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REVIEW

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State-of-the-art treatment of hypertension: established and new drugs

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The treatment of essential hypertension is based essentially on the prescription of four major classes of antihypertensive drugs, i.e. blockers of the renin–angiotensin system, calcium channel blockers, diuretics and beta-blockers. In recent years, very few new drug therapies of hypertension have become available. Therefore, it is crucial for physicians to optimize their antihypertensive therapies with the drugs available on the market. In each of the classes of antihypertensive drugs, questions have recently been raised: are angiotensin-converting enzyme (ACE) inhibitors superior to angiotensin II receptor blockers (ARB)? Is it possible to reduce the incidence of peripheral oedema with calcium antagonists? Is hydrochlorothiazide really the good diuretic to use in combination therapies? The purpose of this review is to discuss these various questions in the light of the most recent clinical studies and meta-analyses. These latter suggest that ACE inhibitors and ARB are equivalent except for a better tolerability profile of ARB. Third generation calcium channel blockers enable to reduce the incidence of peripheral oedema and chlorthalidone is certainly more effective than hydrochlorothiazide in preventing cardiovascular events in hypertension. At last, studies suggest that drug adherence and long-term persistence under therapy is one of the major issues in the actual management of essential hypertension.

Keywords Drug adherence • Angiotensin receptor blockers • Calcium antagonists • Diuretics

Introduction

The management of patients with essential hypertension is based essentially on the prescription of antihypertensive drugs that enable to lower blood pressure to the recommended targets of <140/90 mmHg in the general population and to lower levels (<135/85 mmHg) for some patient groups such as diabetics or patients with chronic kidney diseases.[1,2] During the last 10 years, very few new antihypertensive agents have reached the market and no new therapeutic class has really emerged if one considers renin inhibitors as members of drugs inhibiting the renin–angiotensin system (RAS). Thus, the actual strategy to control blood pressure in hypertension relies on the use of three major classes of antihypertensive drugs, i.e. blockers of the RAS, calcium channel blockers (CCBs), and diuretics (D) as reported in the last 2013 hypertension guidelines of the European Society of Hypertension and European Society of Cardiology.[3] In some clinical conditions such as patients with coronary heart disease and heart failure, beta-blockers still have their place and this is the reason why they have been maintained in the 2013 hypertension guidelines.[3] Drugs, such as peripheral vasodilators, nitrates, or alpha-adrenergic blockers, are no longer recommended as first-line therapies although they might be useful in rare circumstances such as hypertensive blacks with heart failure. Similarly, aldosterone receptor antagonists (aldactone or eplerenone) are reserved for some special indications such as primary aldosteronism, resistant hypertension, or hypertension associated with congestive heart failure.

A systematic review of randomized placebo-controlled studies of the five main categories of blood pressure-lowering drugs, i.e. angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers, diuretics, CCBs, and beta-blockers has actually demonstrated that all five categories of drug produce similar reductions in blood pressure.[4] The average reduction reaches 9.1 mmHg systolic and 5.5 mmHg diastolic at the standard dose and 7.1 mmHg systolic and 4.4 mmHg diastolic at the half-standard dose. However, the tolerability profile of these classes differs significantly, diuretics, CCBs, and beta-blockers causing dose-dependent side-effects, an observation that was not made with ACE inhibitors.[4] Angiotensin II receptor blockers have the best tolerability profile of all antihypertensive drug classes. The main advantage of these five classes of drugs is that they act to lower blood pressure through different mechanisms. Thus, they can be combined effectively and their antihypertensive efficacy is additive. The only exception is the

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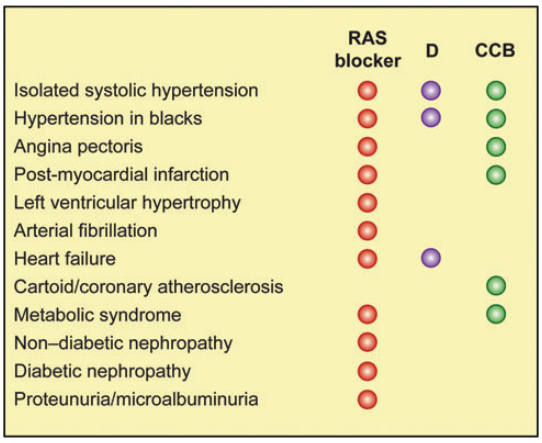

Figure 1 Compelling indications for antihypertensive drug classes according to comorbidities (adapted from Mancia *et al.*[1,3]). RAS blocker, blockers of the renin–angiotensin system; D, diuretics; CCB, calcium channel blockers.

combination of two blockers of the RAS which has been associated with an increased risk of renal events and hyperkalaemia and is therefore not indicated.

Today, although the concept of first-line therapies tends to disappear,[3] most guidelines recommend to start therapy with a RAS blocker or a CCB in most conditions as recommended, for example, by the British guidelines[5] and the most recent ESH-ESC guidelines.[3] However, the choice of the first-line therapy is often determined by the presence or absence of comorbidities as illustrated in *Figure 1*. It is obvious from the most recent European recommendations that RAS blockers are the preferred class to initiate therapy in hypertensive patients with all comorbidities except coronary heart disease.

The purpose of the present review is to discuss some debated issues concerning the first-line therapies of hypertension and to present the ongoing developments of the pharmacology of hypertension.

Angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers: a false debate?

Blockers of the RAS have been available for the management of essential hypertension since the early 1980s with the development of ACE inhibitors. Since then, overwhelming evidence has been built up indicating that ACE inhibitors significantly lower blood pressure and have a very favourable impact on patients' morbidity and mortality not only in essential hypertension, but also in patients with heart failure and patients with diabetic and non-diabetic nephropathies. In the 1990s, angiotensin receptor blockers (ARBs) became available.[6] These latter provided the opportunity to block the RAS at a different level, i.e. at the AT1 receptor with the potential to induce a more complete blockade of the system, all the effects of angiotensin II being inhibited at the receptor level whatever the source of angiotensin II. Clinical studies rapidly demonstrated that ARBs are as effective as ACE inhibitors in lowering blood pressure,[7] but also in reducing proteinuria and retarding the progression of renal diseases. Angiotensin II receptor blockers were also as effective as ACE inhibitors in heart failure.[8,9]

With the accumulation of studies and trials using ACE inhibitors and ARBs, several meta-analyses have been performed to compare the clinical benefits of these two approaches to block the RAS system. These meta-analyses generated some debate about the potential superiority of ACE inhibitors over ARBs in reducing total and cardiovascular mortality and on the impact of ARBs on the incidence of myocardial infarction.[8–10] One of the meta-analysis including more recent studies suggested that ARBs and ACE inhibitors provide similar clinical benefits.[9] However, in a more recent meta-analysis conducted by van Vark *et al.* and including >150 000 patients, RAS blockade was associated with a significant reduction in total and cardiovascular mortality over control treatments, but the authors found a decrease in mortality only in patients receiving an ACE inhibitor and not in those receiving an ARB, though the difference between ARBs and ACE inhibitors did not reach statistical significance.[10] From this meta-analysis, ACE inhibitors were promoted as superior to ARBs with a question mark on the role of ARBs in preventing coronary events. Even more recently, Savarese *et al.*[11] performed another meta-analysis comparing the two classes of RAS blockers in high cardiovascular risk patients without heart failure. In this analysis which included 26 randomized trials in >100 000 patients, both ACE inhibitors and ARBs reduced the risk of the composite endpoints of myocardial infarction, stroke, and cardiovascular mortality. A reduction of the risk of all-cause death was found with ACE inhibitors. The authors, therefore, concluded that ARBs are a valuable alternative to ACE inhibitors in patients in whom ACE inhibitors cannot be used.[11] In this respect, the most important study to cite is undoubtedly the Ongoing Telmisartan Alone and in combination with Ramipril Global Endpoint trial (ONTARGET) which actually compared the ACE inhibitor ramipril to the ARB telmisartan in high cardiovascular risk patients a large proportion of them being hypertensive.[12] As shown in *Figure 2*, there was no significant difference between the ACE inhibitor and the ARB in terms of total or cardiovascular mortality. There was also no difference when looking at myocardial infarction, hospitalization for heart failure or stroke. Thus, the one and only large trial comparing the two treatment options failed to identify any relevant difference except for the incidence of side-effects. Indeed, the tolerability profile of the ARB was superior to that of the ACE inhibitor with significantly less cough and angioedema. Regarding this latter complication which in certain cases may be life threatening, a recent meta-analysis confirm the data of ONTARGET showing that the risk of developing an angioedema was two-fold increase in patients receiving an ACE inhibitor when compared with those receiving an ARB.[12,13] The tolerability profile of drugs in an important determinant of the discontinuation rate in treated hypertensive patients. Thus, a recent Italian survey has demonstrated that the ARBs with a long duration of action have the smallest discontinuation rate when compared with short-acting ARBs or ACE inhibitors in general (*Figure 3*).[14]

More recently, a third approach to the inhibition of the RAS has become available, i.e. direct renin inhibition using aliskiren. This new way of blocking the renin–angiotensin– aldosterone system was very promising as it provided the unique opportunity to block

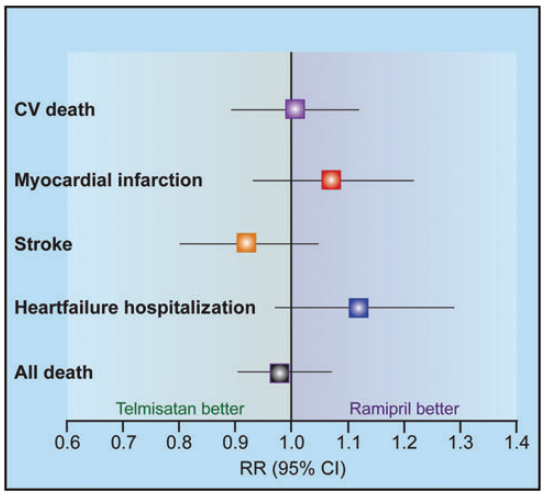

Figure 2 Effect of telmisartan and ramipril on cardiovascular endpoints in the ONTARGET trial (adapted from Yusuf *et al.*[12]).

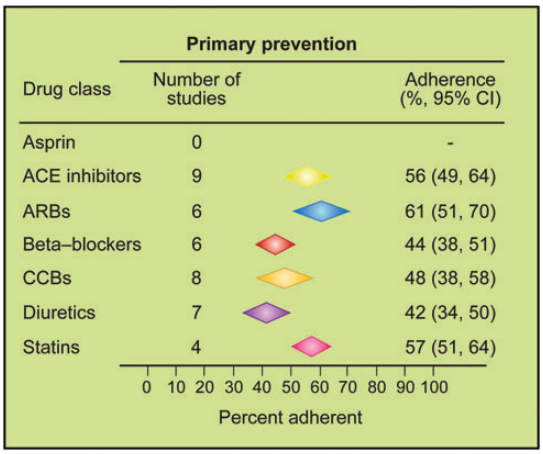

Figure 3 Drug adherences to cardiovascular drugs in primary prevention. Results of a meta-analysis (adapted from Naderi *et al.*[45]).

the RAS at its initial step. In clinical studies, aliskiren was found to be an effective long-acting antihypertensive drug with a comparable efficacy with ARBs and ACE inhibitors.[15] Unfortunately, the mitigated results of the large clinical trials in particular ALTITUDE[16] showing no real benefit on top of another blocker of the RAS in patients with type 2 diabetes has considerably reduced the initial enthusiasm and nowadays, although aliskiren is still available on some markets for the treatment of hypertension alone or in combination with a diuretic or a CCB, its future is compromised as it is difficult to demonstrated added benefits in comparison with ACE inhibitors or ARBs. Of note, recent ESH-ESC guidelines do not recommend the use of aliskiren in association with another blocker of the RAS.[3]

In summary, the ACE inhibitor vs. ARB debate is a false debate as both groups of drugs are very effective and provide important clinical benefits in hypertension. The improved tolerability profile of ARBs give them a slight advantage, but this latter is often counterbalanced by the lower cost of ACE inhibitors although nowadays both most ACE inhibitors and some ARBs are available as generics.

Calcium channel blockers: what about third generation dihydropyridines?

Calcium channel blockers represent an heterogeneous group of antihypertensive drugs that includes verapamil, diltiazem, and dihydropyridines. Today, the long-acting second generation dihydropyridine amlodipine has largely taken the lead in the prescription of CCBs as this compound became generic. Moreover, the results of several large clinical trials such as the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT),[17] the Valsartan Antihypertensive Long-Term Use Evaluation trial (VALUE),[18] the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT),[19] or the ACCOMPLISH trial (Avoiding Cardiovascular events through Combination therapy in Patients Living with Systolic Hypertension)[20] have emphasized the interest of prescribing this type of compound to achieve blood pressure targets in hypertension. Thus, amlodipine is now the most frequent CCB component of fixed-dose combinations in association with a RAS blocker.

In clinical practice, the discontinuation rate of CCBs is rather high and the long-term persistence of CCBs is lower that than observed with RAS blockers.[21] The main reason to discontinue CCBs is the appearance of peripheral oedema. In the VALUE trial in which amlodipine was compared with valsartan, 14.9% of patients developed peripheral oedema with the ARB, and 32.9% with amlodipine.[18] Thus, one-third of patients suffered from this side-effect. It is known that the association of a CCB with a RAS blocker reduces the incidence of peripheral oedema because of the effects of RAS blockade on pre-capillary pressure.[22] Nevertheless, in ASCOT which compared the association of perindopril and amlodipine to the combination of a thiazide diuretic and the beta-blocker atenolol, 23% of patients complained of peripheral oedema, and 14% of joint swelling in the perindopril/amlodipine group.[19] This suggests that even when combined with a RAS blocker, the incidence of peripheral oedema remains high and may be a limiting factor for the long-term persistence of treatment.

Is it possible to reduce the incidence of peripheral oedema using new generations of CCBs? In recent years, several new CCBs of the third generation such as lercanidipine, lacidipine, or manidipine have become available on some markets. The main characteristic of these CCBs is that they induce less peripheral oedema than classical second generation CCBs. Thus, several studies have demonstrated a reduced incidence of peripheral oedema with the use of these new CCBs. Borghi *et al.* have shown that the occurrence of peripheral oedema can be reduced by 50% in patients who developed oedema with amlodipine and were switched to lercanidipine.[23] Similarly, in a large survey (COHORT study), peripheral oedema occurred in 18% of patients treated with amlodipine but only in 7 and 4% of patients receiving, respectively, lercanidipine and lacidipine.[24] In a large Swiss survey in which the patients' therapy was either

initiated with or switched to lercanidipine or lercanidipine was added on top of other treatments, the incidence of ankle oedema was >4% at 6 months.[25] The use of these new third generation CCBs has been shown to improve drug persistence in treated hypertensive patients in comparison with other CCBs with persistence values close to those of a RAS blocker.[26]

Taken together, these results suggest that third generation CCB may help to reduce the incidence of peripheral oedema in hypertensive patients. Today, new fixed-dose combinations are on the market, which combine a RAS blocker and a third generation CCB such as enalapril/lercanidipine.[27] These new associations have been shown to be effective and well tolerated in the management of hypertensive patients including those with diabetic nephropathy.[28] Their major limitation, however, is that these combinations have never been investigated in controlled morbidity/mortality trials.

Diuretics: hydrochlorothiazide or chlorthalidone?

Diuretics belong to the main classes of antihypertensive drugs and their prescription remains high despite the development of new therapeutic classes. Indeed, owing to the high-salt consumption of salt in the population and to the well-recognized role of salt intake in the development of essential hypertension, diuretics have an important role in the management of hypertensive patients. Today, diuretics are infrequently prescribed as a single agent but more commonly in association with a RAS blocker. Several diuretics are available on the market for the treatment of hypertension including hydrochlorothiazide (HCTZ), chlorthalidone, and indapamide. In clinical practice, the prescription of HCTZ outnumbers those of all diuretics essentially because it became the diuretic of reference in all fixed-dose combinations.

Recently, several questions have been raised regarding the place of HCTZ in the management of hypertension.[29] Is HCTZ really the most effective diuretic at the actual recommended doses? Is HCTZ as effective as other diuretics in preventing cardiovascular events such as stroke or myocardial infarction or death? Indeed, analysis of studies tended to suggest that HCTZ is less effective in lowering blood pressure than RAS blockers or CCBs and thereby induce less cardiovascular protection than these latter. Moreover, almost all large trials, such as ALLHAT,[17] SHEP (Systolic Hypertension in Elderly People)[30] or the HYpertension in the Very Elderly Trial (HYVET)[31] demonstrating a cardiovascular benefit of diuretics, have used either chlorthalidone or indapamide but not HCTZ.

Thus, recently, several *post hoc* analysis were conducted to evaluate the antihypertensive efficacy of HCTZ in clinical studies and to compare HCTZ to other diuretics in particular to chlorthalidone. In the study by Peterzan *et al.*, a meta-analysis was performed to investigate the dose–response relationship of the various diuretics used for the treatment of hypertension.[32] The studies included in the analysis involved 4683 patients in >53 comparison arms. According to this analysis, HCTZ, chlorthalidone, and bendroflumethiazide had markedly different potencies with the lowest potency being attributed to HCTZ. However, there was no evidence of a difference in maximum reduction of systolic BP by high doses of different thiazides. The difference in potency observed for blood pressure between thiazide diuretics was also noticed for the changes in serum potassium and uric acid levels. The authors concluded that the difference in antihypertensive efficacy of the various thiazide diuretics was essentially due to their potency. In another analysis, Roush *et al.*[33] have performed a systematic review of randomized trials in which one arm was based on either HCTZ or chlorthalidone followed by two types of network meta-analyses, a drug-adjusted analysis and an office systolic blood pressure-adjusted analysis. Interestingly, for a comparable decrease in blood pressure, the risk of developing a cardiovascular event was found to be higher with HCTZ than with chlorthalidone. Of note, when compared with HCTZ, the number needed to treat with chlorthalidone to avoid one cardiovascular event was 27. The results of this analysis therefore suggest that chlorthalidone is superior to HCTZ in preventing cardiovascular events.

Considering these recent analyses, new drug combinations are being developed in which chlorthalidone rather than HCTZ is associated with a RAS blocker. This is the case, for example, of the angiotensin II receptor blocker azilsartan medoxomil which will be available in association with chlorthalidone.[34,35] Bakris *et al.*[34] actually compared the antihypertensive efficacy of the association of azilsartan + HCTZ to azilsartan + chlorthalidone. Looking at changes in office as well as ambulatory blood pressure, the ARB-chlorthalidone was systematically found to induce a greater fall in blood pressure. In another clinical study, Cushman *et al.* investigated the 12 week blood pressure changes induced by azilsartan/chlorthalidone 40/25 or 80/25 mg in comparison with olmesartan/HCTZ 40/25 mg in hypertensive patients.[35] All fixed-dose combinations induced a marked and 24 h sustained blood pressure reduction but the two doses of azilsartan/chlorthalidone appeared to be superior to the olmesartan/HCTZ combination.

In summary, there is an increasing debate on which diuretic is the most appropriate for the management of hypertensive patients. Although HCTZ has been repeatedly shown to have an additive antihypertensive effect when administered in association with a RAS blocker, some people are questioning the choice of HCTZ in all fixed-dose combinations and suggest that one might actually prefer either chlorthalidone or indapamide for which there is even more clinical evidence of benefits on cardiovascular endpoints. Indeed, both chlorthalidone and indapamide have used favourably in large clinical trials, particularly in elderly hypertensive patients.[31] As stated in the last ESH-ESC guidelines,[3] today no specific recommendation favouring one diuretic can be made based on the actual clinical evidence.

What about beta-blockers?

The use of beta-blockers in the management of hypertensive patients has been questioned in some guidelines and British scientists have disregarded beta-blockers from their guidelines as first-line therapy because of their lower ability to prevent stroke in the ASCOT trial[19] and their inability to lower central blood pressure. In the last ESH-ESC hypertension guidelines[3]; however, beta-blockers remain as a therapeutic option in particular for hypertensive patients with cardiac diseases such as heart failure or coronary heart disease. It is also emphasized that not all beta-blockers have the same properties

and that newer beta-blockers such as nebivolol or carvedilol may not share the same vascular and metabolic effects than atenolol or metoprolol.[36,37] For example, both nebivolol and carvedilol have been shown to lower central blood pressure in contrast to atenolol and metoprolol. Nonetheless, it has to be mentioned that the newer beta-blockers have been investigated essentially in patients with heart failure and very few studies have been conducted with these agents in hypertension.

What is the future of antihypertensive therapy?

The pharmacological treatment of hypertension relies essentially on the drug classes discussed above with their advantages and limitations. Today, few new therapeutic drug strategies are being investigated that might become available in the near future. Endothelin antagonists have been studied in hypertension but because of their side-effect profile (headaches and fluid retention), the focus has now been directed towards the use of these agents in resistant hypertension or hypertension of renal diseases.[38] The combination of an ACE inhibitor and an inhibitor of neutral endopeptidase was investigated in the 1980s and resulted in good antihypertensive efficacy but in increased incidence of angioedema. For this reason, the project was abandoned. More recently, new attempts to combine an ARB with a neprilysin inhibitor have been investigated and suggested that inhibiting the RAS system and enhancing the vasodilatation induced by atrial natriuretic peptides may be an effective way to lower blood pressure.[39,40] A new strategy is also expected in the field of aldosterone blockade with the development of aldosterone synthase inhibitors. Some phases II and III studies are ongoing with these compounds.[41] At last, the potential benefits of rho-kinase inhibition are being explored in arterial hypertension, but there is still a long way to go until this class of compound arrives on the market.[42]

As long as these new treatment modalities are not on the market, physicians will have to do the best they can to control blood pressure with the tools available. In this respect, it is interesting to note the gap between the results obtained in clinical trials where up to 80% of patients can reach target blood pressures and the actual situation of most countries which are at best ~50% of patients with a controlled blood pressure. Besides the issue of therapeutic inertia, one of the most important problems of the management of hypertension is the progressive discontinuation rate of treated patients who do not stay on treatment.[43] The low persistence in hypertension has been clearly evidence in patients treated for hypertension in phase IV studies.[44] A recent meta-analysis has also shown that the long-term adherence to cardiovascular drugs is particularly low in primary as well as in the secondary prevention of cardiovascular diseases.[45] Thus, all efforts should be done to improve drug persistence in hypertension in order to obtain the full-clinical benefits of the prescribed treatments.

Conflict of interest: none declared.

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