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Review Article

COMBINATION TECHNOLOGY FOR TREATMENT OF HYPERTENSION: A REVIEW

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ABSTRACT
Hypertension, elevated blood pressure, is a noteworthy public health concern worldwide due to its significant contribution to the global health burden and its role as a prominent risk factor for the development of a number of disease processes. The control of blood pressure is required in patients with hypertension to produce the maximum reduction in clinical cardiovascular end points, especially in patients with co-morbidities like diabetes mellitus where more aggressive blood pressure lowering might be beneficial. Recent clinical trials suggest that the approach of using monotherapy for the control of hypertension is not likely to be successful in most patients. Combination therapy may be theoretically favoured by the fact that multiple factors contribute to hypertension, and achieving control of blood pressure with single agent acting through one particular mechanism may not be possible. Combining the drugs makes them available in a convenient dosing format, lower the dose of individual component, thus, reducing the side effects and improving compliance.
Keywords: Hypertension; combination therapy; drug therapy.

INTRODUCTION

Hypertension (HTN) or high blood pressure, sometimes called arterial hypertension, is a chronic medical condition in which the blood pressure in the arteries is elevated. This requires the heart to work harder than normal to circulate blood through the blood vessels. Hypertension, elevated blood pressure, is a noteworthy public health concern worldwide due to its significant contribution to the global health burden and its role as a prominent risk factor for the development of a number of disease processes. In the year 2001, high blood pressure accounted for "54% of stroke, 47% of ischaemic heart disease, 75% of hypertensive disease, and 25% of other cardiovascular disease worldwide" (Lawes, Hoorn, & Rodgers, 2008). The negative impact of hypertension on health status is clear, especially taking into account the disability, decreased quality of life, and mortality associated with stroke and cardiovascular disease. In 2001, 7.6 million deaths (13.5% of all deaths) and 92 million disability life-years (6% of total) were attributable to systolic blood pressure greater than 115 mmHg (Lawes et al., 2008). It is distressing to note that such pervasive negative effects are related to such a modifiable cause. In response to a recognized need and new evidence-based suggestions, the World Health Organization (WHO, 2003) released a revision of its statement on the management of hypertension. The WHO estimated that the condition accounted for 4.5% of the global disease burden and attributed the increase in hypertension to increasing contributing factors and coexisting cardiovascular risk factors such as obesity, poor diet, lack of physical activity, and smoking. [1-5]

Hypertension is the most common cardiovascular disorder of modern times. It is found to be the major cause of death in India, as well as in other countries. According to WHO, hypertension is a state of body in which systolic blood pressure is 150 mmHg or more and diastolic pressure is 95 mmHg or more.

COMBINATION THERAPY

National Harris interactive survey for hypertension, in the United States revealed that out of 90% patients taking medication only 50% to 60% were involved in some form of lifestyle change to control BP.[8] Thus majority of patients with hypertension rely on medication for the control of their BP. More recent clinical trials suggest that the approach of using monotherapy for the control of hypertension is not likely to be successful in most patients and especially in those with some comorbidity (eg. DM, heart failure). The achievement of control BP typically requires 2 or more medications in various settings For instance,[6] in a factorial study with 1461 patients randomized to 16 treatment groups, taking telmisartan 0, 20, 40, 80 mg and amlodipine 0, 2.5, 5, 10 mg for 8 weeks, greater BP reductions were observed with combination therapy than with respective monotherapies. Highest dose combination (telmisartan 80 mg plus amlodipine 10 mg) had the greatest least square mean systolic/diastolic BP reductions (26.4/20.1 mm Hg; $P < 0.05$ compared with both monotherapies) with over 90% BP response rates. Peripheral edema was most common in the amlodipine 10-mg group (17.8%) but the rate had notably lowered when amlodipine was used in combination with telmisartan. Similar results were observed with other trial of olmesartan medoxomil/amlodipine combination therapy vs. respective monotherapies where more effective BP reduction and BP control (44.5-54% vs 28.5- 30%) were achieved with combination therapy than with either of monotherapies. Over 70% of patients on combination therapy achieved control BP[7].

SPECIFIC DRUG COMBINATIONS

There are seven major classes of antihypertensive drugs and multiple members of each class; therefore, the number of possible combinations is quite large. In this position paper, two-drug combinations involving classes of pharmacologic agents that reduce CV end points (diuretics, CCBs, ACE inhibitors, ARBs, b-blockers) are emphasized. Combinations of three or more drugs are not reviewed. Specific combinations are designated as preferred or acceptable based on the considerations outlined previously.

RAAS Inhibitor with CCB

The combination of an ACE inhibitor or ARB with a CCB results in fully additive BP reduction.[9-11] Addition of either of these two RAAS inhibitors significantly improves the tolerability profile of the CCB. Through their antisympathetic effects, RAAS inhibitors blunt the increase in heart rate that may accompany treatment with a dihydropyridine- type CCB. In addition, RAAS inhibitors partially neutralize the peripheral edema, which is a dose limiting side effect of these CCBs. The cause of the edema is believed to be arteriolar

dilation, resulting in an increased pressure gradient across capillary membranes in dependent portions of the body. RAAS blockers are thought to counteract this effect through vasodilatation. The Avoiding Cardiovascular events through Combination therapy in Patients Living with Systolic Hypertension trial tested whether initial fixed-dose combination therapy with an ACE inhibitor and CCB differs from initial fixed dose combination therapy with an ACE inhibitor and diuretic on clinical outcomes in high-risk hypertensive patients. Despite comparable BP reduction, the ACE inhibitor/ CCB combination reduced the combined end point of cardiovascular death, myocardial infarction, and stroke by 20% compared with the ACE inhibitor/diuretic combination.[12]

RAAS Inhibitor with Diuretic

The combination of an ACE inhibitor, ARB, or direct renin inhibitor with a low-dose, thiazide-type diuretic results in fully additive BP reduction. Diuretics initially reduce intravascular volume and activate the RAAS, leading to vasoconstriction as well as salt and water retention. In the presence of a RAAS inhibitor, this counter regulatory response is attenuated. Addition of a RAAS inhibitor to a thiazide-type diuretic also improves its safety profile by ameliorating diuretic-induced hypokalemia, but can result in hyperkalemia in susceptible patients. Based on their safety, efficacy, and favorable performance in long-term trials, combinations of an ACE inhibitor or an ARB with a low-dose diuretic are classified as preferred. Most FDCs containing a diuretic use hydrochlorthiazide (HCTZ). Because chlorthalidone is more effective than other diuretics in reducing BP over 24 hours 27 and was the agent used in all but one large US-based hypertension outcome trial, some authorities favor its use over HCTZ.

Renin Inhibitor with ARBs

The combination of a renin inhibitor with an ARB produces partially additive BP reduction and is welltolerated. In a study in which maximum approved doses of valsartan and aliskiren were combined, a 30% additional BP response was observed compared with either monotherapy.[13] The side effect profile of this acceptable combination was comparable with placebo. There are no cardiovascular outcome data with this combination to date.

CCBs with Diuretics

The combination of a diuretic and a CCB results in partially additive BP reduction.[14] Presumably, this partial effect reflects overlap in the pharmacologic properties of the two drugs. CCBs increase renal sodium excretion, albeit not to the same extent as diuretics. Moreover, long-term treatment with both classes is associated with vasodilation, given that volume depletion does not occur with diuretics. From an endpoint perspective, this combination performed well in the Valsartan Antihypertensive Long-term Use Evaluation trial in which HCTZ was added as a second step in patients randomized to amlodipine. As opposed to ACE inhibitor/CCB or ARB/CCB combinations, the CCB with diuretic has no favorable effect on either drug's side effect profile. These combinations are classified as acceptable.

β-Blockers with Diuretics

Although β-blockers reduce CV end points in placebocontrolled trials, meta-analyses (based primarily on the performance of atenolol) suggest that they are less effective than diuretics, ACE inhibitors, ARBs, and CCBs.[15-16] The antihypertensive effects of b-blockers are mediated through reduction in cardiac output and suppression of renin release. As with the ACE inhibitors and ARBs, b-blockers attenuate the RAAS activation that accompanies the use of thiazide diuretics, and their combination results in fully additive BP reduction.[17-18] Addition of diuretics also improves the effectiveness of b-blockers in blacks and others with low renin hypertension. These combinations are classified as acceptable, recognizing that their use is associated with increased risk of glucose intolerance, fatigue, and sexual dysfunction.

Thiazide Diuretics with Potassium-sparing Diuretics

Hypokalemia is an extremely important dose-related side effect of thiazide diuretics. By attenuating hypokalemia, the combination of HCTZ with a potassium-sparing diuretic such as triamterene, amiloride, or spironolactone improves its safety profile. Because of the risk of hypokalemia that can lead to cardiac arrhythmias, and sudden death, HCTZ 50 mg and chlorthalidone 25 mg should generally be used in combination with a potassium-sparing agent (or an inhibitor of the RAAS). Given the latest data demonstrating the importance of aldosterone blockade in obese patients and the efficacy of aldosterone blockade in helping achieve BP goals, the spironolactone/HCTZ combination is particularly well-suited in such individuals.[19] The addition of amiloride to HCTZ reduces hypokalemia and results in variable BP reduction.[20] These combinations are classified as acceptable in people with relatively well-preserved kidney function (ie, estimated glomerular filtration rate >50 mL/min/1.73 m2). At glomerular filtration rate levels below this, the risk for hyperkalemia increases and the diuretic efficacy of HCTZ starts to diminish.[21]

CCBs with b-Blockers

The pharmacologic effects of these two drug classes are complementary, and their combination results in additive BP reduction. In one study, a low-dose combination of felodipine ER and metoprolol ER produced BP reduction comparable to maximum doses of each agent with an incidence of edema similar to placebo.[22] The combination of a b-blocker and a dihydropyridine CCB is acceptable. b-blockers should not generally be combined with nondihydropyridine CCBs such as verapamil or diltiazem because their additive effects on heart rate and A-V conduction may result in severe bradycardia or heart block.

SOME IMPORTANT SPECIAL SITUATIONS

Metabolic syndrome and hypertension

A) Diabetes and Proteinuria

Hypertension may act synergistically with diabetes in increasing the risk of both macrovascular and microvascular comlplications of diabetes[23]. Various trials, some of which have been randomized, have shown decrease in these complications when BP was lowered to safer limits (< 130/80 mm of Hg). This BP control has been found to be difficult to achieve with monotherapy[24]. Indeed, although ACEIs, ARBs, CCBs, diuretics, and β blockers all have compelling indications in diabetes, it is suggested that combination therapy should include, as initial therapy, an agent that interrupts the RAAS. Second drug can be CCBs or diuretics, or ACEI plus an ARB combination.

B) Dyslipidemia and Hypertension

Hypertension and dyslipidemia are conditions that can coexist frequently. National Health and Nutrition Examination Survey (NHANES III) has shown that 64% of patients with hypertension also have dyslipidemia and conversely, approximately 47% of patients with dyslipidemia have hypertension. Hypertension and hypercholesterolemia are the two leading risk factors for heart disease, These two together cause an increase in coronary heart disease related

events.[25] In addition to its anti-hypertensive effect through antagonizing AT1 receptors, telmisartan has a unique property that activates peroxisome proliferator-activated receptor-γ (PPAR-γ) and is suggested to improve insulin sensitivity and reduce triglyceride levels, leading to a reduction of the risk for atherosclerosis. Miura et al. [26] demonstrated that 12 weeks of treatment with telmisartan (in exchange for valsartan or candesartan) resulted in significant decreases in fasting insulin, fasting blood glucose, hemoglobin A1c and triglycerides; and increases in high density lipoprotein cholesterol and adiponectin, suggesting a potential metabolic and anti-atherogenic benefit. Saga Telmisartan Aggressive Research (STAR) study evaluated 197 patients being prescribed 20 to 80 mg of telmisartan for 6 months. Total cholesterol (TC) levels decreased from 200 to 188 mg/dl ($p < 0.05$). Triglyceride levels were decreased 270 to 175 mg/dl ($p < 0.005$) in patients with TG levels ≥ 150 mg/dl [27]. Telmisartan may accelerate reverse cholesterol transport or inhibit net cholesterol absorption through activation of ABC1, lead ing to lowering of TC and Low density lipids-Cholesterol [28]. These results suggest that telmisartan may have the ability to lower cholesterol levels, further controlled studies will be needed to confirm these findings. Thus using a telmisartan alone or in combination with a diuretic/CCB can be efficacious in patients with dyslipidemia.

Heart failure with hypertension

Treatment of hypertension in patients with heart failure must take into account the type of heart failure, systolic dysfunction or diastolic dysfunction, in which there is a limitation to diastolic filling and therefore in forward output due to increased ventricular stiffness. Diuretics, beta blockers, ACEIs, ARBs, and aldosterone antagonists are indicated in the management of heart failure and have been shown to reduce morbidity and mortality in appropriately selected patients with heart failure. Hyperkalemia could be the side effect of some of these drugs so the drugs like ACEIs, ARBs, and aldosterone antagonist in combination should not be used. The choice of agents is based on severity of heart failure, left ventricular ejection fraction, history of myocardial infarction and any other associated comorbidities. In these patients, treatment with ACEIs [29] and β- blockers[30] has been shown to improve symptoms and reduce the risk of death and hospitalization for worsening heart failure. β blockers have now become the most extensively studied class of agents in the treatment of Chronic heart failure (CHF), with a database of over 6000 patients in placebo-controlled studies, and ongoing clinical and mechanistic studies. Despite this, further questions remain regarding the use of these agents in CHF, including their role in the extreme elderly, in patients with DM. 2,289 patients with severe CHF in Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS) study, showed improved clinical status and reduced the risk of death with carvedilol as compared to placebo. However, because patients with the lowest SBP were at highest risk of an event, they experienced the greatest absolute benefit from treatment with carvedilol[31].

Chronic renal failure with hypertension

Hypertension can be caused by chronic kidney disease (CKD) but it itself can worsen the renal failure. The guidelines state that management of hypertension in CKD should focus on reducing BP, with some also emphasizing reducing protein excretion.Choice of agent will primarily depend on the presence of proteinuria as there is a direct relationship between the degree of proteinuria and progression to end stage renal disease. In proteinuric kidney first line agents include an ACEI or ARB, and often requires the addition of a diuretic or a calcium channel blocker. Diuretics are a useful alternative for non-proteinuric patients or as an add-on to reninangiotensin system blockade. Multiple drug therapy is often needed to maintain BP below the 90th percentile target, but adequate BP control is essential for better renal and cardiovascular long-term outcomes. Thiazide diuretics can be used if glomerular filtration rate (GFR) is greater than or equal to 40 mL per minute per 1.73m^2 (body surface area), and loop diuretics are used in GFR less than or equal to 40 to 50 mL per minute per 1.73 m^2.[32]

Hypertension in thyroid disorders

The prevalence of hypertension among patients with hypothyroidism is approximately 3%. Hypertension is much more frequently associated with hyperthyroidism, the prevalence is estimated at 20% to 30%. Hypothyroid state has been shown to accelerate the age-related increases in BP. Studies have shown a significant correlations between DBP and either T4 or T3 suggesting that thyroid hormone deficiency contributes to increase in BP when it is slight to moderate. The mechanism of increased BP in hypothyroidism is not known, but suggested mechanism could be acceleration of structural change of vascular tissue by thyroid hormone deficiency and alteration of autonomic nervous function by thyroid hormone deficiency leading to hemodynamic changes. In patients of thyrotoxicosis, systolic pressures are typically elevated and diastolic pressures are often low, which results in a widened pulse pressure. These findings are attributable to increased cardiac output, stroke volume, heart rate, and cardiac contractility. Although many symptoms of thyrotoxicosis can be controlled with betaadrenergic blockers, catecholamine levels are usually normal or even decreased. Despite the fact that the activity of the RAAS is increased in patients with thyrotoxicosis, ACEIs and angiotensin II receptor blockers do not always reduce BP. Thus, the role of the RAAS in hypertension associated with thyrotoxicosis remains to be defined.

Hypertension in elderly population

The estimated prevalence of hypertension in the United States is 66% in men and women aged 60 years and older, which is the highest among all age groups. A metaanalysis showed that treating hypertension in the elderly yields the greatest benefits in relation to stroke (odds ratio, 0.78) and coronary heart disease (odds ratio, 0.75). Importantly, total mortality and coronary heart disease mortality were found to be significantly reduced. [31] Till date, the most encouraging data supporting aggressive management of hypertension in the elderly population comes from the Hypertension In the Very Elderly Trial (HYVET), a randomized, double-blind placebo trial that enrolled 3,845 patients from 195 centers in Europe, China, Australia, and North Africa. Patients were started with indapamide/placebo and were added with perindopril if BP of 150/80 mmHg was not achieved. Fatal stroke, cardiovascular death, heart failure got reduced by 39%, 23% and 64% respectively in a median follow up of 1.8 years. Thus HYVET and other trials favor mono-therapy or combination therapy with thiazide diuretics, ACEIs and CCBs for hypertension in the elderly [32].

Hypertension in pregnancy and breast feeding

Hypertension complicates 5% to 7% of all pregnancies. A subset of preeclampsia, characterized by new-onset hypertension, proteinuria, and multisystem involvement, is

responsible for substantial maternal and fetal morbidity and is a marker for future cardiac and metabolic disease [33].

Drugs preferred during the pregnancy are

Ist line - Methyl dopa, Beta blocker (propranolol) and Labetalol

IInd line - Metoprolol, atenolol and Calcium channel blocker (nifedipine)

IIIrd line agents-clonidine, diuretics

Three short acting antihypertensive agents-hydralazine, labetalol, and short acting (sublingual or orally administered) nifedipine-are commonly used to control acute, very high blood pressure in women with severe hypertension in pregnancy.

Maternal antihypertensive drugs usually compatible with breastfeeding are Captopril, diltiazem, Enalapril, Hydralazine, Hydrochlorothiazide, Labetalol, Methyldopa, Minoxidil, beta blockers like Propranolol and timolol, spironolactone and verapamil. Individual side effects of drugs have to be looked for, while prescribing these drugs in lactation.

TABLE 1: DIFFERENT STAGES OF HYPERTENSION

Category	Systolic BP (mmHg)	Diastolic BP (mmHg)
Normal Blood pressure	120-139	70-89
Mild hypertension	140-159	90-99
Moderate hypertension	160-179	100-109
Severe hypertension	180-209	110-119
Very severe hypertension	≥ 210	≥ 120

TABLE 2: CHOICE OF ANTIHYPERTENSIVE DRUG CLASS

Drugs	Indications
Diuretics	Old age, Black race, Heart failure
β-Blockers	Youth, Angina pectoris, Atrial fibrillation (to control ventricular rate)† Essential tremor, Hyperkinetic circulation, Migraine headaches†, Paroxysmal supraventricular tachycardia†, Post-MI (cardioprotective effect)*†, Systolic heart failure
Long-acting Ca channel blockers	Old age, Black race, Angina pectoris Arrhythmias (eg, atrial fibrillation, paroxysmal supraventricular tachycardia) Isolated systolic hypertension in elderly patients (dihydropyridines)* High CAD risk (nondihydropyridines)*
ACE inhibitors	Youth ,Left ventricular failure due to systolic dysfunction*, Type 1 diabetes with nephropathy*, Severe proteinuria in chronic renal disorders or diabetic glomerulosclerosis, Erectile dysfunction due to other drugs
Angiotensin II receptor blockers‡	Youth, Conditions for which ACE inhibitors are indicated but not tolerated because of cough Type 2 diabetes with nephropathy, Left ventricular failure with systolic dysfunction, Secondary stroke

CAD = coronary artery disease.

TABLE 3: COMBINATION DRUGS FOR THE TREATMENT OF HYPERTENSION WITH THEIR BRAND NAME

Drugs	Brand name
Diuretic combinations	
Amiloride and hydrochlorothiazide (5 mg/50 mg)	Moduretic
Spironolactone and hydrochlorothiazide (25 mg/50 mg, 50 mg/50 mg)	Aldactazide
Triamterene and hydrochlorothiazide (37.5 mg/25 mg, 50 mg/25 mg)	Dyazide
Triamterene and hydrochlorothiazide (37.5 mg/25 mg, 75 mg/50 mg)	Maxzide25mg,Maxzide
Beta blockers and diuretics	
Atenolol and chlorthalidone (50 mg/25 mg, 100 mg/25 mg)	Tenoretic
Bisoprolol and hydrochlorothiazide (2.5 mg/6.25 mg, 5 mg/6.25 mg, 10 mg/6.5 mg)	Ziac
Metoprolol and hydrochlorothiazide (50 mg/25 mg, 100 mg/25 mg, 100 mg/50 mg)	Lopressor HCT
Nadolol and bendroflumethazide (40 mg/5 mg, 80 mg/5 mg)	Corzide
Propranolol and hydrochlorothiazide (40 mg/25 mg, 80 mg/25 mg)	Inderide
Propranolol ER and hydrochlorothiazide (80 mg/50 mg, 120 mg/50 mg, 160 mg/50 mg)	Inderide LA
Timolol and hydrochlorothiazide (10 mg/25 mg)	Timolide
ACE inhibitors and diuretics	
Benazepril and hydrochlorothiazide (5 mg/6.25 mg, 10 mg/12.5 mg, 20 mg/12.5 mg, 20 mg/25 mg)	Lotensin HCT
Captopril and hydrochlorothiazide (25 mg/15 mg, 25 mg/25 mg, 50 mg/15 mg, 50 mg/25 mg)	Capozide
Enalapril and hydrochlorothiazide (5 mg/12.5 mg, 10 mg/25 mg)	Vaseretic
Lisinopril and hydrochlorothiazide (10 mg/12.5 mg, 20 mg/12.5 mg, 20 mg/25 mg)	Prinzide
Lisinopril and hydrochlorothiazide (10 mg/12.5 mg, 20 mg/12.5 mg, 20 mg/25 mg)	Zestoretic
Moexipril and hydrochlorothiazide (7.5 mg/12.5 mg, 15 mg/25 mg)	Uniretic
Angiotensin-II receptor antagonists and diuretics	
Losartan and hydrochlorothiazide (50 mg/12.5 mg, 100 mg/25 mg)	Hyzaar
Valsartan and hydrochlorothiazide (80 mg/12.5 mg, 160 mg/12.5 mg)	Diovan HCT
Calcium channel blockers and ACE inhibitors	
Amlodipine and benazepril (2.5 mg/10 mg, 5 mg/10 mg, 5 mg/20 mg)	Lotrel
Diltiazem and enalapril (180 mg/5 mg)	Teczem
Felodipine and enalapril (5 mg/5 mg)	Lexxel
Verapamil and trandolapril (180 mg/2 mg, 240 mg/1 mg, 240 mg/2 mg, 240 mg/4 mg)	Tarka
Miscellaneous combinations	
Clonidine and chlorthalidone (0.1 mg/15 mg, 0.2 mg/15 mg, 0.3 mg/15 mg)	Combipres
Hydralazine and hydrochlorothiazide (25 mg/25 mg, 50 mg/50 mg, 100 mg/50 mg)	Apresazide
Methyldopa and hydrochlorothiazide (250 mg/15 mg, 250 mg/25 mg, 500 mg/30 mg, 500 mg/50 mg)	Aldoril
Prazosin and polythiazide (1 mg/0.5 mg, 2 mg/0.5 mg, 5 mg/0.5 mg)	Minizide

COMBINATION OF MORE THAN 2 DRUGS

Few patients may require a third or fourth drug to adequately manage BP. Preference should be given to the selection of an agent from a different class than the initial 2 drugs in the combination therapy. Addition of the third drug may be in the form of spironolactone (requires the assessment of renal functions and potassium), minoxidil, hydralazine, carvedilol and rest of the drugs depending on the specific conditions being treated. Centrally acting drugs should be the last option due to potential side effects.

CONCLUSION

All of the current guidelines suggest that ≥ 1 antihypertensive agent is required in most patients with hypertension to reach BP goals that will effectively reduce the cardiovascular risk. Therapy with 2 drugs separately or with fixed combinations that include agents with complementary actions. JNC-VII guidelines in hypertension, strongly recommend diuretics as first-step therapy for most hypertensive patients. Thiazide-type diuretics are at least as effective as b-blockers, Calcium antagonists, and ACE inhibitors in reducing CV outcomes. Combine drugs are very effective in the elderly and very elderly patients.

ABBREVIATIONS

BP: Blood Pressure; DM: Diabetes Mellitus; DBP: Diastolic Blood Pressure; JNC: Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure; ESH: European Society of Hypertension; SBP: Systolic Blood Pressure; FDC: Fixed Dose Combinations; HCTZ: Hydrochlorothiazide; ARB: Angiotensin Receptor Blockers; CCB: Calcium Channel Blockers; ACEI: Angiotensin-Converting Enzyme Inhibitor; RAAS: Renin-Angiotensin-Aldosterone System; ASCOT: Anglo- Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm; CRF: Chronic Renal Failure; MI: Myocardial Infarction; CVD: Cardio Vascular Disease; AT1: Angiotensin II-type 1; TC: Total Cholesterol; CHF: Congestive Heart Failure; CKD: Chronic Kidney Disease; GFR: Glomerular Filteration Rate; UAE: Urinary Albumin Excretion; and UAER: Urinary Albumin Excretion Rate.

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