Optimal Antihypertensive Combination Treatments

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INTRODUCTION

Over the past three decades it has been consistently shown that optimal blood pressure (BP) control significantly reduced cardiovascular (CV) morbidity and mortality [1]. Despite solid evidence in favour of benefits derived from BP reductions, however, hypertension control in treated hypertensive patients remains suboptimal worldwide [2, 3]. In addition, proportions of diagnosed and treated hypertensive patients remain largely unchanged over the last two decades [4]. Multiple factors may be advocated to explain this observation, including variation in healthcare access and availability [5, 6], attitudes amongst clinicians towards hypertension [7, 8], inaccuracy in BP measurements [9] and underuse or under dosage of antihypertensive drugs in both monotherapy and in combination therapy [10, 11].

On the basis of these considerations, it is beyond the aim of this article to discuss the socioeconomic impact on healthcare and BP measurement techniques. Instead it will seek to explain the importance of attaining early optimal BP control and the use of combination therapy as a new paradigm for the modern clinical management of hypertension.

Importance of Blood Pressure Control

Current recommendations from international guidelines strongly emphasise the need to achieve target BP levels as promptly as possible in all hypertensive patients [1, 12, 13]. These thresholds, however, may vary depending on the individual patient’s total (or global) CV risk. It is this risk profile, therefore, that should influence the assessment of what would constitute an acceptable target BP, how aggressively it will be pursued and the choice among different classes and dosages of antihypertensive medications used to achieve this goal. When treating low-risk hypertensive patients, the aim should be to reduce the systolic BP value to <140 mmHg and the diastolic BP value to <90 mmHg.

In patients with diabetes, nephropathies, cerebrovascular disease and possibly coronary disease, however, even more aggressive targets should be adopted with systolic value BP <130 mmHg and diastolic BP values of <80 mmHg, if tolerated or not contraindicated. In this latter regard, although the guidelines recognise the possibility of a J-curve phenomenon, in which excessive lowering of BP levels, mostly for the systolic BP, in patients may lead to an increase in the incidence of coronary events, particularly in those with previous history of impaired coronary blood flow or diagnosed coronary atherosclerosis, they continue to advocate pursuing lower BP targets, if tolerated by patients [14].

Treatment strategies

The treatment strategies for BP lowering can be divided into two broad groups, non-pharmacological and pharmacological interventions. The choice between these two options should be based on individual global cardiovascular risk, rather than on absolute levels of BP. Whatever the individual global cardiovascular risk profile, however, pharmacological actions should always be accompanied by non-pharmacological interventions on life-style habits, to rapidly and persistently achieve the recommended BP targets.

Non-pharmacological treatment strategies

Non-pharmacological treatment strategies should be encouraged in all hypertensive patients, unless contraindicated (e.g. physical inability, physiological disorders, mental disturbances), to reduce BP levels, both as first-line approach and as concomitant tool in treated hypertensive patients. These include smoking cessation, moderation of alcohol consumption, salt restriction, diet modification, weight loss and physical exercise [15]. Although the success of these interventions may vary from patient to patient and adherence tends to diminish over time [16], they should be implemented in all patients being treated for hypertension and in those patients with high normal BP and concomitant risk factors for CV disease.

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The advice on lifestyle modification should be accompanied by adequate support and appropriate levels of education on how to  amend current behavioural habits. Patients will need to be followed up regularly for two reasons. The first is so that the advice regarding lifestyle changes can be repeated and reinforced from time to time. The second is that the BP will need to be monitored regularly so that pharmacological treatment can be instigated when appropriate and before any significant CV damage develops.

**Pharmacological treatment strategies**

Pharmacological strategy can be implemented in patients with grade 1 hypertension and above. Furthermore, it should also be considered in patients with high normal BP and high cardiovascular risk, such as those with diabetes mellitus, cardiovascular or renal disease.

There are five major classes of antihypertensive drugs all of whom have been demonstrated to lower BP and improve cardiovascular outcomes in hypertensive patients, independently of age, gender, presence or absence of diabetes mellitus or other comorbidities. These classes are Angiotensin Converting Enzyme (ACE) Inhibitors, Angiotensin Receptor Antagonists (ARB), β-Adrenergic Blockers (BB), Calcium-Channel antagonists (CCB) and Thiazide Diuretics. All these classes are reasonable choices for as first-line treatments for hypertension; however, one should take into consideration the presence of other disease processes which may benefit or be exacerbated by the use of one class rather than the others, possible drug interactions and side-effects, dosing regimen and its impact on compliance, cost and any previous treatments with a specific class which may have been successful or failed in that patient.

**Monotherapy or combination therapy**

Blood pressure homeostasis is regulated by a number of different physiological pathways, which are variously involved in each individual patient. It is perhaps not surprising that antihypertensive monotherapy, which only acts on a specific pathway, may not achieve the recommended BP targets in the majority of treated hypertensive patients, due to activation of compensatory mechanisms. An example of this is the observed increase in heart rate through activation of the sympathetic nervous system (SNS) and release of catecholamine following administration of short acting nifedipine. Another example is the escape phenomenon of ACE blockade during chronic antihypertensive treatment with ACE inhibitors.

To overcome this potential limitation of monotherapy, and in view of the beneficial effects obtained by early and rapid BP control (VALUE, ASCOT, RAPID, INCLUSIVE, ACCELERATE), one may increase the dose of a particular antihypertensive in stepwise fashion to a maximum recommended dose or a trial of sequential monotherapy. A recent meta-analysis of 42 clinical trials, however, showed that this therapeutic approach may be a suboptimal way to achieve BP target. This meta-analysis compared the introduction of combination therapy against the doubling of dose in monotherapy and found that combination therapy is more effective in achieving BP target. This meta-analysis compared the introduction of combination therapy against the doubling of dose in monotherapy and found that combination therapy is more effective in achieving BP target.

For example, the addition of valsartan to amlodipine mitigated the development of ankle oedema. As a typical dose response curve suggests, the greater increase in dose, the narrower the therapeutic window becomes, with side-effects becoming more prominent. Thus, a wide use of combination therapy may improve overall BP lowering efficacy and reduce dose-dependent side effects.

On the basis of these considerations, it has been widely acknowledged that monotherapy is usually insufficient in achieving the BP targets in the long term; yet, physicians who have practice in the clinical management of hypertension tend to use this approach as first line approach for hypertension treatment. Large randomised, controlled clinical trials, such as the Losartan Intervention for Endpoint Reduction trial (LIFE), the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) and the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT), had consistently shown the need to use combination therapy to reach the recommended BP targets.

For example, in the LIFE trial, more than 90% of patients required combination therapies to achieve their BP targets; in ALLHAT trial, only 26% of patients were on monotherapy, while in the ASCOT trial, 86% of the amlodipine arm and 90% of the atenolol arm patients were on combination therapies at the close of the trial. This trend to use combination therapy was also observed in older hypertension trials and epidemiological studies. More recently, however, the Avoiding Cardiovascular Events through Combination Therapy in Patients Living with Systolic Hypertension (ACCOMPLISH) trial demonstrated for the first time the beneficial effects of first-line combination therapies in reducing incidence of major cardiovascular events - mostly stroke - in high-risk hypertensive patients. In fact, in this trial patients were randomised to receive as first-line therapy a combination strategy based on ACE inhibitor (benazepril) with either thiazide diuretic (hydrochlorothiazide) or calcium-channel blocker (CCB) (amlodipine). In the presence of quite comparable BP reductions between the two treatment groups, a significant reduction of primary and secondary endpoints was reported in patients randomised to ACE inhibitor plus CCB than in those who receive ACE inhibitor plus diuretic.

It is recommended that combination therapy should be considered as initial antihypertensive therapy in patients with stage 2-3 hypertension, in individuals with high or very high cardiovascular risk, or in those in whom early and strict BP control is preferable. Furthermore, it also recommended that single pill combination therapy should be considered, whenever possible, to aid treatment concordance, although this issue is still debated. Non-concordance with anti-hypertensives remains a major contributor to uncontrolled hypertension. Recently Bunker et al showed that over half of the patients referred for further management of ‘resistant hypertension’ in a typical UK hypertension clinic had issues with non-concordance. This was demonstrated by a blood pressure response following directly observed anti-hypertensive therapy within blood pressure target. Potentially therefore extended use of single-pill combination therapies may contribute to achieve better BP control in hypertension practice, mostly by improving concordance to prescribed antihypertensive drug treatment. A recent meta-analysis, in fact, demonstrated better adherence and compliance with fixed rather than with free combination therapies, in the presence of comparable efficacy in lowering BP levels, both for systolic and diastolic BP, and in achieving BP normalisation between two treatment groups.
At present it is difficult to ascertain whether synergistic pharmacological mechanisms or intense BP control is the prime reason for the observed advantage in combination therapies [28]. In randomised clinical trials, single pill combination therapies are undoubtedly superior in achieving BP control over each of its own component [29-31] and this effect is also seen in patients with diabetes or the metabolic syndrome [32-34]. Moreover, the speed of achieving BP targets are also quicker with combination therapy [34].

Despite a lack of definite evidence to support early and intense BP control, however, indirect observations from large randomised clinical trials suggested that early intensive BP treatment may be linked to long-term favourable cardiovascular outcomes. [24], [25] [33]. In ALLHAT the beneficial effect on stroke was related to early BP control during the first 6 months of antihypertensive initiation. In the Valsartan Antihypertensive Long-Term Use Evaluation (VALUE) trial, the observed lower incidence of myocardial infarction and stroke in the amlodipine arm was also attributed to earlier BP control at months 1 and 6 compared to that reported in the valsartan arm.

Further, in ASCOT-Blood Pressure Lowering Arm (BPLA) the difference in cardiovascular outcomes was also associated with earlier and better BP reductions within the first year of amlodipine-based therapy compared to atenolol-based therapy. These observations are in line with the hypothesis that prompt blood pressure control within 6 months and ideally within 1-3 months provide favourable cardiovascular outcome [36]. Since the use of sequential monotherapy [20] or add-on therapy may not be able to rapidly and effectively achieve these BP goals, especially in some specific subgroups of hypertensive patients, namely those with diabetes or nephropathies, fixed-dose dual combination therapy may have a pivotal role in achieving prompt BP control as shown in the ACCOMPLISH trial, where BP targets were achieved in 73% of patients within 6 months of initiation of single pill combination antihypertensive therapies [37].

WHICH COMBINATION

To a certain extent, understanding the pathophysiological mechanisms involved in the development and progression of high BP levels, can predict the pharmacological efficacy of antihypertensive combination therapies. In particular, while some combination therapies can be used in most hypertensive patients, others are more suited to specific subsets of hypertensive patients, according to several compelling indications.

Angiotensin converting enzyme inhibitors/angiotensin receptor blocker (ACE inhibitor/ARB) and diuretics

Combination therapies based on drugs able to counteract the deleterious effects of abnormal activation of the renin-angiotensin aldosterone system (RAAS), namely ACE inhibitors and ARBs, have proven evidence in lowering BP levels and in reducing cardiovascular morbidity and mortality in different clinical settings. Randomised control trials have consistently demonstrated their ability in preventing the incidence or reducing the risk of recurrence of major cardiovascular events, including myocardial infarction, stroke, heart failure and cardiovascular death, in patients with hypertension, diabetes, left ventricular hypertrophy or dysfunction, coronary disease, renal disease, or congestive heart failure. These drugs have been effectively and safely combined with diuretics, mostly thiazide diuretics (but even loop diuretics and indapamide), both in fixed and in free combination therapies. Recent evidence available demonstrated the BP lowering efficacy of combination therapies based on ACEi/ARB plus CCBs (mostly amlodipine) or diuretics. Currently there is only one randomised control trial demonstrating the efficacy of ACE inhibitor plus CCB combination therapy with respect to the reduction of cardiovascular mortality (ACCOMPLISH).

However there is no evidence for ARB plus CCB combination therapy. In addition, beyond their BP lowering efficacy, both ACE inhibitors and ARBs had been demonstrated to reduce the progression or promote the regression of all hypertension-related target organ damages. With regard to tolerability profile, ARBs are considered to be better tolerated than ACE inhibitors in patients with hypertension, diabetes or high cardiovascular risk [38].

In this regard, recent comprehensive meta-analyses [38] of all available randomised control trials confirmed a better tolerability profile for RAAS blocking agents, mostly ARBs, compared to any other antihypertensive drug classes, including ACE inhibitors, CCBs, beta-blockers and diuretics. It is worth noting that ACE intolerance may develop at any time point after treatment is started. For example in the high-risk population enrolled in the ONGoing Telmisartan Alone and in combination with Ramipril Global Endpoint (ONTARGET) trial, patients without known history of ACE intolerance at baseline developed ACEi intolerance and they were later enrolled in the Telmisartan Randomised Assessment Study in Angiotension converting Enzyme inhibitor intolerant subjects with Cardiovascular Disease (TRANSCEND) trial. Ramipril alone and in combination with Telmisartan, were associated with a significantly higher proportion of discontinuations due to adverse events, mainly cough and angioedema than those treated with telmisartan.

Calcium channel blockers (CCB) and diuretics

This combination therapy is currently not recommended as first-line antihypertensive therapy in hypertensive patients. It is sometimes combined with diuretic therapy in the hope that diuretics could reduce peripheral oedema caused by CCBs. There are two pathophysiological reasons to explain why this is not the right choice. Firstly, the peripheral oedema caused by CCBs is due to arterial dilatation without venodilatation. This in turn leads to an increase hydrostatic gradient in the capillary bed, hence inducing peripheral oedema. This phenomenon is substantially unrelated to fluid retention. In addition, CCBs, which have potent vasodilatory action on renal afferent arterioles, may increase glomerular filtration rate, which also induces a mild natriuresis.

Secondly, the additive BP lowering efficacy with CCBs and diuretics is likely to be small, as their actions on vasodilatation and volume contraction both stimulate renin leading to the unopposed activation of the RAS enzymatic cascade [39]. It is interesting to note the outcome of an observational study, which demonstrated this combination to have a higher CV mortality risk when compared to other combination [40].
Thiazides and potassium-sparing diuretics

The 7th report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure [1, 24] had recommended the use of thiazide or thiazide-like diuretics ‘either alone or combination therapy is required’ as first-line strategy to rapidly and effectively reduce BP levels to targets. Such a position was substantially based on the consideration, which remains unchanged over time, that hypertension is largely uncontrolled in North-American countries, leading to a growing burden of cardiovascular disease. This is also based on large body of evidence demonstrating the efficacy of thiazide in preventing cardiovascular events, mostly by their effective BP reductions [18, 24, 41]. A recent position paper [44] however, seems to reconsider this approach, and indicates diuretic as one of the potential therapeutic options to lower BP levels, mostly in combination therapy, in view of the high risk of discontinuations and drug-related side-effects.

The combination of thiazide and potassium-sparing diuretics is effective for individuals who have low renin hypertension (e.g. Afro-Caribbeans and elderly individuals), although they represent a minority of hypertensive patients. Its favourable cardiovascular outcome as a combination had been shown in the Medical Research Council (MRC) hypertension in the elderly trial [42]. This combination is also efficient in maintaining potassium balance compared to lone therapy with thiazide or loop diuretics. It is important to note that in ALLHAT, [24] the thiazide-like diuretic chlorthalidone group had the highest overall incidence of new onset diabetes; however, the clinical significance of this remain unresolved [24, 25, 41, 43].

β-blockers based combination regimen

Combination therapies based on beta-blockers are currently not recommended as first-line antihypertensive therapy in hypertensive patients. Several combination strategies can be based on these drugs. Combining β-blocker with CCBs represents a valid option, as the CCB-associated SNS and RAA activation could be alleviated through β-blockade. Certainly in patients with ischaemic heart disease, its dual action as anti-anginal is useful. It is also logical to combine β-blockers with thiazide diuretics as the increase in renin associated with diuretic therapy could be blocked by β-blockade. However, evidence from ASCOT [25] showed that atenolol and diuretics regimen had less favourable cardiovascular outcome and higher incidence of new onset type 2 diabetes compared to an amlodipine-based regimen. In addition, the amlodipine-based regimen had a better overall BP reduction (by 2.7/1.7 mmHg).

The reason for a less favourable cardiovascular outcome with β-blockers may be due to inferior reduction in central BP [44, 45]. The British Hypertension Society has thus far recommend β-blockers in only a subset of patients but not as initial therapy [46]. The evidence of inferior outcome in β-blocker therapy is largely based on outcome data from atenolol. The data on newer generation of β-blockers, such as Nebivolol, is less clear.

Angiotensin converting enzyme inhibitors/angiotensin receptor blocker (ACE inhibitor/ARB) and CCB

This combination may represent the most applicable combination therapy for most hypertensive patients including added risk patients such as [47] patients with chronic kidney disease (CKD), coronary artery disease (CAD), type 2 diabetes, obesity or metabolic syndrome. The activation of RAS induced by CCB can be effectively counterbalanced by the concomitant use of either ACE inhibitor or ARB. In addition, CCB-associated peripheral oedema could be reduced by a balanced arterial and venodilation through reduction or blockade of circulating angiotensin II [37]. It is also suggested that this combination can provide favourable lipid and glucose profile, additive improvement in endothelial function, reduction in microalbuminuria and have better 24-hour BP control [29, 48, 49].

In a double blind 4x4 factorial design study 562 patients with stage 1-2 hypertension were randomised to receive either placebo, telmisartan, amlodipine or both drugs in combination for 8 weeks. At the beginning and end of the treatment period, patients’ BP was evaluated using 24hr ambulatory monitoring; the study demonstrated a significant reduction in BP in when using combination therapy as compared to either monotherapy. When looking at the highest doses given (Telmisartan 80mg and Amlodipine 10mg) the mean reduction in BP was -11/-6.9 and -11.9/-6.9, respectively; this is in contrast to a reduction in BP of -22.4/-14.6 when using combination therapy at the same doses (P<0.0001) [29]. Similar results are also observed at lower doses of the drugs (Figure 1).

As mentioned above, the ASCOT data showed that ACE inhibitor plus CCB-based regimen conferred superior cardiovascular outcome compared to ACE inhibitor plus diuretic-based regimen, in the presence of quite comparable BP reductions. Several pathophysiological hypothesis have been advocated to try to explain these additional advantages, provided by ACE inhibitor plus CCB combination therapy, beyond their BP lowering efficacy. Among these, one relevant item could be related to its efficacy in central blood pressure reduction [44, 51]. In the recent ACCOMPLISH trial [37], a direct comparison between ACE inhibitor plus CCB and ACE inhibitor plus diuretic regimen showed a favourable BP control over 3 years in the former than in the latter group (131.6/73.3 mmHg vs. 132.5/74.4 mmHg, respectively; p<0.001).

In addition, the ACE inhibitor plus CCB group had less cardiovascular events compared to ACE inhibitor plus diuretic group (9.6% vs. 11.8% p<0.001). In both arms, BP control was improved from baseline (38% c140/90 at baseline and 75% at trial close out), hence affirming the improvement in BP control with upfront combination therapy. The better outcome seen in the ACE inhibitor plus CCB group could be related to the higher proportion of diabetic patients enrolled in ACCOMPLISH. It may also be that the two regimens had differential effects of central aortic BP [51].
Angiotensin converting enzyme inhibitors and angiotensin receptor blocker (ACE inhibitor and ARB)

This combination therapy is currently not recommended as first-line antihypertensive therapy in hypertensive patients [12]. This has even been recently reaffirmed in a position paper [52] by the European Society of Hypertension, after considering the results of several randomised clinical trials, mostly the ONTARGET trial, in which the use of this combination strategy was not associated to additional cardiovascular benefits, rather to an increased risk of side-effects and discontinuations (mostly driven by the use of the ACE inhibitor, ramipril) in high-risk individuals.

However, it should also be acknowledged that there is limited evidence testing the safety and efficacy of this combination strategy in essential hypertensive patients. Yet, evidence are available demonstrating the cardiovascular benefits in specific subgroups of high-risk patients, like those with end-stage renal disease, coronary artery disease (VALsartan In Acute myocardial Infarction [VALIANT], Optimal Trial in Myocardial Infarction With the Angiotensin II Antagonist Losartan [OPTIMAAL]) and advanced congestive heart failure (The Valsartan Heart Failure Trial [Val-HeFT], Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity [CHARM]-Added). Furthermore, the interim results of the ALTITUDE study, a placebo-controlled phase III trial assessing the use of aliskiren in addition to either an ACEi or an ARB in high CV risk type 2 diabetes patients, led to its early termination and a review by both the food and drugs administration (FDA) and the European Medicines Agency (EMA). Preliminary analysis suggested no evidence of any benefit when compared aliskiren to placebo on top of optimal antihypertensive strategy (including either an ACEi or an ARB) in this high-risk population.

Triple combination therapy with ARB/CCB/thiazide diuretic

Recent randomised clinical trials investigated the efficacy and safety of triple combination therapies, mostly based on ARB/CCB/thiazide diuretic at different dosages in lowering BP levels in patients with different degrees of essential hypertension, with or without additional risk factors or comorbidities. In an open-label study the combination of olmesartan/amlodipine/HCTZ at different doses was effective in lowering the mean BP below the recommended BP goals in 66.9% of patients with moderate-to-severe hypertension at week 52 [53].

Furthermore a multicentre, randomised, double-blind, parallel-group study, aimed at determining whether a triple combination of olmesartan, amlodipine, and HCTZ produced greater BP reductions as compared to dual combination therapies of the individual components in patients with moderate to severe hypertension, demonstrated that the proportions of patients reaching the BP target of <140/90 mm Hg at week 12 was 69.9% in the triple combination treatment group and 52.9%, 53.4% and 41.1% in the treatment groups receiving olmesartan/amlodipine 40/10 mg, olmesartan/HCTZ 40/25 mg and amlodipine/HCTZ 10/25 mg, respectively (P <0.001, triple combination versus each dual combination) [54].

More recently, in the prospective, open-label, titrate-to-goal Blood Pressure Control in All Subgroups with Hypertension (BP-CRUSH) trial [55] patients with treated hypertension uncontrolled on monotherapy were switched to fixed-dose amlodipine/olmesartan (5/20 mg) or olmesartan / amlodipine/HCTZ (40/10/25 mg). The mean office cuff BP changes from baseline during the titration periods were -14.2±0.4 / -7.7±0.3 mmHg and -25.1±0.7 / -13.7±0.4 mmHg in the two groups, respectively [59].

Although the guidelines do recommend treatment with triple therapy combination as a last line option in patients who are unresponsive to dual therapy treatment [56]; it is important to note however, that there is a difference between hypertension that is truly resistant to two drug combination therapy and that which is a result of poor compliance.

Figure 1: Effects of treatment with telmisartan and/or amlodipine on 24hr ambulatory blood pressure [50].
Only a minority of patients treated appropriately with two drug combinations according to the recommendations of the guidelines, and are adherent to their therapy, fail [27]. It is important to note that failure of treatment due to poor medical compliance will not be solved with triple therapy and if anything it is likely to be exacerbated by the addition of yet another drug. In addition diuretics have the poorest treatment adherence profile of all the antihypertensive classes [37] and their use should be reserved for patient subgroups in which their diuretic effects are required, e.g. patients with HF and/or CKD.

Furthermore the combination of a long acting RAASi and CCB, such as telmisartan and amlodipine is as effective as treatment with shorter acting RAASi, CCB and HCTZ; in addition it is unclear if the beneficial effects gained by the combination of RAASI and CCB are attenuated or even negated by the addition of a diuretic, in the view of the lack of these effects in the combination of RAASi and diuretics.

**Direct Renin Inhibition**

Recently a new and novel approach to RAAS blockade has been introduced into clinical practice. The approach is directed at the inhibition of the initial and rate-limiting step of the enzymatic-protein RAAS cascade, namely the production of angiotensin I via the cleavage of the substrate angiotensinogen by the renin enzyme [38]. Blocking the catalytic activity of the renin enzyme via competitive inhibition leads to blockade of the entire downstream RAS cascade [38]. Thus, DRI acts through the inhibition of different pathways as compared to ACE inhibitors and ARBs, and it inhibits the active renin/renin receptor coupling, although the exact function of renin receptor has not been clarified [59, 60]. The use of aliskiren, a DRI, in hypertension has showing consistent efficacy in patients when added to other antihypertensive drug classes, including hydrochlorothiazide [61], CCBs [62], ACE Inhibitors [63] or ARBs [64].

However, it is important to note that when used as monotherapy it is a rather weak antihypertensive and its impact on morbidity or mortality in comparison with the more established treatments approaches to RAS blockade has not been demonstrated. In addition there is no evidence of its benefit on outcomes when used as a combination therapy with other RAASI, in fact the ONTARGET study suggested that dual RAAS blockade should be limited to specific patient subgroups such as those with advanced CKD.

**CONCLUSION**

Effective, rapid and sustained BP control is mandatory to reduce CV mortality and morbidity globally. The optimal BP targets need to be tailored to each individual global CV risk profile. Nowadays, there are five major classes of antihypertensive drugs that can be used either in monotherapy or in combination therapy. There is evidence to suggest that single pill combination medical therapy is superior as it effects more rapid and sustained BP control and has good levels of compliance. There are a number of combinations that are available but the RAAS based combination regimens seem to offer benefit over other combinations. The ideal combination to RAAS, depending on the situation, appeared to be either CCBs or diuretics. In patients with added cardiovascular risk, the RAAS/CCBs combination may be preferred.

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REFERENCES (Continued)


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