I Brazilian Position Paper on Antihypertensive Drug Combination

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Arterial hypertension (AH) is a highly prevalent disease, and is a major cardiovascular (CV) risk factor[1]; therefore, achieving blood pressure (BP) control goals as soon as possible is paramount to reduce that risk[2]. That means that approximately 70% of hypertensive individuals will need antihypertensive drug combination[3], and up to 30% of hypertensive individuals are estimated to use four or more drugs to achieve BP control[4]. Thus, drug combination is currently described as an important strategy to manage AH, providing effective and safe BP reduction.

Drug choice is based on effective BP reduction and CV outcomes. Despite the existence of a significant number of drugs to treat AH, their control rates are still very low, contributing to the high CV morbidity and mortality rates observed in Brazil and worldwide[1,2].

According to the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) and the Hypertension Optimal Treatment (HOT) Study, only 26% and 33% of the patients, respectively, could control their BP with monotherapy, while in the Losartan Intervention for Endpoints Reduction (LIFE) Study, 90% of the patients needed combined therapy for that purpose[3] .

Drug combination is mainly aimed at increasing antihypertensive efficacy, with fewer adverse events. It is worth noting the importance of considering therapy adherence. The pathophysiology of AH involves multiple factors and mechanisms, making its control difficult when only one drug is used, because counterregulatory mechanisms that attenuate the antihypertensive effect of the drug can occur. The association of drugs with different mechanisms of action has a greater impact on BP reduction as long as there is pharmacokinetic compatibility and no disparity of effects and properties[3-5].

Thus, the choice of the drugs to be combined should contemplate two aspects: synergism of the mechanisms of action and opposition to counterregulatory mechanisms triggered after the beginning of therapy with a certain drug. The desired antihypertensive efficacy is more likely to be achieved by using lower doses of the drugs involved. Thus, fewer adverse events are observed, with no loss of antihypertensive drug potency[3-5].

Keywords

Hypertension / therapy; Antihypertensive Agents / pharmacology; Antihypertensive Agents / therapeutic use.

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Another important aspect is that drugs should be preferably combined in a single galenic presentation, facilitating their administration, and assuring lower cost, with a consequent improvement in treatment adherence[2,6].

Evidence of clinical trials

Data available have suggested that most of the hypertensive population requires combined therapy to achieve BP control goals[1]. A meta-analysis of 354 double-blind randomized clinical trials has found mean BP reductions with monotherapy of only 9.1 mm Hg and 5.5 mm Hg for systolic BP (SBP) and diastolic BP (DBP), respectively. There were only few differences in the responses to the following drugs assessed: diuretics; beta-blockers (BBs); angiotensin-converting-enzyme inhibitors (ACEIs); type 1 angiotensin-receptor blockers (ARBs); and calcium channel antagonists (CCAs)[7]. In the ALLHAT, only 26% of the patients achieved the BP control goal with monotherapy, even considering the goal for diabetic patients (36% of the patients) of < 140/90 mm Hg, rather than 130/80 mm Hg as recommended by several guidelines at the time[4]. In the HOT Study, only 33% of the patients met the DBP goal with monotherapy; 45% required two drugs and 22% needed three drugs to meet that goal[8]. The mean SBP at the end of the HOT Study was 141 mm Hg, indicating that an even higher percentage of patients would have needed combined therapy to meet the goal of < 140 mmHg[5]. In the LIFE Study, treatment to meet the recommended goal (<140/90 mmHg) was aggressively pursued in elderly patients with left ventricular hypertrophy (LVH). Considering an initial mean BP of 175/98 mm Hg, more than 90% need to use at least two antihypertensive drugs[9]. The Strategies in Treatment of Hypertension (STRATHE) Study, in which treatment was initiated with a combination of low doses and compared to monotherapy, has found a greater percentage of individuals in the low-dose combination group who met the BP control goal (BP < 140/90 mm Hg) as compared to those receiving sequential monotherapy (62% vs. 49%, p = 0.02)[10].

Based on the criteria of efficacy, tolerability, likelihood of higher adherence, evidence of CV and kidney protections, and safety, the associations of antihypertensive drugs can be divided as follows: preferential; acceptable; less usual; and unusual (Chart 1)[11]. Chart 2 summarizes the current recommendations for drug association in AH treatment[12]. It is worth noting that non-pharmacological measures of lifestyle change should be always emphasized to improve AH control and prevention of its complications.

Benefits of adherence to drug combination

Current guidelines recommend and encourage the use of fixed drug combinations (FDC) to make adherence to

treatment easier[2]. In addition, previous studies have shown that complex drug treatment and polypharmacy have a deleterious effect on treatment adherence and persistence[12].

As compared to non-FDC, FDC improves treatment adherence and persistence because of the following advantages:

- Daily single dose and fewer tablets to be ingested, resulting in higher convenience to the patient, and lower risk of dose confusion[13];

- Potential lower cost, due to the reduced number of tablets[13];

- Better BP control, possibly due to simultaneous and/or synergic action in multiple pathophysiological AH factors and attenuation of therapeutic inertia[14]. Greater 24 hour BP stability in synergic FDC, with adequate trough-peak ratio and doses, promoting higher CV protection[4];

- The goal is met earlier, leading to a faster reduction in CV risk[4] and greater patients' trust in physicians and drugs[13];

- Lower rate of adverse events[13], because FDC often associates two drugs at non-maximum doses capable of reducing BP without leading to the adverse events that result from their use at higher doses; or the undesired effects of the drugs are balanced or even suppressed because of their combined action.

Blood pressure should be reduced over days or weeks, rather than abruptly within a few hours, which can lead to either mild adverse events, such as vertigo and visual blurring, or even severe events, especially in the elderly[13]. To avoid adverse events in patients with co-morbidities or orthostatic hypotension, previous dose adjustment with the non-FDC is necessary, and should be initiated with low doses.

Chart 1 -Combinations of antihypertensive drugs

Preferential
• ACEI + CCA
• ACEI + Diuretic
• ARB + CCA (dihydropyridine)
• ARB + Diuretic
Acceptable
• Diuretic + BB
• CCA (dihydropyridine) + BB
• CCA + Diuretic
• DRI + Diuretic
• DRI + CCA
• Thiazide diuretic + Potassium-saving diuretic
Less usual
• ACEI + BB
• ARB + BB
Unusual
• CCA (non-dihydropyridine) + BB
• ACEI + ARB
• ACEI + DRI
• ARB + DRI
• Central sympatholytic drug + BB

** BB: beta-blocker; ACEI: angiotensin-converting-enzyme inhibitor; ARB: type 1 angiotensin-receptor blocker; CCA: calcium channel antagonists; DRI: direct renin inhibitor.*

Evidence in cardiovascular outcomes

The benefits of combined therapy have been demonstrated in a meta-analysis showing reductions of 63% and 46% in stroke and coronary artery disease (CAD), respectively, as compared to monotherapy[7]. The Valsartan Antihypertensive Long-term Use Evaluation (VALUE) and (International Verapamil SR and Trandolapril (INVEST) Study have evidenced that BP reduction in a shorter period of time reduces the risk of events and death[15,16].

The Avoiding Cardiovascular Events through combination Therapy (ACCOMPLISH) Study, which tested a new treatment strategy for AH, has compared two FDC (Benazepril + Amlodipine vs. Benazepril + hydrochlorothiazide). In the benazepril + amlodipine group, a 15% reduction in CV morbidity and mortality was observed in high CV-risk hypertensive patients as compared to the other group, leading to early interruption of the study by the data monitoring committee[17].

Some combinations, however, need to be reassessed, and should be avoided until new evidence appears, because they might not be beneficial to patients. In the Ongoing Telmisartan Alone and in Combination with Ramipril Trial (ONTARGET) and in the Aliskiren Trial in Type 2 Diabetes Using Cardio-Renal Endpoints (ALTITUDE) with double renin-angiotensin system blockade, there was no reduction in morbidity and mortality, but significant worsening of kidney function and hypotension[18,19].

Double combinations of antihypertensive drugs

There are several classes of antihypertensive drugs, making a large amount of combinations possible (Figure 1).

• Renin-angiotensin system inhibitors + diuretics

The combination of an ACEI, an ARB or a DRI with a thiazide diuretic (hydrochlorothiazide, chlorthalidone or indapamide) at low doses results in a significant additional effect on BP reduction. In addition, that association attenuates the reflex activation of the renin-angiotensin-aldosterone system (RAAS) by diuretics and hypokalemia in susceptible patients[20].

Chart 2 - Recommendations for the association of antihypertensive drugs

- Consider combined therapy to meet BP goals.
- Whenever possible, use preferential or acceptable combinations.
- Reserve unusual combinations for special cases, in which there is evidence of benefits.
- Initiate combined therapy routinely to individuals who need BP reductions ≥ 20 mm Hg and/or 10 mm Hg for SBP and DBP, respectively (stages 2 and 3).
- Initiate combined therapy to stage 1 individuals at high and very high risk, or when the second drug can improve the side effect profile of the initial therapy.
- Use, if possible, fixed associations in only one tablet/capsule or grouped combinations to improve adherence to treatment.
- If the goal is not met with the double combination, reassess adherence and other causes of lack of control, and, if necessary, use combinations of three or more drugs.
- The use of formulated antihypertensive drugs is not recommended.

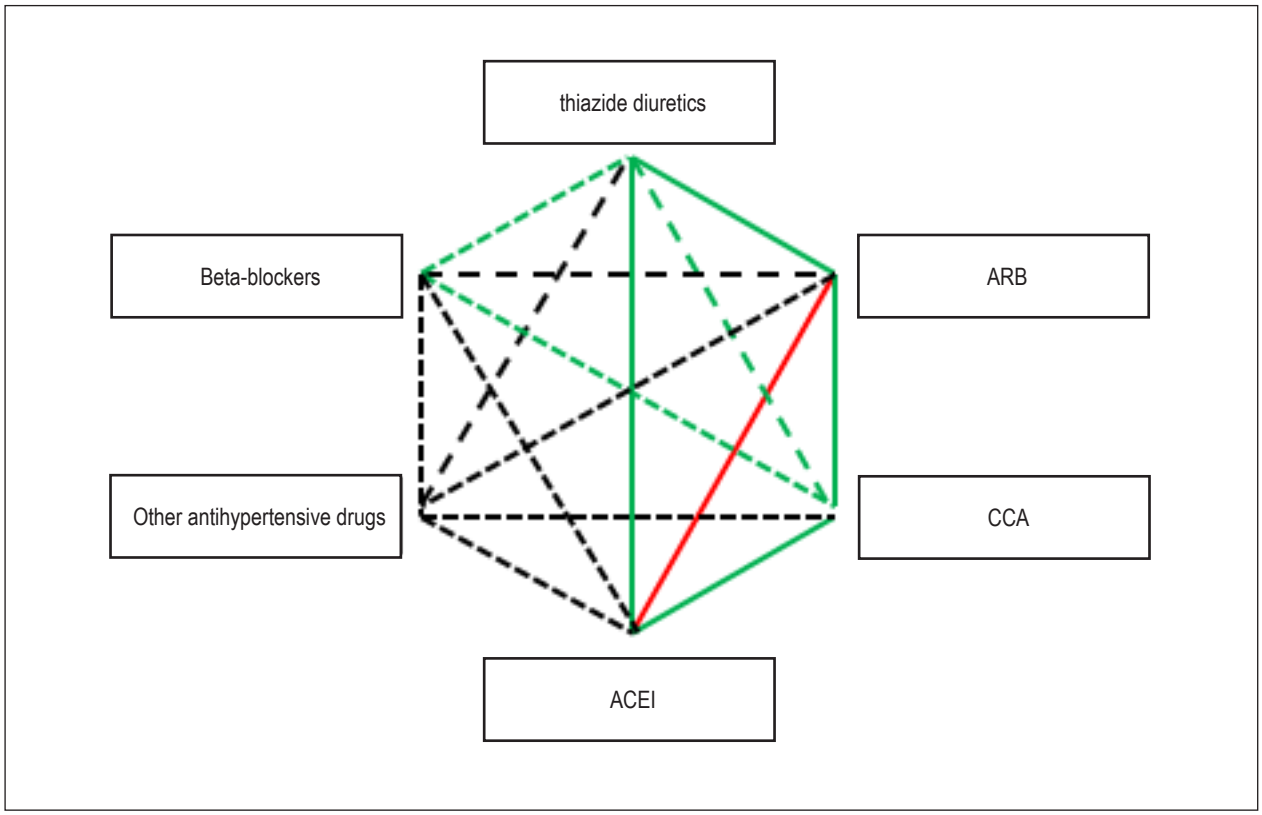

Figure 1 - *Possible combination of antihypertensive drugs: continuous green line (preferential combinations); dotted green line (acceptable combinations); dotted black line (less usual combinations); red line (unusual combinations). Modified from Mancia et al. 2013 ESH/ESC Guidelines for the management of arterial hypertension. ARB: angiotensin receptor blocker; CCA: calcium channel antagonist; ACEI: angiotensin-converting-enzyme inhibitor.*

Based on the efficacy, safety and favorable performance of those agents, fixed combinations of ACEI or ARB with diuretics are preferential. Most fixed combinations use hydrochlorothiazide as a diuretic, although chlorthalidone has shown to be more effective in reducing BP and CV outcomes[21].

The best evidence of the reduction of overall and CV mortality in hypertensive individuals by use of the association of ACEI or ARB with thiazide diuretics was observed with indapamide, which also needs to be considered preferential relative to hydrochlorothiazide[22].

• Renin-angiotensin system inhibitors + calcium channel antagonists

That combination results in a significant BP reduction[23] and improves, via sympatholytic and venodilating actions of ACEI or ARB, tolerance to CCA, attenuating reflex tachycardia and peripheral edema caused by the predominant arteriole dilation of CCA[24]. The ACCOMPLISH study has compared clinical outcomes in high-risk hypertensive patients receiving the combinations of ACEI + CCA or ACEI + diuretics. The ACEI + CCA group showed a higher and significant BP reduction and a 20% decrease in the incidence of combined outcomes (CV mortality, myocardial infarction and stroke) as compared to the ACEI + diuretics group. It is worth noting that 60% of the patients had diabetes and a high percentage showed evidence of CAD[17].

• Calcium channel antagonists + thiazide diuretics

That combination results in an additive effect with small repercussion on BP, probably due to the overlap of their pharmacological effects[25]. Calcium channel antagonists increase the renal excretion of sodium, although not with the same potency of diuretics, and, in the long run, both showed vasodilation with no volume depletion. The VALUE study[15] has shown no unfavorable effects of the addition of hydrochlorothiazide to patients randomized to use amlodipine. Therefore, that is considered a possible combination.

• Beta-blockers + thiazide diuretics

Although BBs have shown the ability to reduce clinical outcomes in placebo-controlled studies, meta-analyses (mainly with atenolol) have suggested that BBs are less effective than diuretics, ACEIs, ARBs and CCAs[26]. Similarly to ACEIs and ARBs, BBs attenuate the RAAS activation induced by diuretics resulting in additional BP reduction. The addition of diuretics also improves BB effectiveness in Afrodescendant individuals and others with AH and

low renin levels. It is worth noting that such association might increase the risk for developing glucose intolerance, fatigue and sexual dysfunction[27].

• Thiazide diuretics + potassium-saving diuretics

The fixed combination of either hydrochlorothiazide or chlorthalidone with amiloride can potentiate even more BP reduction, preserving potassium plasma levels (important in the AH treatment, considering the potassium vasodilating actions), and reducing the incidence of hypokalemia[28]. In addition, there is evidence of the superiority of chlorthalidone relative to hydrochlorothiazide, because of its longer half-life, greater potency and higher number of studies showing a reduction in CV outcomes[4]. The association with amiloride is considered acceptable in individuals with preserved kidney function (glomerular filtration > 50 mL/min/1.73 m^2). Glomerular filtration rates below that value increase the risk of hyperkalemia[29].

• Calcium channel antagonists + beta-blockers

The pharmacological effects of those two classes of drugs are complementary in reducing BP. The Metoprolol Succinate-Felodipine Antihypertension Combination Trial (M-FACT), a combination of low doses of felodipine and metoprolol, both of prolonged release, has reported a BP reduction comparable to that of maximum doses of each drug separately, and edema incidence similar to that of placebo[30]. The combination of BB with dihydropyridine CCA is considered acceptable, but that with non-dihydropyridine CCA, such as verapamil and diltiazem, should be avoided because of its additional effect on heart rate and atrioventricular conduction, which can result in severe bradycardia and/or atrioventricular blocks.

Unusual combinations

• Angiotensin-converting-enzyme inhibitors + type 1 angiotensin-receptor blocker

The combination of ACEI with ARB is not recommended. That combination has a small additional effect on BP reduction, comparable to the reduction determined by each agent isolated. The ONTARGET trial has reported that patients on the telmisartan/ramipril combination, as compared to others using those drugs in isolation, showed no improvement in CV outcomes despite the additional BP reduction, on average, 2.4/1.4 mm Hg; in addition, more side effects were observed with that combination than with those drugs in isolation[18-31].

• Direct renin inhibitor + renin-angiotensin system inhibitors

That combination has an additive effect on BP reduction; however, studies on morbidity and mortality reduction with that association have found no benefits, therefore, it is not recommended[19].

• Renin-angiotensin system inhibitors + beta-blockers

Those drugs are cardioprotective and frequently administered to individuals with CAD and/or heart failure. When combined, however, a small additional BP reduction, comparable to that of their isolated use, is observed[32]. Therefore, that is a less effective association when the goal is BP reduction.

• Beta-blockers + central action drugs

Beta-blockers and central action drugs (clonidine and alpha-methyldopa) interfere with the sympathetic nervous system. The extent of BP reduction with that combination has not been assessed. That combination can cause important bradycardia or atrioventricular block. In addition, individuals on that combination, who suddenly discontinued their treatment, had rebound hypertension. Therefore, that is considered a less effective combination[33].

Triple and quadruple combinations

Triple combination

In 15% to 20% of hypertensive patients, the double combination is estimated not to be effective to achieve BP goal, requiring the triple combination[2].

The triple combination in one single tablet has proven to be more effective than the separate use of the three drugs, relative to both treatment adherence and abandonment risk, with improvements of 29% and 24%, respectively[6].

The use of the triple combination in one single tablet has been associated with faster BP control and consequent greater reduction in CV risk as compared with monotherapy followed by the double combination, contributing, thus, to improve therapeutic inercia[34].

When triple therapy is indicated, combining an ACEI or ARB with a CCA and a diuretic is recommended as the most rational and effective association[2].

Calhoun et al[35], assessing the association of valsartan, amlodipine and hydrochlorothiazide, have found more marked BP reductions and a higher proportion of goals achieved as compared with the double combinations of those drugs. In the Triple Therapy with Olmesartan Medoxomil, Amlodipine and Hydrochlorothiazide in Hypertensive Patients (TRINITY) Study, the triple combination of olmesartan, amlodipine and hydrochlorothiazide has resulted in a significant reduction in SBP and DBP as compared with each double association[36]. The triple association of aliskiren, amlodipine and hydrochlorothiazide has yielded reductions of 16.3 ± 8.2 mm Hg and 11.4 ± 4.9 mm Hg in SBP and DBP, respectively, in patients with severe AH, and such reductions were greater than those obtained with double combinations[37].

Quadruple therapy

The combination of four drugs in AH relates to resistant hypertension[38]. The choice of the fourth drug involves a lot of discussion, because of the lack of studies with appropriate design to answer that question, regarding both antihypertensive efficacy and CV protection. The mineralocorticoid receptor blocker is the most indicated fourth drug to be associated, because it promotes significant additional BP reductions, as shown in the Anglo-Scandinavian Cardiac Outcomes Trial

(ASCOT), regardless of the aldosterone/renin plasma activity ratio[39]. In case of either intolerance to spironolactone or not achieving BP goal, the fourth drug can be clonidine, BB or direct vasodilators.

Strategy in left ventricular hypertrophy

The major manifestation of hypertensive disease is LVH, present in 36% to 41% of the patients and an independent predictor of CV complications. Patients with LVH have a 2-4 times increased risk for cardiac and cerebrovascular events[40]. The presence of target-organ lesions, regardless of the hypertensive stage, already indicates high to very high CV risk, and the combination of antihypertensive drugs should be the initial strategy[1]. In monotherapy, the most effective drugs to reduce LVH are ARBs and ACEIs, followed by CCAs, BBs and diuretics. Some clinical trials comparing those classes of drugs have eventually used double or even triple combined therapy to reduce BP and achieve the goals proposed. Several studies have reported that double or triple combinations were more effective to reduce left ventricular mass and CV mortality[41-43].

Patient with chronic kidney disease

Chronic kidney disease (CKD) in hypertensive individuals is usually associated with volume overload and RAAS activation. Those patients require combined therapy, in which RAAS blockers should be preferred in association with other antihypertensive drugs[44].

The use of ACEIs or ARBs is more effective in preventing the progressive deterioration of kidney function than that of other antihypertensive drugs, in patients with and without diabetes, with and without proteinuria[45].

For patients with AH and CKD without proteinuria, the first-line drug class has not been well established, and, thus, other drug classes can be used. In those patients, hydrosaline retention often occurs, thus requiring the use of diuretics (thiazide and loop diuretics)[46].

Other drugs that can be associated in the presence of CKD are CCAs, which are considered the second or third option to treat AH with CKD[46,47]. Although no significant differences in BP reduction were observed with the use of dihydropyridines (amlodipine and nifedipine) and non-dihydropyridines (verapamil, diltiazem), the latter have been able to reduce proteinuria, either in monotherapy or in association with ACEIs or ARBs[48].

Aldosterone antagonists have reduced proteinuria when used in association with ACEIs or ARBs, and can be the third or fourth option in drug combination in selected cases and in gross proteinuria[49,50]. However, the possibility of hyperkalemia should be considered.

Although aliskiren improves albuminuria, its association with ACEIs or ARBs has the risk of kidney function worsening, hyperkalemia and hypotension in hypertensive individuals with diabetes and CKD[51].

The use of BB in the presence of CKD is indicated when there is CAD and/or heart failure associated[46].

Combinations in diabetes and metabolic syndrome

The presence of diabetes or metabolic syndrome characterizes the patient as of high CV risk, and combined therapy is indicated. The preferential combinations are either ACEIs or ARBs in association with CCAs, because of metabolic neutrality. When a third drug is needed, a thiazide diuretic at low doses is preferred[52,53].

The Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE) study, using perindopril and indapamide combined for patients with diabetes, has shown a reduction in overall mortality and in micro- and macrovascular outcomes; therefore, that is a treatment alternative[22].

Combinations in coronary artery and cerebrovascular diseases

For hypertensive individuals with CAD or after acute myocardial infarction, the therapeutic classes of BBs, ACEIs, ARBs and dihydropyridine CCAs have priority of use. The association of an ACEI and a BB is preferential, mainly after myocardial infarction. If intolerance to an ACEI occurs, it should be replaced by an ARB. Thiazide diuretics and aldosterone antagonists have a more restrict indication.

In patients with cerebrovascular disease, the association of thiazide diuretics and ACEIs is preferential, and an ARB can replace the ACEI, if not tolerated. The CCA is more restrict to acute cerebral events, its use being reserved to six hours after the event or in patients whose BP is greater than 180/115 mmHg[54,55]. Evidence has suggested that the benefit of reducing cerebrovascular disease in hypertensive individuals is mainly due to BP reduction. Thus, all drugs available and their rational combinations can be used[55].

Certain drug combinations are more favorable in the presence of CAD and AH. Associating a BB with an ACEI can suggest a less usual combination, but that is the most effective in that situation.

Drug combinations in patients with CAD
Preferential double combinations
• BB + ACEI
• BB + ARB
• BB + CCA (dihydropyridine)
Preferential triple combinations
• BB + ACEI or ARB + CCA (dihydropyridine)
• BB + ACEI or ARB + thiazide diuretics

Drug combination in the elderly

The antihypertensive drug treatment in the elderly reduces CV outcomes and helps to prevent CKD and dementia syndromes[56]. The use of combined therapy in the elderly, preferably of FDC, provides the opportunity to solve some frequent situations of that age group, such as isolated systolic hypertension, and improves arterial stiffness and adherence to treatment.

Combined therapy should be initiated with low doses, which should be increased slowly and gradually, and periodic review of its effect performed. That is important, because the hypotension symptoms in the elderly often present atypically as sleepiness, vertigo and mental confusion.

Creatinine clearance should be estimated in all elderly patients, because CKD is common in that age group and plasma creatinine does not reflect kidney function. The Cockcroft and Gault equation is the most used for that purpose[57].

The greatest evidence of a reduction in CV outcomes in the elderly is the Hypertension in the Very Elderly Trial (HYVET), which used ACEIs in association with indapamide[58]. Current evidence suggests that the association of a RAAS blocker with a dihydropyridine CCA can be better to reduce CV outcomes[59]. The benefits of that combination, at least in part, are speculated to be associated with a greater reduction in central BP[60].

Thiazide diuretics can have beneficial effects on osteoporosis, which is frequent in female elderly. Patients older than 80 years are at higher risk for arterial hypotension and co-morbidities. The SBP reduction to 150-140 mm Hg in that age group had a great impact on decreasing CV mortality and morbidity[58,61].

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