which did not present its series of outcomes due to the use of the drug but is in relation to deep vein thrombosis [21–23].

Thus, in view of these systematic reviews with meta-analyses, published in high-impact journals, it can be defined that all of them correlated the presence of outcomes, due to the use of ACEI or ARB, only in certain populations, for example, in patients with thrombosis or diabetics. Thus, only a general panorama is provided, despite the magnitude of the use of medications and their outcomes, in a population with essential hypertension. Thus, the relationship of a pathology, not necessarily related to hypertension, or the presence of a comorbid syndrome such as DM2 in hypertensive patients would present relationships with other complexes to safely affirm the direct effect of antihypertensive medication on outcomes.

However, as an attempt to increase the number of patients and studies involved in the final analysis, all used studies that presented some of the biases in the previously cited items, such as the extrapolation of hypertensive populations in groups Non-hypertensive majority, or the use of other therapies in the control group other than placebo.

4. ACEI × ARB correlation

Our analysis of the literature regarding the use of ACEI or ARB in the hypertensive population selected 17 studies over the past 10 years, covering a total of 73,761 patients [17].

Of these 17 articles, 12 studies were randomized for therapy with ARB (n = 24,697) compared to control (n = 24,722), while five compared the use of ACEI (n = 12,170) with the control group (n = 12,172) [24].

All patients in the studies were considered as prehypertensive or hypertensive according to the definition of each study, and the mean base pressure ranged from 123 to 169 mmHg. The mean age of the patients ranged from 51 to 76.9 years, with the follow-up time of the studies ranging from 2.25 to 5.5 years.

4.1 Total mortality

A total of 15 studies (n = 70,983) reported events related to total mortality. Two studies [25, 26] were statistically significant in reducing mortality compared to the control group (OR = 0.831, 95% CI, [0.730–0.945], P = 0.005) and (OR = 0.563, 95% CI, [0.341–0.931], P = 0.025), respectively. In addition, the results showed a significant total difference between ACEI and control group (OR = 0.851, 95% CI,

[0.776–0.935], P = 0.001). In relation to the ARB and control group, no significance was evidenced (OR = 1024, 95% CI, [0.960–1.091], P = 0.471) (**Figure 1**).

4.2 Cardiovascular mortality

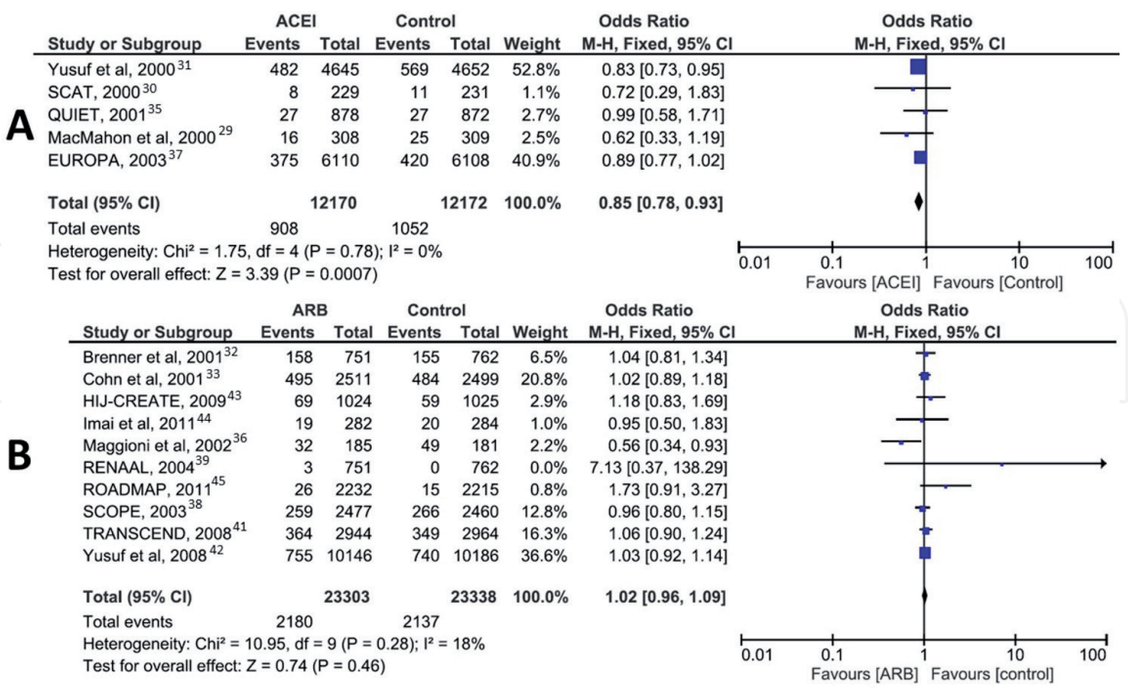
The cardiovascular mortality was analyzed in 13 studies (n = 64,460). One study [27] showed a significant reduction in the cardiovascular mortality for ACEI compared to the control group (OR = 0.733, 95% CI, [0.625–0.860], P = 0.000).

As for the ARB, the opposite was observed in one study, with an increase in the risk in the event when comparing with the control group [28] (OR = 5.011, 95% CI, [1.449–17.334], P = 0.011).

Thus, the studies with ACEI showed a reduction in the cardiovascular mortality (OR = 0.775, 95% CI, [0.689–0.872], P = 0.000), while for the use of ARB there was no significant reduction compared to the control group (OR = 0.947, 95% CI, [0.849–1.056], P = 0.324) (**Figure 2**).

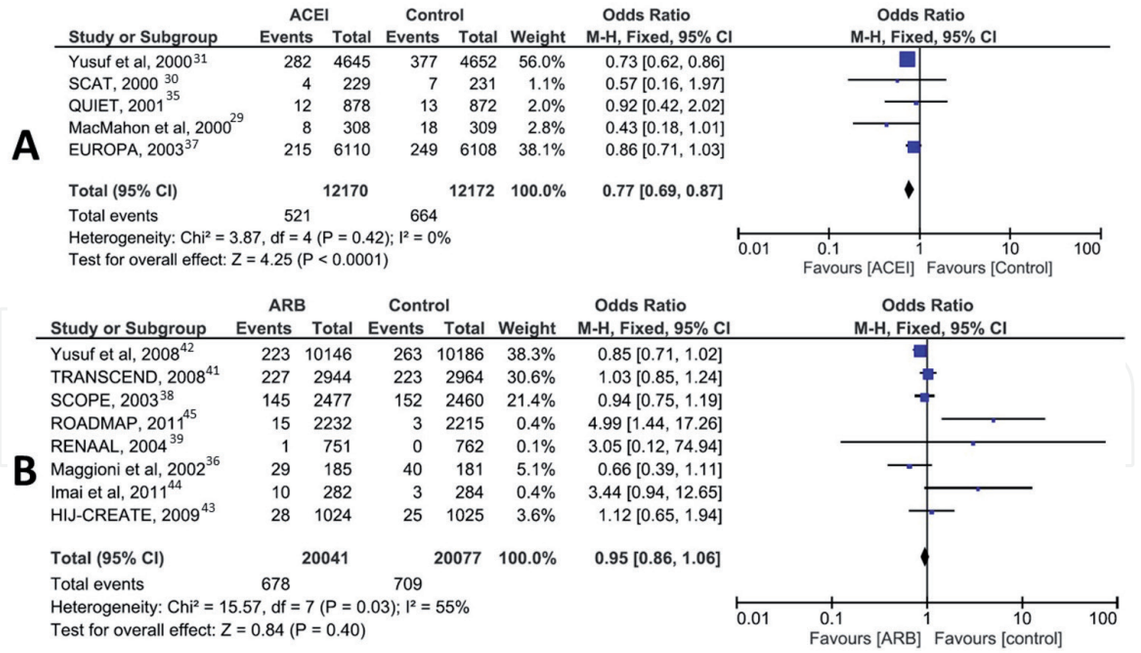
4.3 Acute myocardial infarction

Regarding the occurrence of AMI, two studies evaluating ACEI were beneficial for the reduction of the event (OR = 0.785, 95% CI, [0.689–0.895], P = 0.000), (OR = 0,769, 95% CI, [0.658–0.899], P = 0.001). Related to the therapy with ARB, only one study showed statistical significance to decrease AMI when compared to the control group (E-COST, 2005) (OR = 0.428, 95% CI, [0.202–0.905], P = 0,026). A total of 14 studies (n = 67,237) showed that both ACEI and ARB are positive in the reduction of such event when compared to the control group therapy, with greater significance for ACEI (OR = 0.784, 95% CI, [0.712–0.863], P = 0.000) on ARB (OR = 0.906, 95% CI, [0.834–0.985], P = 0.020) (**Figure 3**).



Meta-analysis using the size of the population of the studies for A: Use of ACEI and B: Use of ARB. SCAT = Simvastatin/Enalapril Coronary Atherosclerosis Trial, EUROPA = European Trial On Reduction of cardiac events with Perindopril in stable coronary Artery disease, RENAAL = Randomized Evaluation of Normal versus Augmented Level Replacement Therapy, ROADMAP = Randomized Olmesartan and Diabetes Microalbuminuria Prevention, SCOPE = The Study on Cognition and Prognosis in the Elderly, TRANSCEND = Telmisartan Randomized Assessment Study in ACE-Intolerant Subjects with Cardiovascular Disease.

Figure 1.
Forests plots summarizing the correlation of (A) ACEI and (B) ARB use for overall mortality.



Meta-analysis using the size of the population of the studies for A: Use of ACEI and B: Use of ARB. SCAT = Simvastatin/Enalapril Coronary Atherosclerosis Trial, QUIET = Quinapril Ischemic Event Trial, EUROPA = European Trial On Reduction of cardiac events with Perindopril in stable coronary Artery disease, RENAAL = Randomized Evaluation of Normal versus Augmented Level Replacement Therapy, ROADMAP = Randomized Olmesartan and Diabetes Microalbuminuria Prevention, SCOPE = The Study on Cognition and Prognosis in the Elderly, TRANSCEND = Telmisartan Randomized Assessment Study in ACE-Intolerant Subjects with Cardiovascular Disease, HIJ-CREATE = Heart Institute of Japan Candesartan Randomized Trial for Evaluation.

Figure 2.
Forest plots summarizing the correlation of (A) ACEI and (B) ARB use for cardiovascular mortality.

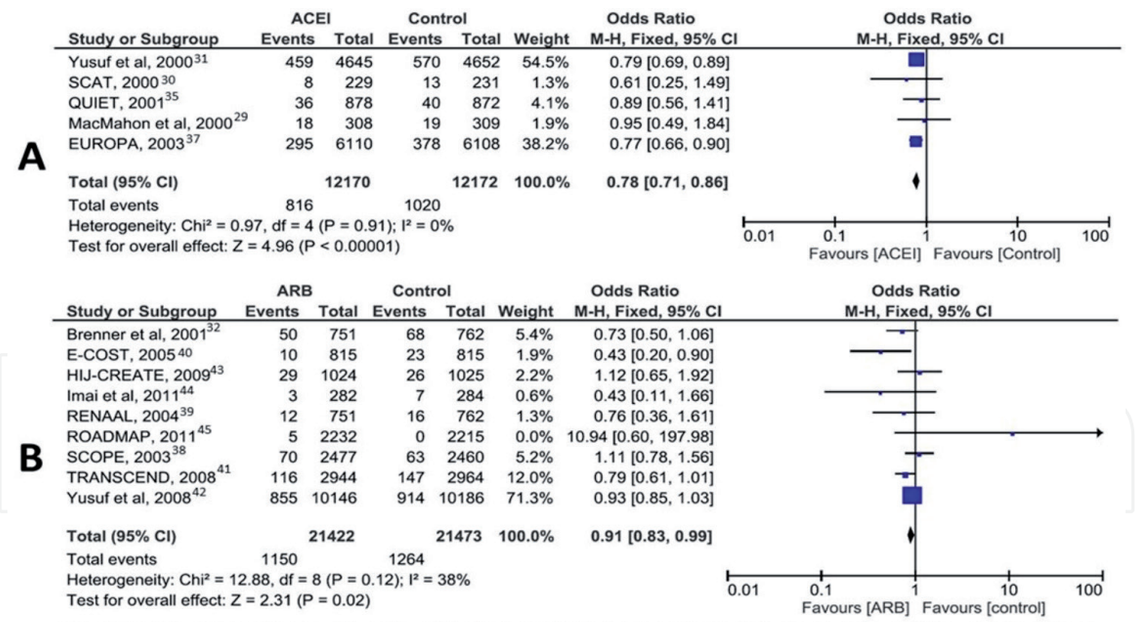


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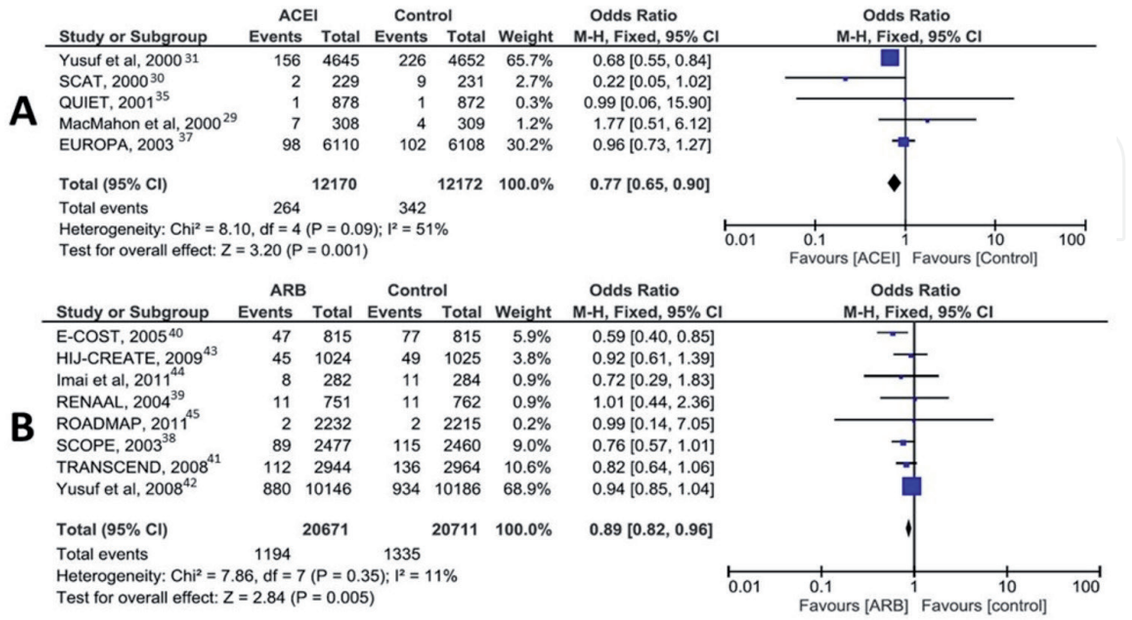
Figure 3.
Forest plots summarizing the correlation of (A) ACEI and (B) ARB use for acute myocardial infarction.

4.4 Stroke

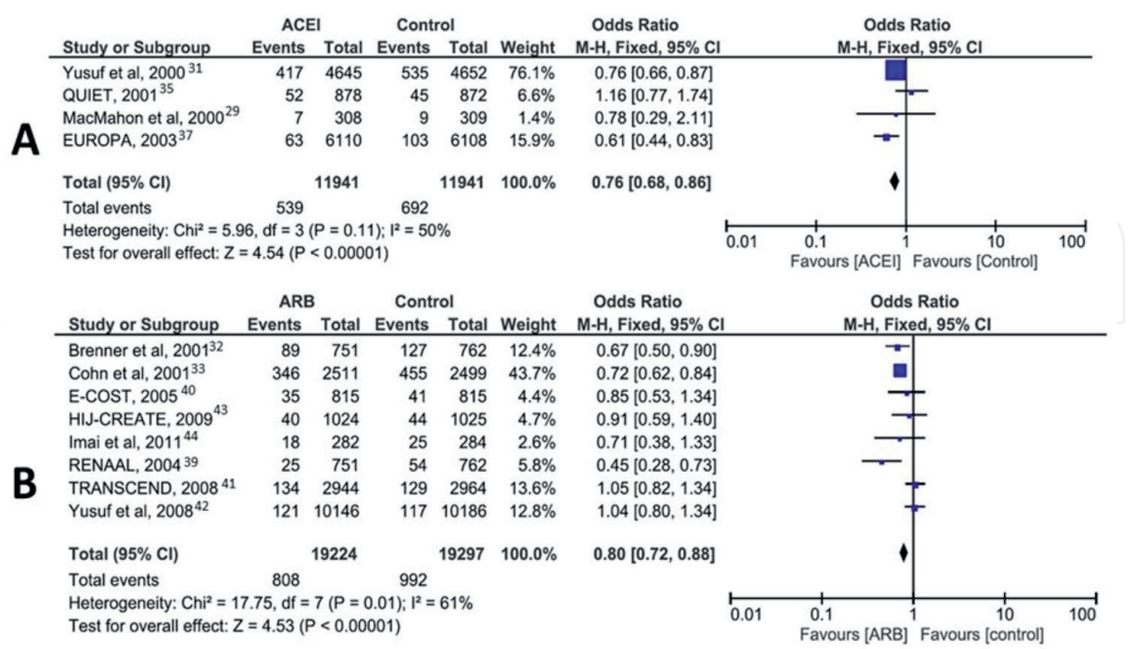
Of the 13 studies (n = 65,724) that evaluated stroke, 2 of them, 1 involving ACEI (OR = 0.681, 95% CI, [0.553–0.838], P = 0.000) and another involving ARB (OR = 0.587, 95% CI, [0.402–0.855], P = 0.005), showed statistical significance

for reduction of stroke when compared to the control group. Similar to the results for AMI, the reduction of stroke, compared to the control group, was significative in the two classes of medications, with a more expressive reduction for ACE (OR = 0.770, 95% CI, [0.654–0.908], P = 0.002) on BRA (OR = 0,890, 95% CI, [0.820–0.965], P = 0.005) (**Figure 4**).



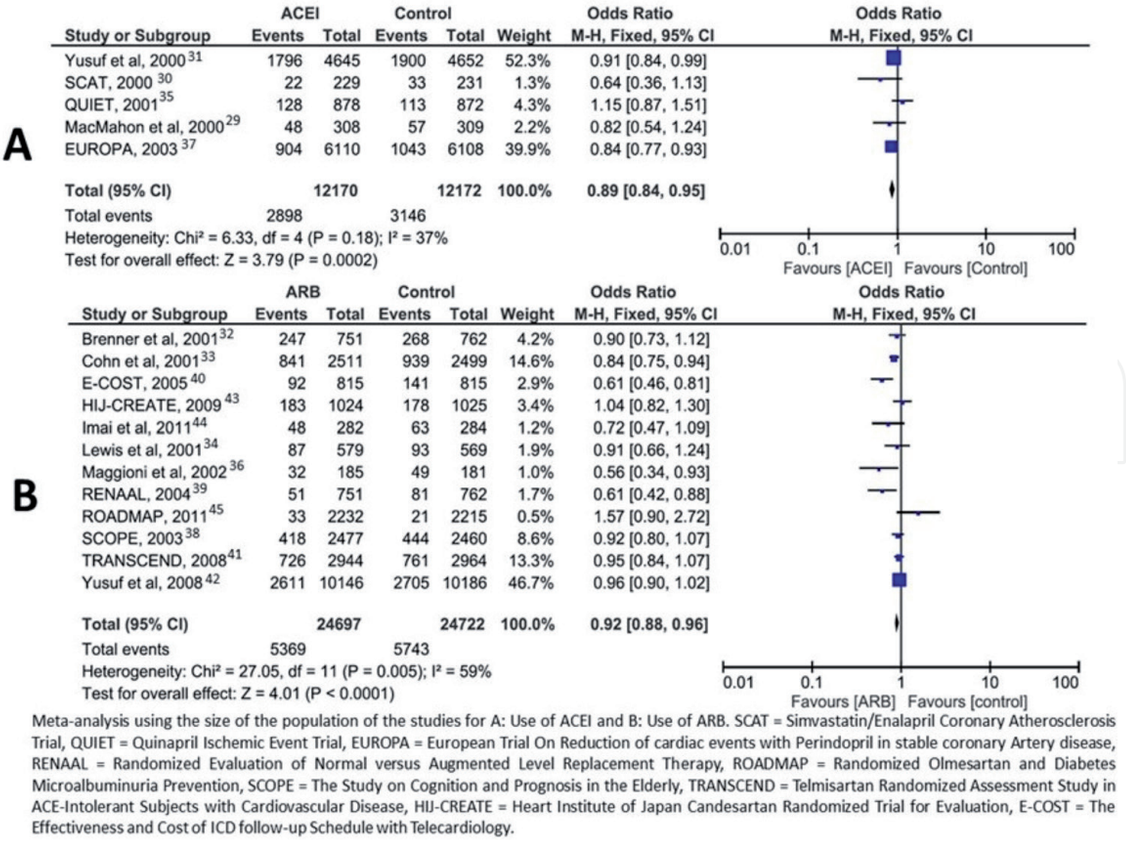
Meta-analysis using the size of the population of the studies for A: Use of ACEI and B: Use of ARB. SCAT = Simvastatin/Enalapril Coronary Atherosclerosis Trial, QUIET = Quinapril Ischemic Event Trial, EUROPA = European Trial On Reduction of cardiac events with Perindopril in stable coronary Artery disease, RENAAL = Randomized Evaluation of Normal versus Augmented Level Replacement Therapy, ROADMAP = Randomized Olmesartan and Diabetes Microalbuminuria Prevention, SCOPE = The Study on Cognition and Prognosis in the Elderly, TRANSCEND = Telmisartan Randomized Assessment Study in ACE-Intolerant Subjects with Cardiovascular Disease, HIJ-CREATE = Heart Institute of Japan Candesartan Randomized Trial for Evaluation, E-COST = The Effectiveness and Cost of ICD follow-up Schedule with Telecardiology.

Figure 4.
Forests plots summarizing the correlation of (A) ACEI and (B) ARB use for stroke.



Meta-analysis using the size of the population of the studies for A: Use of ACEI and B: Use of ARB. QUIET = Quinapril Ischemic Event Trial, EUROPA = European Trial On Reduction of cardiac events with Perindopril in stable coronary Artery disease, RENAAL = Randomized Evaluation of Normal versus Augmented Level Replacement Therapy, TRANSCEND = Telmisartan Randomized Assessment Study in ACE-Intolerant Subjects with Cardiovascular Disease, HIJ-CREATE = Heart Institute of Japan Candesartan Randomized Trial for Evaluation, E-COST = The Effectiveness and Cost of ICD follow-up Schedule with Telecardiology.

Figure 5.
Forests plots summarizing the correlation of (A) ACEI and (B) ARB use for heart failure.



Meta-analysis using the size of the population of the studies for A: Use of ACEI and B: Use of ARB. SCAT = Simvastatin/Enalapril Coronary Atherosclerosis Trial, QUIET = Quinapril Ischemic Event Trial, EUROPA = European Trial On Reduction of cardiac events with Perindopril in stable coronary Artery disease, RENAAL = Randomized Evaluation of Normal versus Augmented Level Replacement Therapy, ROADMAP = Randomized Olmesartan and Diabetes Microalbuminuria Prevention, SCOPE = The Study on Cognition and Prognosis in the Elderly, TRANSCEND = Telmisartan Randomized Assessment Study in ACE-Intolerant Subjects with Cardiovascular Disease, HIJ-CREATE = Heart Institute of Japan Candesartan Randomized Trial for Evaluation, E-COST = The Effectiveness and Cost of ICD follow-up Schedule with Telecardiology.

Figure 6.
Forests plots summarizing the correlation of (A) ACEI and (B) ARB use for all the outcomes.

4.5 Heart failure

A total of 12 studies (n = 62,403) analyzed heart failure. Two comparing the use of ACEI with a control group caused a significant reduction of the outcome, (OR = 0.759, 95% CI, [0.663–0.869], P = 0.000] and (OR = 0.607, 95% CI, [0.443–0.833], P = 0.002). The same was observed for three studies with ARB (OR = 0.718, 95% CI, [0.617–0.836], P = 0.000), (OR = 0.672, 95% CI, [0.502–0.900], P = 0.008) and (OR = 0.451, 95% CI [0.278–0.734], P = 0.001). Thus, the two therapies analyzed were significant in the reduction of the event, with proximity of both classes in relation to the reduction of heart failure compared to the control group: ACEI (OR = 0,762, 95% CI, [0.677–0.857], P = 0.000) and BRA (OR = 0,799, 95% CI, [0.724–0.882], P = 0.000) (**Figure 5**).

4.6 Total outcomes

Analyzing all the outcomes described, the 17 studies (n = 73,761) showed that both the uses of ACEI (OR = 0.890, 95% CI, [0.837–0.945], P = 0.000) and of ARB (OR = 0.916, 95% CI, [0.877–0.956], P = 0.000) are favorable to a significant reduction in the occurrence of mortality events (**Figure 6**).

5. Discussion

The blockade of the renin-angiotensin-aldosterone system, regardless of the level in which it is performed, by itself, is a demonstrably relevant factor in lowering blood pressure. Both the inhibition of angiotensin-converting enzyme (ACEI) and the blockade of the AT-1 receptor of angiotensin II (ARB) provide a decrease in the

smooth muscle contraction in the arterial endothelium and thus lead to a reduction in the pressure values in both drug regimens [5].

With this basis, associated with the data presented in the results, it was already expected that, when comparing the use of ACEI or ARB with the control group, there was a decrease in the development of myocardial infarction, stroke, and heart failure (in favor of the first group [ACEI or ARB]). The decrease in blood pressure constitutes an agent that directly causes an improvement in the circulatory system and in the perfusion system, and, as a consequence, there is a decrease in vascular pathologies, especially in the present study, for these outcomes. Thus, the first plausible analysis of conclusion is that both the uses of ACEI and the ARB are efficient in decreasing blood pressure values as well as in the decrease of the hard outcomes. Quantitatively, it is noteworthy that the values, in these three outcomes, are more relevant in favor of the use of ACEI, when compared with the use of ARB, as seen in the charts of **Figures 4–6**. Despite this numerical superiority, in medical practice, both medications are relevant and preventive in terms of the three outcomes and therefore have their use indicated.

However, despite the synergistic effects of these medications in the hypertensive condition, their association is contraindicated. This contraindication is based on the fact that its association, when compared with its isolated use, does not cause improvement of cardiovascular outcomes, although there is an additional reduction in blood pressure [25]. In addition, the concomitant use of both medications presents, based on concrete evidence, an increase of at least 10% in the relative risk of cancer [26].

However, when analyzing the total mortality and cardiovascular mortality, there were differences. For these outcomes, as shown in **Figures 2** and **3**, the use of ACEI proved to be significant in relation to the statistic, while the use of ARB showed no differences compared to the control group. This fact, regarding the total mortality, corroborates with the data presented by van Vark [16] where there was a 10% decrease in mortality due to all causes, over 4 years, with the use of ACEI, while the use of ARB does not rush any impact. However, related to the cardiovascular mortality, this same review did not present differences between the two drugs, whereas, in our review, the differences were statistically significant [14].

Given this, a reduction in the values of overall and cardiovascular mortalities with the use of ACEI, and in view of the follow-up time of the studies allocated here (from 27 to 66 months), we relate this difference observed to an increase or decrease in the serum concentration of some endogenous molecular factor, i.e., produced by the angiotensin-renin system itself.

Based on the physiological analysis of the blockade of ACEI and ARB drugs in the angiotensin-aldosterone cascade, we found that the role of ACE inhibitors occurs by inhibiting the conversion of angiotensin I into angiotensin II, while the ARB acts later in this process, blocking the receptor of the molecule of angiotensin II. Thus, there is a decrease in the serum values of angiotensin II in the use of ACEI, which does not occur with the use of ARB [27].

Based on this mechanism of action, the use of ACEI ultimately provides higher levels of polypeptide hormones, being the most physiological importance in this context, the bradykinin [28].

Bradykinin is an inflammatory polypeptide, which is responsible for the maintenance of the inflammation cascade as well as for providing vasodilation, a necessary step so that the molecular and cellular agents of the inflammatory cascade can act on the site of possible injury. Its inactivation is performed mainly by carboxypeptidase II (kininase type II) of the lung parenchyma. Coincidentally, the kininase II, which inactivates bradykinin, is the same inhibited by the ACEI. Therefore, these medications, in addition to decreasing the concentration of angiotensin II, a potent

vasoconstrictor, collaborate to increase the pool of bradykinin, a physiological inflammatory vasodilator. Thus, there is an even greater increase in the hypotensive effects as well as a greater synergism regarding the reduction of other outcomes from vasoconstriction, caused by hypertensive conditions [29–31].

Thus, the benefits of using ACE inhibitors, resulting from the increase in the amount of bradykinin in the body, seem to have an additional benefit in the population with essential hypertension. This fact stems from the knowledge, about 80 years ago, of the modulating roles of bradykinins in the renin-angiotensin system, not only in the mechanism of vasodilation but also in the ventricular remodeling in patients with hypertension [32, 33].

As for the other outcomes such as infarction, stroke, and heart failure, the increase in circulating bradykinin in these patients, due to its already explained vasodilating properties, also has a positive effect. Among these effects, we highlight the performance in the maintenance of the coronary reserve as well as in the consequent prevention of infarction [34]. In addition, bradykinin was also identified as an endogenous factor that, associated with other molecules, favors the maintenance of myocardial perfusion and consequently promotes the prevention of ventricular remodeling in heart failure [34].

Related to the prevention of stroke, as was verified in the quantitative difference between these outcomes when compared to the population using ACEI, the increase in bradykinin implies the increase of the cerebral arterial flow [35, 36].

However, although we observe that the use of ACEI is intimately related to the decrease in infarction, stroke, and heart failure, these effects do not present a significant difference when compared to the use of ARB (**Figures 3–5**).

This characteristic is due to the fact that, even if the ACEIs have a significant increase in the concentration of bradykinins, its use is also implicated in the increase of other molecular factors which, in turn, present a myriad of receptors with often antagonistic functions. This may facilitate, hinder, or even have no effect on the action of the bradykinin in those outcomes but rather present more complex interactions in the function of these pathologies [37–39].

Some of these substances have already been discovered, such as prostaglandins and prostacyclins. However, the cellular molecule-receptor interaction and the best detailing of its cardiovascular-protective properties still lack studies to discover its relations with bradykinin and, above all, the relationship between the use of ACEI and the hypertensive condition in infarction, stroke, and heart failure. Thus, so far, it is only possible to infer the main role of bradykinin and a possible nonspecific interference of these factors in such pathologies [40–42].

Now, related to total and cardiovascular mortalities, we believe that the reduction of these outcomes observed in the use of ACEI may be closely related to the increase in the bloodstream of bradykinin. This fact is justified in view of the benefits that bradykinin promotes, in the long term, in the maintenance of vascular integrity. This molecule has a positive impact on the prevention of microvascular alterations, which occur in certain diseases, in this case hypertension. This prevention tends to take place because bradykinin, via B2 receptors, protects the viability of the endothelium exposed to necrosis and apoptotic in hostile environments [43]. These situations are not observed when using the ARB. This is because its mechanism of action does not involve a pathway that changes the concentration of other mediators of blood pressure regulation, in addition to angiotensin II. Therefore, the use of ACEI is more effective than the use of ARB in these long-term outcomes.

As a consequence of this difference in the outcomes, total mortality and cardiovascular mortality, a decrease in the total outcomes with the use of ACEI was also predicted, as shown in **Figure 6**.

Moreover, analyzing the consumption of ACEI and ARB, it is observed that in recent years the consumption of ACEI decreased, while the ARB showed significant growth. In the face of the literature and the present study, it can be corroborating that this situation does not present a relevant scientific basis [44].

6. Limitations of the ACEI × ARB analysis

The main limitation of this review involves the variation between the population samples, such as the different doses of the medications and the control group, and the studies with different follow-up times. In addition, some studies called therapy as a placebo without exactly specifying this information.

Also, for medical and ethical reasons, the vast majority of studies made it clear that both groups in use of ACEI and in use of placebo were already using other antihypertensive drugs. Thus, it cannot be inferred whether these medications in use could influence the information presented here.

It is also noteworthy that the study was based on analyzing the outcomes of different classes, ACEI and ARB. Thus, it should be considered that differences between the various drugs of each class are possible.

7. Conclusion

Through the use of ACEI and ARB, the pressure levels present significant reductions with both medications. Also, in the long term, the two therapies provide a decrease in the risk of hard outcomes such as acute myocardial infarction, stroke, and heart failure. However, the use of ACEI is effective in the reduction of the overall and cardiovascular-related mortality, facts not seen using the ARB. Thus, it is assumed that this reduction is due to the higher concentration of bradykinin, in the use of ACEI, due to its cardiovascular-protective properties, and not linked to the pressure drop only.

Conflict of interest

The authors declare no conflict of interest.

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