Misleading guidelines for the diagnosis and management of hypertension

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ABSTRACT

The new international guidelines for the diagnosis and management of hypertension proposed higher thresholds for the diagnosis of hypertension in patients with higher cardiovascular risk, such as patients with diabetes, chronic kidney disease, and the elderly. The premise for the new recommendations was the results of randomized clinical trials, such as the ACCORD trial. Nonetheless, the results of the ACCORD trial were within the predicted by the meta-analysis of risk and confirmed by meta-analysis of clinical trials, particularly for stroke. The decision to use 140 mmHg as the therapy goal would be to deny diabetic patients the benefit of preventing a large proportion of strokes. In addition, the meta-analysis conducted in the United States did not address prehypertension, ignoring many trials performed with patients presenting prehypertension and cardiovascular disease, showing the benefit of further lowering blood pressure. The guidelines recommended angiotensin receptor blockers as one of the first options for all patients and particularly patients with diabetes and chronic kidney disease. Three recently published meta-analyses and review showed that these agents are practically inert in the prevention of all-cause death and cardiovascular events. In conclusion, there is evidence showing that hypertension should be more aggressively prevented and treated, and that angiotensin receptor blockers should not be the first option to start the treatment.

Keywords: *Hipertension; guidelines; diabetes*

International guidelines for the diagnosis and management of hypertension were recently released[1,2]. A historical trend of lowering blood pressure (BP) thresholds to diagnose hypertension in high-risk individuals was unexpectedly reversed. BP targets for the treatment were modified accordingly. Therefore, some individuals who were hypertensive before are now normotensive. Other guidelines still recommend the previous diagnostic limits and goals of treatment[3-5], resulting that one individual may be hypertensive in some countries and normotensive in others. The guidelines are more homogeneous in the recommendations for treatment, particularly in regard to the liberal options of drugs to start the treatment. This open recommendation includes drugs without unbiased evidences of effectiveness, such as Angiotensin Receptor Blockers (ARBs). In this point of view, I discuss the reasons and misconceptions concerning the establishment of diagnostic thresholds and the shortcomings in the recommendations of antihypertensive drugs.

What are the thresholds to diagnose hypertension?

The guidelines of the European Society of Hypertension and European Society of Cardiology were the first to recommend new thresholds for the diagnosis of hypertension. According to them, the target values in the treatment of hypertension in patients with diabetes were set at 140/85 mmHg[1] instead of 130/80 mmHg, as recommended by the previous guidelines[6]. In addition, the new guidelines recommended that drug treatment should be started at BP higher than 160 mmHg in elderly patients.

The European guideline is sometimes confusing, referring to diagnostic thresholds and to goals of treatment in other tables. For instance, the recommendations for elderly patients are contradicted in the next recommendation, which states that antihypertensive drug treatment may also be considered in the elderly (at least when younger than 80 years) when systolic blood pressure (SBP) is in the 140–159 mmHg range, provided that antihypertensive treatment is well tolerated. Since BP-lowering drugs are well tolerated, it is possible to assume that we should start treating patients at lower BP levels (140 mmHg, as in the previous guideline), since it is impossible to know a priori if the patient will tolerate the treatment.

The Eighth Joint National Committee (JNC 8) report[2] presented a radical shift from the (JNC 7)[7]. The report addressed only drug treatment, excluding the overall evaluation of the patient, methods of BP measurement, strategies to diagnose identifiable causes of secondary hypertension, lifestyle recommendations, and other aspects related to the overall management of hypertension. In regard to diagnostic thresholds and goals of treatment, the (JNC 8) was clearer than the European guidelines, and did present higher diagnostic values for BP in some conditions as well. For non-elderly adults, the report maintained 140/90 mmHg as diagnostic of Hypertension and also as a goal of treatment. For individuals over 60 years, the report established 150 mmHg of systolic BP as the new diagnostic limit and the target of treatment, keeping 90 mmHg for diastolic BP. The most radical modification, however, was in patients with diabetes and chronic kidney disease (CKD). The current recommendations are the same as those for adults without diabetes (140/90 mmHg), in comparison with 130/80 mmHg recommended in the JNC 7 report. The JNC 8 report did not address prehypertension, a condition proposed in the JNC 7 and that is a current focus of research, both in terms of risk for cardiovascular disease and therapeutic approach.

The guidelines from the National Institute for Health and Clinical Excellence (NICE) were issued in 2011[3]. This guideline was the first to include out-of-office BP measurement, either by Ambulatory Blood Pressure (ABP) monitoring or Home Blood Pressure (HBP) monitoring, as additional criteria to diagnose hypertension. The algorithms are more complex, but the office BP was set at 140/90 mmHg for adults younger than 80 years old, with or without diabetes or CKD.

The current Brazilian guidelines were not updated recently and are still similar to the previous European guidelines[4]. The recently released recommendations from the Brazilian Ministry of Health[5] maintain 130/80 mmHg as the treatment target in patients with diabetes, CKD, high cardiovascular risk, and secondary prevention of stroke.

Where do we stand in face of the paradoxical changes in the major guidelines and the differences between guidelines? Should we follow the new recommendations or should we keep a more aggressive approach to lower BP, particularly in patients with higher cardiovascular risk? I believe that the reasons to establish new thresholds were not fully revised and that it is necessary to take in consideration the full set of evidence to support our decisions.

The authors of the American and the European guidelines based their new target recommendations for BP treatment on the results of randomized clinical trials (RCT). They should be complimented by the initiative, which recognizes the primacy of the results of RCT to justify medical decisions. Nonetheless, they misinterpreted the results of the ACCORD trial[8]. Moreover, they left aside the results of many trials that were done with patients with normal BP, assuming that these trials were not applicable to patients with hypertension. We had the opportunity to deeply discuss these and other issues related to goals of treatment and the J-shaped phenomenon[9]. In summary, I present below the main points that support my view.

The wrong interpretation of the ACCORD trial

The ACCORD study tested the hypothesis that lowering blood pressure beyond guidelines recommendations would confer higher cardiovascular protection[8]. The trial assessed the incidence of cardiovascular events in patients with diabetes assigned to intensive therapy, targeting a systolic pressure of less than 120

mm Hg, as compared with the standard therapy, targeting a systolic pressure of less than 140 mm Hg. The incidence of the primary endpoint, coronary heart disease events, was not statistically different between treatment arms, and serious adverse events were three times more frequent in the intensive arm. Therefore, the experts recommended 140/90 mmHg as the goal in the management of hypertension for patients with diabetes. Nonetheless, there are sound evidence-based reasons to dissent from this view and to recommend low blood pressure targets to prevent cardiovascular disease.

Strategy trials, such as the ACCORD trial, are less susceptible to confounding than cohort studies, but are not fully free of potential confounding. Reasons include the possibility that BP reduction in a proportion of patients treated intensively and the interruption of drug treatment at lower BP levels could be harmful. The results of the ACCORD trial were within the predicted by the meta-analysis of risk[10] and confirmed by the meta-analysis of clinical trials[11]. There was a 13% reduction in the incidence of coronary artery disease, in comparison with 22% predicted by the meta-analysis of clinical trials (figure 1). It is noteworthy that the estimate of the meta-analysis was based in 71 studies with 9,811 events, in comparison with 126 events of the ACCORD trial. For stroke, the relative risk reduction in the ACCORD trial was identical to that predicted by the meta-analysis of 45 studies, with 5,420 events (figure 1). It is of note the magnitude of the benefit, a relative risk reduction of 41%. The absolute incidence of stroke in the ACCORD trial was unexpectedly low. Taking into account the higher incidence of stroke in our country, and its devastating consequences, the decision to use 140 mmHg as the goal of therapy would be to deny diabetic patients the benefit of preventing a large proportion of strokes.

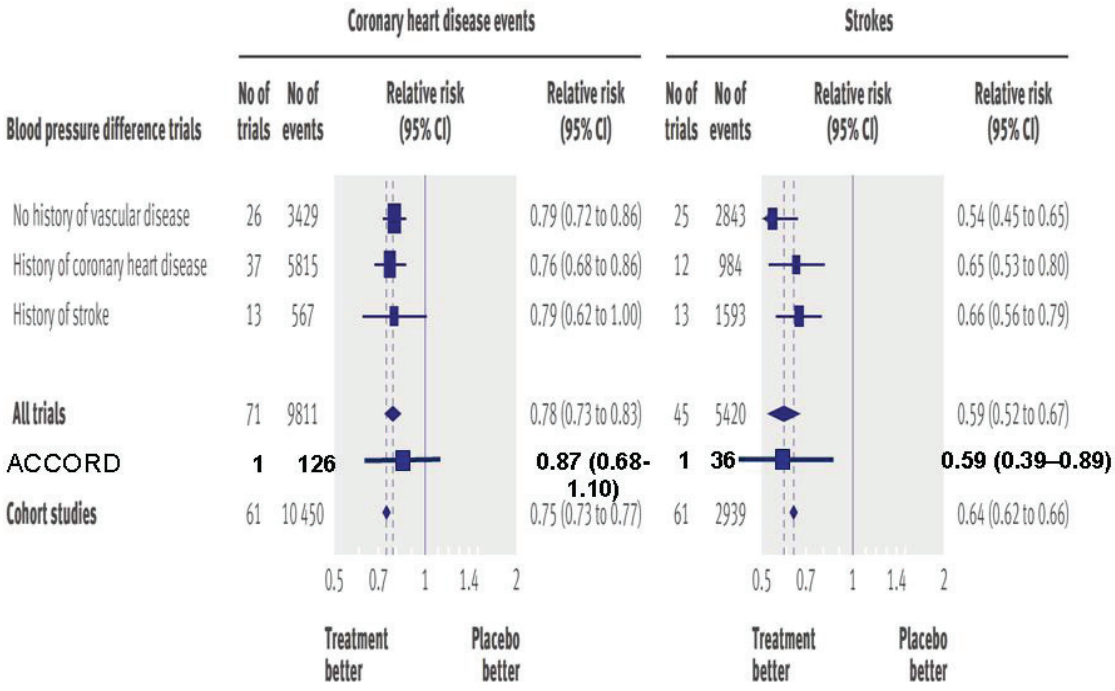

Figure 1: Relative risk for coronary heart disease and stroke in blood pressure-difference trials, in epidemiological studies and in the ACCORD trial. Reproduced, with permission, from reference 11.

The benefit of treating patients with low blood pressure in patients with subclinical or clinical disease

Previous trials done in patients with clinical or subclinical cardiovascular disease (heart failure, stroke, myocardial infarction, evidence of atherosclerosis, and diabetes) demonstrated significant reduction of cardiovascular events with the use of blood pressure lowering agents independently of baseline blood pressure[12]. Table 1 presents the results of the more representative studies[13-19]. The benefit of treatment was mostly attributed to blood pressure-independent effects of the agents tested in these studies, the so-called pleiotropic effects. Nonetheless, the intensity of blood pressure reduction itself could explain the benefits of treatment. The meta-analysis by Law and co-authors[11] demonstrated that the prevention of coronary artery disease and stroke with further reduction of blood pressure was independent of its values at the beginning of these trials (figure 2).

Table 1: Clinical trials showing the effectiveness of blood pressure-lowering drugs in the prevention of cardiovascular events in patients with normal blood pressure.

Clinical condition	References	Active treatment	Primary outcome	RRR (95% CI)
Diabetes mellitus*	**13**	**Ramipril**	**MI, stroke or CV death**	**25% (12 to 36)**
Any evidence of atherosclerosis in the coronary, cerebral, or peripheral territories	**14**	**Ramipril**	**MI, stroke or CV death**	**22% (14 to 30)#**
	15	**Perindopril**	**MI, CV death or cardiac arrest**	**20% (9 to 29)#**
Recovered from stroke	**16**	**Indapamide plus perindopril**	**Stroke**	**42% (19 to 58)**
Asymptomatic heart failure	**17**	**Enalapril**	**CV deaths**	**12% (-3 to 26)**
Overt heart failure	**18**	**Enalapril**	**CV deaths**	**18% (6 to 28)**
	19	**Captopril**		**21% (5 to 35)**

RRR: relative risk reduction

* In individuals aged at least 55 with another major cardiovascular risk factor (elevated cholesterol levels, low HDL-cholesterol, cigarette smoking, or microalbuminuria).

MI: myocardial infarction; CV: cardiovascular

estimate for the entire cohort, not significantly different between normotensive and hypertensive individuals

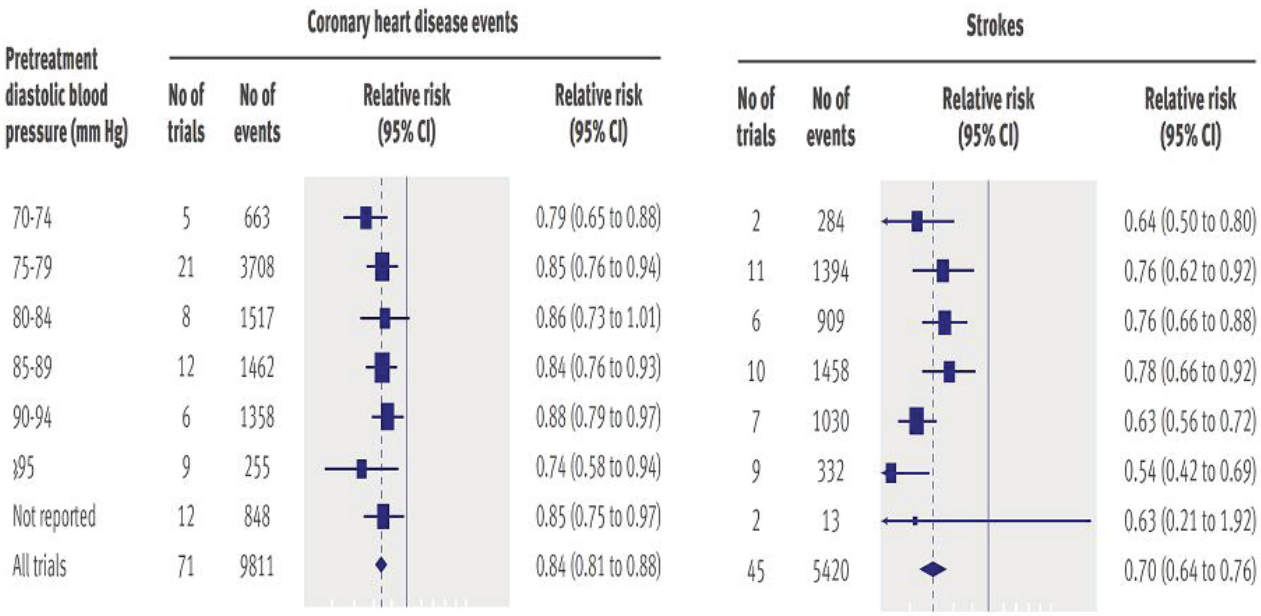

Figure 2: Relative risks for coronary events and stroke in patients stratified by blood pressure at the beginning of randomized controlled clinical trials. Reproduced, with permission, from reference 11.

There is a proof of the concept that high blood pressure is the major risk of for cardiovascular disease[20]. The magnitude of the benefit in clinical trials regarding the control of high BP was within the estimations of risk provided by cohort studies. For a reduction of 10 mmHg in systolic or 5 mmHg of diastolic blood pressure, the relative risk reduction of coronary heart disease was 22% (95% CI from 27 to 17%) in a meta-analysis of clinical trials, close to the estimation of reduction of 25% (23 to 27%) provided by a meta-analysis of cohort studies. The corresponding values for stroke were 41% (33 to 48%) in clinical trials compared to a cohort risk prediction of 36% (34 to 38%)[20].

Besides the risks of prehypertension for cardiovascular disease, it is a precursor of full hypertension in high proportion of individuals. Many studies have identified the cardiovascular risks of prehypertension and the incidence of hypertension [21-24]. In Porto Alegre, four in five individuals from 40 to 49 years old with prehypertension became hypertensive in 10 years[25]. Studies examining the benefit of drug treatment in patients with prehypertension free of cardiovascular disease are warranted[26], as the PREVER-prevention trial, a nationwide RCT on the way in Brazil[27]. The PREVER-prevention trial enrolled about 700 participants, who are being followed for 21 months. In the meantime, it is worthy to present the option to start low doses of BP agents for individuals with prehypertension without co-morbidities who do not respond to the prescription of lifestyle modification[28].

Taken together, these pieces of evidence support the view that most guidelines moved to the wrong direction. Evidence still do not show the whole picture, and should be accompanied for indirect evidences and findings in analogous models to build the theory. If someone wants to live more than 100 years, he or she should keep blood pressure below 120 by 80 mmHg, which are the BP values of worldwide centenarians.

Misleading indications to start drug treatment

This is another sensitive issue. I strongly disagree with the recommendations of all guidelines to employ ARBs as a one of the first options for all patients and particularly with the preference to use these drugs in patients with diabetes and CKD. I have challenged this recommendation in manuscripts and letters about this topic in the last 14 years, and it seems that I may be right. Let's see a summary of the evidence or lack of evidence.

ARBs are among the worldwide leading brands of blood pressure-lowering agents. This

preference, endorsed by guidelines, is based on their neutral or beneficial metabolic effects, and on putative cardiac and renal protective effects independent of their blood pressure-lowering effect – the pleiotropic effects. The corporate bias, allied with a massive commercial promotion, may explain part of this preference[29]. Large clinical trials designed to demonstrate such effects, mostly comparing ARBs with placebo on top of the usual treatment, have failed to demonstrate additional cardiovascular protection by ARBs and suggested that they may be associated with worse renal outcomes[30-38]. I reviewed the results of the major clinical trials where an ARB was compared with an active treatment or placebo[39]. The only study where an ARB was superior to the comparator in the prevention of cardiovascular outcomes in patients with hypertension or at high cardiovascular risk was the LIFE trial[30]. Nonetheless, atenolol was an inadequate comparator[40], and more patients on losartan used diuretics[41]. Figure 3 summarizes the risks for major cardiovascular outcomes in studies that compared ARBs with other agents and with placebo.

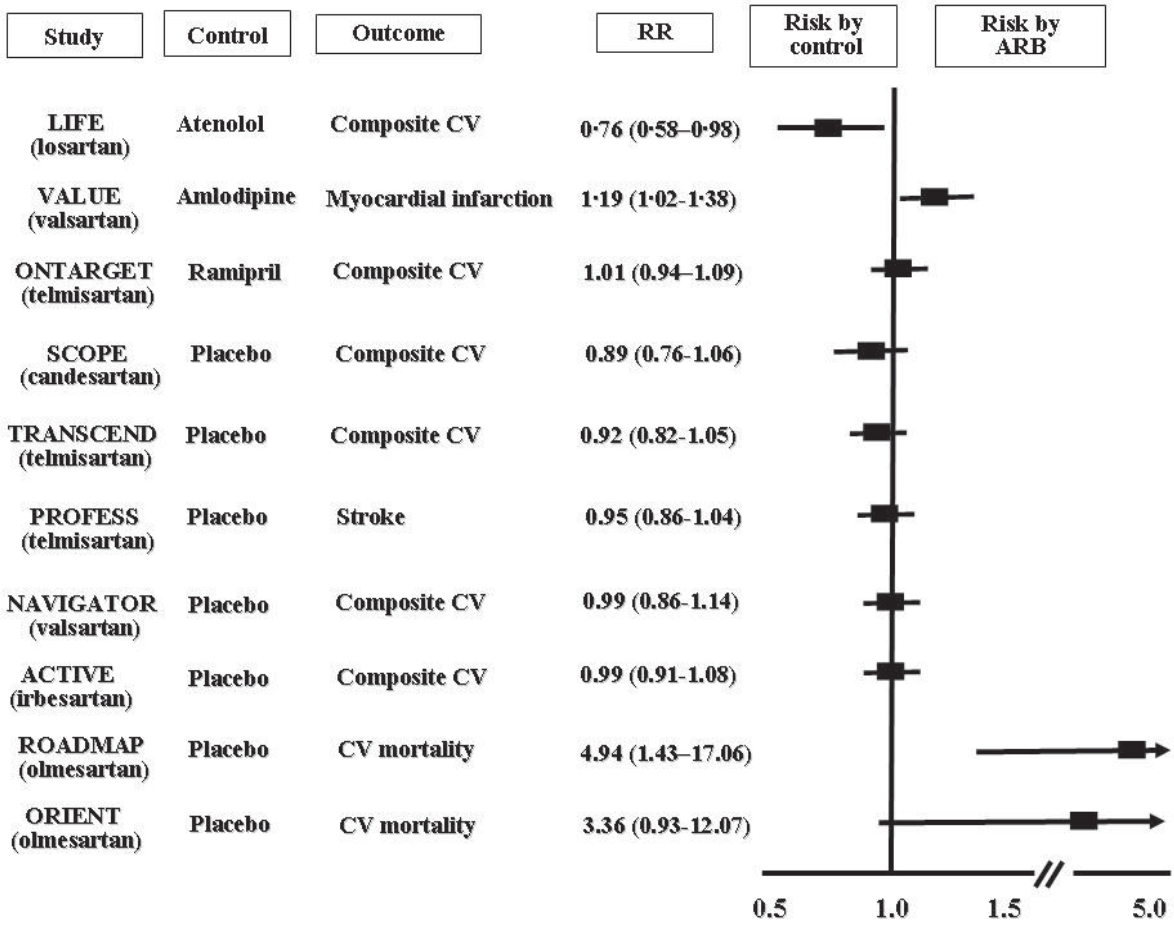

Figure 3: Relative risks and 95% confidence intervals for the occurrence of cardiovascular outcomes in clinical trials comparing ARBs with other drugs or placebo in patients with hypertension or high cardiovascular risk; the outcomes were the primary outcome of the studies or a co-primary or secondary outcome with significant difference between the trial arms (references in the text). Reproduced, with permission, from reference 39.

Putative cardiac and renal pleiotropic effects of ARBs are the basis for their preferential indication to prevent the recurrence of atrial fibrillation and to protect the kidney. The evidence comes mostly from experimental studies, placebo-controlled trials, and from a post-hoc analysis of the flawed LIFE trial. New findings are casting doubt upon these preferential indications for ARBs. The efficacy of ARBs in the prevention of atrial fibrillation was not confirmed by four large studies specifically designed to investigate this outcome[36,42-44]. At least six large studies with ARBs suggest that these agents may have adverse effects over the kidneys, particularly when used together with angiotensin converting enzyme (ACE) inhibitors. In the RASS study[45], a complex but well-designed trial in patients with type 1 diabetes and normoalbuminuria, the 5-year cumulative incidence of microalbuminuria was 6% in the placebo group, 4% in the enalapril group, and 17% with losartan (P=0.01). The addition of telmisartan to ramipril in order to get dual blockade of the renin-angiotensin axis in the ONTARGET trial[46] was associated with an increase of 33% in the incidence of renal impairment (P<0.001) and a trend for higher rate of renal dialysis (P=0.10). The ROADMAP trial[37] reported a higher reduction in glomerular filtration rate in patients treated with olmesartan instead of placebo. In the ACTIVE trial[36] the incidence of renal dysfunction leading to discontinuation of the drug almost doubled in patients treated with irbesartan. In the TRANSCEND trial[33], the decrease in glomerular filtration rate was greater with telmisartan than with placebo.

Three meta-analysis of RCT that compared ARBs with active or placebo comparators showed that they were inert in the prevention of total mortality and major cardiovascular outcomes. The first explored the efficacy of ARBs in the prevention of myocardial infarction and other cardiovascular outcomes[47]. Patients had various criteria for enrollment in the trials, such as hypertension, heart failure, diabetes, stroke, atrial fibrillation, and others. In total, 37 randomized clinical trials, with 147 020 participants, were included. When compared with placebo or active treatment, ARBs were inert in the prevention of myocardial infarction (relative risk 0.99, 95% confidence interval 0.92 to 1.07), death, cardiovascular death, or angina pectoris.

The second meta-analysis investigated the efficacy of Renin–Angiotensin–Aldosterone System (RAAS) inhibitors over cardiovascular morbidity–mortality trials[48]. The trials should have at least two-thirds of the patients diagnosed with hypertension. The cohort included 158,998 patients. RAAS inhibition was associated with a 5% reduction in all-cause mortality (HR: 0.95, 95% CI: 0.91–1.00), and a 7% reduction in cardiovascular mortality (HR: 0.93, 95% CI: 0.88–0.99). The effect was entirely due to ACE inhibitors (HR: 0.90, 95% CI: 0.84–0.97). ARB treatment had no effect in the prevention of all-cause mortality (HR: 0.99, 95% CI: 0.94–1.04).

A more recent meta-analysis presents another piece of concern about the status of ARB in the prevention of cardiovascular disease[49]. This meta-analysis was restricted to patients with diabetes. Compared to placebo or other active treatment, in 23 studies with 32,827 diabetic patients, angiotensin converting enzyme inhibitors (ACEIs) significantly reduced the risk of all-cause mortality by 13% (RR, 0.87; 95%CI, 0.78-0.98) and CV deaths by 17% (0.83; 0.70-0.99). ACE inhibitors were effective in the prevention of major CV events, myocardial infarction and heart failure. In contrast with the effectiveness of ACEIs, ARBs were ineffective to reduce the risk for all-cause mortality (RR, 0.94; 95%CI, 0.82-1.08) in 13 studies with placebo or no treatment control, with a total of 23,867 patients. With the exception of a reduction in the risk of heart failure, ARBs were ineffective in the prevention of CV death rates (1.21; 0.81-1.80) and major CV events (0.94; 0.85-1.01). According with the results of this meta-analysis, the preference for an ARB may be denying diabetic patients the benefit of treatment. The number needed to treat with an ACEi to prevent one death is approximately eight. Since ARBs did not prevent all-cause deaths, choosing an ARB would be associated with a risk of one death for every eight patients treated with an ARB instead of an ACEi (NNK (number needed to kill)= 8).

Besides these frustrating findings in meta-analyses and large clinical trials, several studies on ARBs are under legal scrutiny. Three studies were retracted from the literature because of scientific fraud[50-52]. A former director of Novartis Pharma's scientific affairs department was recently arrested on suspicion of falsifying clinical data to overstate the benefits of the Swiss drug manufacturer's hypertension drug valsartan[53]. These disclosures led to the replacement of the president and two other senior executives of the Japanese subsidiary of Novartis.

The PREVER treatment trial is the first large double-blind RCT that is comparing an

ARB (losartan) with an association of diuretics (chlorthalidone and amiloride)[54]. The trial enrolled about 700 patients, who are being followed for 21 months. The outcomes are blood pressure and target organ damage: glomerular filtration rate, microalbuminuria, and left ventricular hypertrophy estimated by ECG. Results are planned for the end of this year.

It's almost inexplicable how ARBs have reached the leadership in the preference of physicians to treat hypertension and prevent cardiovascular disease, in face of this overwhelming volume of evidence demonstrating that they are probably inert or have minor effects in the prevention of cardiovascular disease. The corporate bias, defined as the distortions in the planning, presentation or interpretation of RCT that favor the drugs from the sponsor of the RCT[29], has surely an influence. But more than the legitimate interest of corporations to sell their products, scientists in the field of hypertension, who are the authors of guidelines, had a critical role in promoting the benefits of these drugs. The results of individual and large RCT were mostly negative, but the scientists in the field of cardiovascular prevention in patients with hypertension and diabetes favored the results of small and sometimes biased RCTs, most of them looking at the effects on surrogate endpoints, and the findings from the overwhelming number of experimental studies in animal models. The agenda for the investigation of diagnostic and therapeutic methods for the diagnosis and prevention of cardiovascular disease cannot be left only to the discretion of the big-Pharm[55]. Scientists should preserve their independence and work for the universities who pay their salaries.

CONCLUSION

High blood pressure plays a key role in the development of cardiovascular disease and should be more aggressively prevented and treated than the recommended by current guidelines. The preference for angiotensin receptor blockers is not supported by evidences and may deny patients the benefits of proved blood pressure-lowering agents.

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