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RESEARCH ARTICLE
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"EFFECT OF ANTI-HYPERTENSIVE DRUGS FACTORS ON SYSTOLIC BLOOD PRESSURE (SBP) IN ELDERLY POPULATION: A STUDY FROM A TERTIARY CARE HOSPITAL IN DELHI"

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Abstract

Background: Hypertension (HTN) is a major public health problem in all age group, but isolated systolic hypertension (ISH) is the commonest form of hypertension in elderly population, and it is a better predictor of cardiovascular morbidity and mortality compared to diastolic blood pressure.

AIM: Aim of the present study is to evaluate the effectiveness of various anti-hypertensive drugs and their combinations on systolic blood pressure in elderly patients.

Materials & Method: This prospective observational study was conducted on the patient attending OPD & IPD of HAHC Hospital, Jamia Hamdard, New Delhi. All the elderly hypertensive with elevated systolic BP were included in the study, after explaining the details about the study and taking written consent data were recorded on a proforma. The patients were followed every regularly and the effect of drugs on SBP were assessed and recoded at monthly interval. Data were analyzed by using IBM SPSSv20.

Results: This study documented that among the 220 hypertensive patients who completed the study 51% were female. The maximum numbers of patients were from of age group of 56 to 65 years (44.54%). This study also shows that 40.90% patients were tobacco user. In the single drug therapy telmisartan (40mg) shows best efficacy (21.61% reduction in SBP) followed by ramipril (19.3%) and amlodipine (17.15%). In two drug therapy Carvedilol + thiazide diuretic shows 27.21% reduction in systolic blood pressure followed by CCB+ diuretics 26.7% reduction, CCB+ β1 blocker (24.57%reduction), ARBS + CCB (19.03% reduction). In the triple drug therapy CCB+ β1 blocker + ARBs show 23.91% reduction in systolic blood pressure followed by CCB+ ACEI + diuretic shows 21.60%reduction.

Conclusion: Uncontrolled or poorly controlled systolic hypertension is a major risk factor for cardiovascular morbidity and mortality in the elderly population. Proper controlled of SBP by using appropriate medicine may improve the quality of life and productivity of the elderly population.

Our study shows that telmisartan as single drug therapy provides good control of SBP followed by ramipril and amlodipine but a combination of two drugs carvedilol with thiazide diuretic, a combination of CCB with beta blocker or ARBs with CCB provides over all better control of systolic hypertension in elderly population.

Key words: Elderly population, Telmisartan, Systolic Hypertension, Combination Drug Therapy
Introduction

Background

The demographic shift and a rising proportion of people living to older ages are due to the reduction of infectious disease as the leading cause of death and lowering fertility rates. Population aging has ensued. Reducing infectious disease mortality is the main cause of population ageing. The average life expectancy in developing nations has climbed from 41 years in 1950 to over 62 years in 1990, and the WHO anticipates that it will continue to rise [1]. This decline in mortality rates can be attributed to several factors, including an improvement in living standards for the majority of the population over a relatively long period of time, a technological breakthrough in medicine, including the development of new effective drugs and vaccines, and a technological breakthrough in healthcare. By 2020, more than 700 million seniors will live in developing nations. According to Balasubrabanyam et al. (1999), the rapid growth of an aging population with a high prevalence of chronic, noncommunicable, and disabling diseases is a major socioeconomic and public health issue for families, communities, and the nation [2]. Reilly's 2007 research found that 60-year-olds account for most population growth. According to Reilly et al. (2007), the number of 60-yearolds will triple from 673 million in 2005 to 2 billion in 2050. In 2050, 64 percent of elderly persons in emerging nations will rise to 80 percent. Many developing nations lack the infrastructure to provide high-quality secondary and tertiary care and are shifting toward a community-based strategy [3]. Public health systems need primary care facilities. This is typically better than distant tertiary care for elderly people since it is accessible, community based, and culturally acceptable [4]. Ageing increases chronic illness prevalence. Chronic illness kills approximately 70% of people in the Asia Pacific area (WHO, 2006), and many chronic and non-communicable diseases may be prevented or postponed [5]. Global social and urbanization affect emerging nations. This has significantly impacted Indian lifestyle and health habits, putting individuals at risk of dying from chronic, non-communicable illnesses.

These arguments proved that poor nations age faster than prosperous nations. According to Yesudian et al. (1998), an aging population will provide a major obstacle to future growth, especially in emerging nations [6]. Global public health is threatened by the rising older population. By 2020, age-related factors will cause 75% of deaths in emerging nations. In 2002, the World Health Organization estimated that diabetes, cancer, and circulatory problems caused most of these fatalities [7]. Hypertension is most common in elderly people, the fastestgrowing group in industrialized and developing countries. Oparil et al. (2006) found that hypertension prevalence and severity increase with age [8]. Uncontrolled high blood pressure and diabetes are the biggest cardiovascular disease risk factors. Hypertension increases with age, and both illnesses increase cardiovascular disease risk, according to Porapakkham et al. (2008) and Weycker et al. (2006). Kannel et al.'s 1979 study found that diabetic women had three times more cardiovascular disease than non-diabetic women[9]. Diabetic males and women experienced this.

According to the World Health Organization (WHO), hypertension has become a major public health concern that affects all ages, although elderly individuals in developing nations are at higher risk. (Waldestin and his colleagues found that almost sixty percent of sixty-year-olds had hypertension [10]. The epidemiological shift generates communicable and noncommunicable illness burdens in most emerging nations. In the early 3000s, noncommunicable diseases are spreading worldwide. In emerging nations, where the demographic and socio-economic change limits the ability to manage the double burden of infectious and non-infectious diseases in a poor setting with weak health services, a trend is growing. Developing nations exhibit this pattern. By 2020, non-communicable diseases will kill seven out of ten emerging nations. Cardiovascular disease, diabetes, cancer, and chronic pulmonary disease dominate non-communicable disease research funding. These disorders are seen worldwide, but underdeveloped nations are more affected [11].

Seniors are becoming more diabetic in the US. This demography is growing in share. 41% of the 7.8 million diabetics in 1993 were over 65. Due to complex co-morbidities, Chau and Steven et al.'s 2001 study found type 2 diabetes therapy in seniors difficult. At least half of older people are ignorant of their sickness [12].

Aging and non-communicable diseases like diabetes and hypertension are the biggest health issues for older people in developing countries like India. Hypertension and diabetes prevalence studies in elderly Indians are rare.
Hypertension affects nearly 60% of over-60s, according to Waldestin et al. (2005). Most studies have not examined whether hypertensive persons are aware of their condition. Singh et al. (2000) state that cost-effective high-risk management is essential.

CURRENT SCENERIO

Hypertension is indicated by systolic and diastolic blood pressures exceeding 140 and 90 mm Hg, respectively. Hypertension is also associated with systolic blood pressure exceeding 160 mm Hg. According to the World Health Organization (2013), maintaining normal systolic and diastolic blood pressure is very critical for the heart, brain, and kidneys, as well as general health and wellness [13]. ISH is a rise in systolic blood pressure but normal diastolic blood pressure. It can arise alone or alongside other medical issues. Like essential hypertension, this condition was once considered a natural aspect of aging [14]. Systolic hypertension alone considerably increases the risk of coronary disease, stroke, and congestive heart failure (3-6). Cardiovascular disease causes 17 million deaths annually, or one third of the total 7. Hypertension causes 9.4 million deaths worldwide each year 8. Hypertension causes 45% of heart disease and 51% of stroke fatalities. Hypertension causes renal disease [15]. In 2008, 40% of persons aged 25 and older worldwide have hypertension, up from 600 million in 1980. 7.46% of adults in Africa have hypertension, compared to 35% in the Americas. American hypertension rates are lowest. Hypertension is 35% in high-income countries. This is far lower than other populations. 7–8. nations with lower and intermediate incomes have more people and more hypertensive patients than nations with higher incomes. Because more people live in low- and moderate-income nations. Low- and middle-income countries also have a higher rate of undiagnosed, untreated, and uncontrolled hypertension than high-income ones. This is because their health care systems are not as evolved as those in high-GDP countries. High blood pressure (BP) was the third most significant risk factor for disease burden in a 2010 South Asian research [16]. Hypertension, or high blood pressure, burdens the nation's healthcare system and cardiovascular health. High blood pressure causes 57% of stroke deaths and 24% of CHD deaths in India [17]. Cardiovascular illness causes both.

The WHO lists high blood pressure as one of the leading causes of mortality in those under 60. High blood pressure may cause 7.5 million deaths worldwide each year. This causes 57 million DALYs—3.7% of the total [18]. Hypertension—high blood pressure—is a major risk factor for coronary heart disease and ischemic and hemorrhagic strokes. Blood pressure immediately and continuously increases the risk of stroke and coronary heart disease. High blood pressure impacted approximately 40% of 25-year-olds worldwide in 2008 [19]. High blood pressure and uncontrolled hypertension decreased somewhat between 1980 and 2008.

Hypertension caused this. Population expansion and aging have increased the number of persons with uncontrolled hypertension from 600 million in 1980 to over 1 billion in 2008. Population growth and average age increased this rise. Africa has the greatest prevalence of high blood pressure (46% for both sexes) among WHO areas. World's highest rate. Over 40% of Africans have high blood pressure, with women having a higher proportion than men. No matter gender. With 35% of men and women with high blood pressure, the WHO Region of the Americas has the lowest frequency. The WHO Americas Region has the lowest blood pressure prevalence. In this location, men had a substantially

greater frequency (39% vs. 32%). Men have more hypertension than women in all WHO regions. Disparity is widespread. Only Europe and the Americas have statistically significant gaps. Hypertension rates were 40% across poor, lower medium, and upper middle income countries alike. High-income nations had 35% prevalence [20]

In 2010, the WHO ranked hypertension, or high blood pressure (BP), as the third most important risk factor for attributable disease burden in south Asia. Hypertension strains India's cardiovascular health and healthcare systems. 57% of stroke deaths and 24% of CHD deaths in India are caused by hypertension. The Global and Regional Burden of Disease and Risk Factors study (2001) examined population health data for attributable fatalities and disease burden. High blood pressure in south Asia was the second most common health issue, behind child underweight for age. In 2058, 20.6% of Indian men and 20.9% of Indian women had hypertension, according to worldwide data. By 20257, 22.9 and 23.6 percent of Indian men and women would have hypertension. Recent Indian research found that 25% of urbanites suffer hypertension, compared to 10% of ruralites [21]. In 2008, the WHO reported 32.5% of Indians had high blood pressure (33.2% men and 31.7% women).12. In a multi-center Indian study on hypertension awareness, treatment, and management (HTN13), only 25.6% of treated patients had acceptable blood pressure control. Blood pressure and problems are constantly related. At 115/75 mmHg, the risk of cardiovascular disease (CVD) doubles and rises with each 20/10 mm Hg increase. Asian Indians with considerably reduced blood pressure (BP) may have an increased risk of cardiovascular events. Systolic hypertension—the most common type—predicts cardiovascular/ cerebrovascular events and end-stage renal disease better than diastolic blood pressure17. Older people have more systolic hypertension. Hypertension increases with age. In 1980, a community-based study in Mumbai found that blood pressure rises with age, with 15% of the population having the condition, 34.5% over 55 years old, 38.5% over 65 years old, and 44.4% over 70 years old [22]. The number of Indians 65 or older is expected to climb from 51 million in 2005 to 65 million in 2015 and 76 million in 2020. ISH is the most frequent kind of hypertension in adults over 20. Borderline isolated systolic hypertension increases the risk of full-blown hypertension and cardiovascular disease both short-term and long-term22. ISH was 4.3% according to JNC-7 standards, with males at 5.1% and females at 3.6% [23]. Isolated systolic hypertension prevalence rose considerably with age. Age, BMI, and smoking were independent risk factors for isolated systolic hypertension after a multivariate logistic regression analysis. 23. Antihypertensive treatment in hypertensive men and women between 70 and 84 significantly reduces cardiovascular disease and overall mortality24. Another study examined isolated systolic hypertension in 158,906 persons aged 30–69 who were originally tested for the Hypertension Detection and Follow-up Program (HDFP). 30–69-year-olds participated. The recent Multiple Risk Factor Intervention Trial (MRFIT) revealed ISH prevalence in HDFPs to be just slightly higher than the prior trial. Conclusions are equivalent. ISH-screened elderly people had higher death rates than those with SBP less than 160 mm Hg after 8 years of follow-up, as did younger age groups (except for the 30 to 49year age group on antihypertensive drugs, where deaths were very low) [24]. 87% of 50- to 59-year-olds with uncontrolled hypertension had isolated systolic hypertension. This age group needed a larger systolic blood pressure decrease to accomplish treatment objective than younger individuals. This treatment gap must be addressed by intensifying antihypertensive medication and boosting awareness of middle aged and older high-risk patients.

ISOLATED SYSTOLIC HYPERTENSION

Wilkinson et al., 2000 and Midha et al., 2010 found that isolated systolic hypertension (ISH) is caused by aging and benign, like essential hypertension. Cross-sectional, longitudinal, and randomized controlled investigations show that ISH significantly increases cardiovascular risk. The Seventh Report of the Joint National Committee (JNC-7) on prevention, detection, evaluation, and treatment of high blood pressure states that in people over 50, systolic blood pressure greater than 140 mmHg is a more important cardiovascular disease (CVD) risk factor than diastolic blood pressure [25]. Midha

et al. 2010 found that ISH has been recognized for a long time. It causes cardiovascular accidents and myocardial infarction. ISH prevalence studies in underdeveloped countries like India are few [26].

According to Tanu Midha et al., 2010, JNC-7-defined ISH prevalence was 4.3%, 5.1% in males and 3.6% in women [27]. Age significantly increased ISH prevalence. Age, BMI, and smoking were independent ISH risk variables in multivariate logistic regression.

Bruce M et al., 1992 presented his large cohort study of white males (317,871). 57-year-olds at first screening for the Multiple Risk Factor Intervention Trial (MRFIT) were investigated for baseline blood pressure levels and subsequent CHD, stroke, and all-cause death [28]. Isolated systolic hypertension (ISH), defined as SBP greater than 160 mm Hg and DBP less than 90 mm Hg, was 0.67% among white men screened for MRFIT and increased with age from 0.31% to 1.7%. Men over 50 with ISH had the greatest 6-year CHD and all-cause death rates compared to diastolic hypertension and normal pressure. ISH patients had a 3.0 (95% confidence range 1.3 to 6.8) relative risk of stroke mortality compared to those with SBP less than 160 mm Hg and DBP less than 90 [28]. At any DBP, SBP was the main predictor of all cause and CHD death. ISH determinants and treatment effectiveness in under-60s should be examined.

Stanley S et al., 2001 reported that isolated systolic hypertension was the majority subtype of uncontrolled hypertension in subjects aged 50 to 59 years, comprised 87% of subjects in the sixth decade, and required a greater reduction in systolic blood pressure to reach treatment goal than in younger subjects. This treatment gap requires better knowledge of this middle aged and older high-risk group and more aggressive antihypertensive medication.
Mandal et al. (2012) evaluated Bhotia of Chamoli district, Uttaranchal, for isolated systolic hypertension (ISH) [29]. Bhotia had 4.92% ISH. Men had 2.5% and women 2.42%. ISH increased with age in the research. ISH risk variables for Uttaranchal Bhotia were age, abdominal obesity, cigarette use, and education.

PHARMACOLOGIC TREATMENT

H. Mitchell Perry et al., 2004 has mentioned that antihypertensive drug treatment reduced the incidence of both hemorrhagic and ischemic (including lacunar) strokes. Reduction in stroke incidence occurred when specific systolic blood pressure goals were attained. The Systolic Hypertension in the Elderly Program (SHEP) was the first completed trial investigating isolated systolic hypertension. Results showed that treatment of hypertension reduced all strokes, both fatal and nonfatal, by 36%; all myocardial infarctions (MIs), both fatal and nonfatal, by 27%; all coronary heart disease by 27%; and all cardiovascular disease by 32%. Total mortality was reduced by 13% [30]. Reductions were also demonstrated in the number of transient ischemic attacks (TIAs), and episodes of congestive heart failure. Few clinical trials have been carried out by Daniel Abad-Pérez et al., 2013 to test the effect of oral nitrates on isolated systolic hypertension, even though these agents seem to be effective. Treatment with extended-release isosorbide mononitrate could improve control of systolic blood pressure without severe side effects, thus helping to reduce the morbidity and mortality of the disease. Vasodilators used in combination with beta-blockers and diuretics and indicate the greater therapeutic efficacy of minoxidil [31]. Sarafidis P et al., 2008 has concluded that if systolic blood pressure ≥ 20 mmHg above goal BP and is not controlled by triple drug therapy then start renin-angiotensin system-based combination therapy (ARBs + ACEI) +
chlorthalidone/CCB + β1 blocker (carvedilol/ nebivolol)/ aldosterone receptor blocker (if obese) is the first line treatment for resistant hypertension [32].

Weber et al., 2014 has documented in ASH/ISH hypertension guidelines that ARBs/ACE inhibitor + CCB/thiazide diuretic + Combination of CCB + ACE inhibitor/ARB + thiazide diuretic are first line triple drug therapy for white and other non-black patients ≥ 60 yr [33].

James Paul et al., 2014 has recommended that starting therapy with ≥2 drugs when SBP is >160 mm Hg and/or DBP is >100 mm Hg, or if SBP is >20 mm Hg above goal and/or DBP is >10 mm Hg above goal. If goal BP is not achieved with 2 drugs, select a third drug from the list (thiazide-type diuretic, CCB, ACEI, or ARB), avoiding the combined use of ACEI and ARB. Titrate the third drug up to the maximum recommended dose. Weber et al., 2014 has also revealed that in ARBs/ACE inhibitor + CCB/thiazide diuretic are first line dual drug therapy for white and other non-black patients ≥ 60 yr. James Paul et al., 2014 has documented that in dual drug therapy thiazide-type diuretic + CCB or thiazide-type diuretic or ACEI/ARBs/CCB, is first line drug therapy for black and non-black patients and ACEI + ARBs for all race patients.

Diuretic Therapy

The rationale for thiazide-type diuretics as the preferred first-line treatment for uncomplicated hypertension is based on randomized trials such a ALLHAT [34]. (Research Group the ALLHAT Officers and Coordinators.,2002) In this trial of 33,357 patients, the thiazide-type diuretic chlorthalidone was compared with the calcium channel blocker (CCB) amlodipine and the angiotensin converting enzyme (ACE) inhibitor lisinopril. (A fourth arm using doxazosin was stopped early because of efficacy concerns.) Over a mean follow-up period of 5 years, there was no difference in the incidence of fatal coronary heart disease (CHD) or nonfatal MI among the 3 treatments. The major flaw of this study was the choice of chlorthalidone rather than hydrochlorothiazide (HCTZ). Although chlorthalidone produces superior blood pressure control to HCTZ, and is the true evidence-based choice, HCTZ, because of its familiarity and inclusion in most combination products, is the more widely prescribed agent in America [35]. This suggests that the results of ALLHAT are not completely generalizable to the everyday practice of medicine. Side effects of thiazide diuretics include hypokalemia, hyperuricemia, hypercalcemia, impaired glucose tolerance, and erectile dysfunction (ranking second to beta-blockers) [35]. Loop diuretics are also useful in the treatment of hypertension, particularly for patients with impaired renal function (glomerular filtration rate [GFR] <30-50 mL/min/m2), congestive heart failure, and resistant hypertension. The loop diuretic torsemide may be the preferable agent for hypertension because its long half-life allows once daily administration in most patients. Side effects also include hypokalemia and hyperuricemia. In persons aged 60 years and over with isolated systolic hypertension, antihypertensive steppedcare drug treatment with low-dose chlorthalidone as step 1 medication reduced the incidence of total stroke by 36%, with 5-year absolute benefit of 30 events per 1000 participants [36]. Major cardiovascular events were reduced, with 5 - year absolute benefit of 55 events per 1000. The SHEP antihypertensive drug regimen lowered BP of both diabetic and non-diabetic patients, with few adverse effects. For both diabetic and non-diabetic patients, all outcome rates were lower for participants randomized to the active treatment group than for those randomized to the placebo group. Thus, 5-year major CVD rate was lower by 34% for active treatment compared with placebo, both for diabetic patients (95% confidence interval [CI], 6%-54%) and non-diabetic patients (95% CI, 21%-45%) [37]. Absolute risk reduction with active treatment compared with placebo was twice as great for diabetic vs non-diabetic patients (101/1000 vs 51/1000 randomized participants at the 5-year follow-up), reflecting the higher risk of diabetic patients. Low-dose diuretic-based (chlorthalidone) treatment is effective in preventing major CVD events, cerebral and cardiac, in both non-insulin-treated diabetic and non-diabetic older patients with ISH (J. David Curb et al., 1996). Elderly patients with ISH, valsartan given alone or in combination with HCTZ 1 2.5 mg showed similar efficacy but better tolerability than amlodipine-based treatment [38].

John B. Kostis et al., 2005 has concluded that diuretic treatment in subjects who had diabetes was strongly associated with lower long-term CV mortality rate (adjusted HR 0.688, 95% CI 0.526 to 0.848) and total mortality rate (adjusted HR 0.805, 95% CI 0.680 to 0.952) [39]. Thus, chlorthalidone-based treatment improved long-term outcomes, especially among subjects who had diabetes. Subjects who had diabetes associated with chlorthalidone had no significant increase in CV events and had a better prognosis than did those who had preexisting diabetes.

POTASSIUM SPARING DIURETICS/ALDOSTERONE RECEPTOR BLOCKERS

Potassium sparing diuretics have been available for many years and recently the aldosterone blockers (spironolactone and eplerenone) have gained much attention. While all agents in this class preserve potassium at the distal renal tubule, the sodium channel blockers (amiloride and triamterene) and aldosterone blockers work via different mechanisms [35]. The former block sodium channels directly, whereas the latter binds to the aldosterone receptor in the distal tubule to prevent aldosterone activation of the distal sodium channel. Spironolactone and eplerenone also block aldosterone activity in the heart, kidney, and blood vessels, which may explain the improved outcomes in post-MI patients, and patients with heart failure. Major limitations of these agents include hyperkalemia and for spironolactone - progesterone-related effects such as gynecomastia [40].

ACE INHIBITORS & ARBS

ACE inhibitors and ARBs, via different mechanisms, interfere with the renin-angiotensin aldosterone system (RAAS). ACE inhibitors block the conversion of the peptide angiotensin I to angiotensin II (a potent vasoconstrictor), whereas ARBs directly occupy angiotensin II subtype 1 receptors. Many agents in both classes are available. These classes of drugs are considered safe and equally effective, but ARBs, because of their more direct mechanism of action, may be associated with fewer side effects [41]. ACE inhibitors typically can cause angioedema, cough (up to 15% of patients), acute renal failure, hyperkalemia, anemia, cholestasis, and neutropenia. ARBs can also cause angioedema (although the incidence is approximately $1/100^{th}$ that of ACE inhibitors), hyperkalemia, and acute renal failure. Both classes are contraindicated during pregnancy. Multiple clinical trials have demonstrated the efficacy of ACE inhibitors in hypertensive patients, and there are compelling indications for their use post MI, and in patients with heart failure, diabetes, chronic kidney disease, and stroke [42]. For example, in the HOPE trial, 9,297 high-risk patients with vascular disease or diabetes plus one other cardiovascular risk factor (e.g., hypertension, smoking, hypercholesterolemia) were randomized to 10 mg daily of the ACE inhibitor ramipril or placebo. (The Heart Outcomes Prevention Evaluation Study Investigators, 2000) The ACE inhibitor produced a relative 22% reduction in the composite endpoint of MI, stroke, or death from cardiovascular events (14% versus 17.8%, P<0.001). Other trials have demonstrated similar findings. (Fox KM for the European Trial., 2003)

Compelling indications for ARBs include heart failure, prior MI, diabetes, stroke and chronic kidney disease. In the recently completed large-scale ONTARGET trial (n=25,620), patients with vascular disease or high-risk diabetes were randomized to ramipril, the ARB telmisartan, or a combination of the two, and were followed for a median of 56 months for the composite endpoint of cardiovascular death, MI, stroke, or hospitalization for heart failure.(The ONTARGET Investigators.,2008) No statistically significant difference in the primary endpoint was observed among the treatments, and the strategies were considered equivalent by the investigators (16.5% versus 16.7% versus 16.3%, respectively). This trial has helped settle the debate regarding the equivalence of ACE inhibitors and ARBs. The investigators also concluded that the combination of the two classes is not warranted in the treatment of uncomplicated hypertension. Initiation of antihypertensive treatment involving ACE inhibitors in older subjects, particularly men, appears to lead to better outcomes than [43] treatment with diuretic agents, despite similar reductions of blood pressure.

E A Karpanou et al., 2006 has revealed in his study that Pulse Pressure (PP) was decreased least with diuretics (-5 mm Hg) and most with angiotensin II receptor blockers (ARBs) and calcium antagonists (-15 mm Hg), followed by angiotensin-converting enzyme inhibitors (ACEI) (-12 mm Hg) α- and β-blockers (-10 and -9 mm Hg), differentiating among antihypertensive classes (P<0.001). The magnitude of PP fall was related to the degree of left ventricular (LV) mass reduction (P<0.001), seen best with ARBs (r=0.42) and least with ACEIs (r=0.18). Of the antihypertensive medications used in everyday practice, PP decrease may be achieved best with ARBs and calcium antagonists, whereas diuretics confer poor response. PP was decreased least with diuretics (-5 mm Hg) and most with ARBs

and calcium channel blockers (-15 mm Hg), followed by ACEI (-12 mm Hg) - and -blockers (-10 and 9 mm Hg), differentiating among antihypertensive classes (P<0.001). Of the antihypertensive medications used in everyday practice, PP decrease may be achieved best with ARBs and calcium antagonists.

S S Franklin et al., 2008 has documented in his study that initial combination therapy with a renin-angiotensin system (RAS) inhibitor and diuretic has the potential to rapidly and effectively reduce BP across a range of baseline BPs, with a comparable adverse event profile to monotherapy [44].
It is aforementioned that benazepril–amlodipine combination was superior to the benazepril–hydrochlorothiazide combination in reducing cardiovascular events in patients with hypertension who were at high risk for such events [45]

DIRECT RENIN INHIBITOR

The direct renin inhibitor aliskiren (Tekturna®, Novartis pharmaceuticals) is the first in a new class of antihypertensive agents to become available in over 10 years. Unlike ACE inhibitors and ARBs, which interfere with the RAAS at various points, aliskiren directly inhibits renin, thereby suppressing the RAAS cascade at its start, and theoretically eliminating some of the downstream production of angiotensin II seen with other agents. Early data indicates that aliskerin is at least as effective as ACE inhibitors and ARBs, and possibly slightly better [46].
Aliskerin's side effects include hyperkalemia, renal failure, and diarrhea. Clinical trials in cardiovascular and renal disease are forthcoming and should help clarify aliskerin's role in the treatment of hypertension.

BETA-BLOCKERS

In early versions of JNC, beta-blockers were considered first-line therapy, but in JNC 7 betablockers were considered either add-on therapy to thiazide-type diuretics, or as initial therapy in patients with compelling indications. Recent European hypertension guidelines have relegated beta-blockers to fourth-line agents, after diuretics, RAAS blockers, and CCBs in patients with uncomplicated hypertension [35]. There are 3 main types of beta-blockers: the older beta nonspecific agents; the beta-1-specific agents; and beta-blockers with additional properties. The older nonspecific agents (e.g. propranolol) were associated with more adverse events (Table 10) so that over the last 20 years the beta-1-specific agents, including atenolol, metoprolol, and bisoprolol, became mainstays for hypertension. Their limitations are their constitutional symptoms, with frequent complaints of fatigue and erectile dysfunction. The newer beta-blockers have additional properties, including antioxidant (carvedilol) and antiendothelin (nebivolol) effects. These agents tend to produce better central aortic blood pressure control than other beta-blockers, which may explain why these agents, and particularly carvedilol, produce better outcomes. Since they seem to produce better outcomes with better tolerability than the older agents, they may restore an important role for betablockers in hypertension, particularly in patients with classic compelling indications such as heart failure, prior MI, angina, and in those with high sympathetic drives, as seen with sleep apnea and anxiety [35].

CALCIUM CHANNEL BLOCKERS

Two types of CCBs are available for the management of hypertension: dihydropyridines and non-dihydropyridines. The dihydropyridines such as amlodipine and nifedipine produce excellent blood pressure control by directly relaxing the smooth muscles surrounding muscular arteries [47]. The same mechanism underlies their most common side effect, peripheral edema, which results from arterial vasodilation but not venous dilation. To combat this effect, patients require a vasodilator such as an ACE inhibitor or ARB, which are balanced vasodilators, or long-acting nitrates such as isosorbide mononitrate. The dihydropyridines are also sold in combination with ACE inhibitors and ARBs. The non-dihydropyridines include verapamil and diltiazem. Both reduce blood pressure by inducing

vasodilation and by decreasing myocardial contractility [48]. Both are useful in patients with concomitant arrhythmias such as supraventricular tachycardias including atrial fibrillation.

These agents may cause bradycardia (especially when given with beta-blockers), constipation, and edema. Compelling indications for CCB include high CAD risk and older age. Fourteen weeks of lacidipine treatment significantly reduced blood pressure in older Korean patients with mild-to-moderate hypertension. The efficacy of lacidipine was not inferior to that of amlodipine besylate and tolerability was comparable between the 2 treatment groups [49]. Wang J Liu et al.,1996 , Collaborative Group Coordinating Center., 1992, Goa KLSorkin et al.,1987, Liu LWang et al., 1998 , Ji-Guang Wang et al., 2000 have suggested that In elderly Chinese patients with isolated systolic hypertension, stepwise antihypertensive drug treatment, starting with the dihydropyridine calcium channel blocker nitrendipine, improved prognosis. The benefit was particularly evident in diabetic patients; for cardiac end points it tended to be larger in nonsmokers. Otherwise, the benefit of active treatment was not significantly influenced by the characteristics of the patients at enrollment in the trial. In older persons with isolated systolic hypertension, stepped-care treatment based on low-dose chlorthalidone exerted a strong protective effect in preventing heart failure. Among patients with prior MI, an 80% risk reduction was observed [50].

Among elderly patients with isolated systolic hypertension, antihypertensive drug treatment starting with nitrendipine reduces the rate of cardiovascular complications. Treatment of 1000 patients for 5 years with this type of regimen may prevent 29 strokes or 53 major cardiovascular endpoints [51].
Antihypertensive treatment prevents stroke and other cardiovascular complications in older Chinese patients with isolated systolic hypertension. Treatment of 1000 Chinese patients for 5 years could prevent 55 deaths, 39 strokes or 59 major cardiovascular endpoints. In 1988, Collaborative Group Coordinating Center started the placebo-controlled Systolic Hypertension in China (Syst-China) trial to test the hypothesis whether antihypertensive drug treatment could prevent stroke in older Chinese patients with isolated systolic hypertension. Active treatment was initiated with the dihydropyridine calcium channel blocker nitrendipine, with the possible addition of captopril, hydrochlorothiazide, or both drugs. In the recently published intention-to-treat analysis of the Syst-China trial, active treatment decreased the stroke rate by 38% (P = .01) from 20.8 to 13.0 end points per 1000 patient-years. In addition, all cardiovascular end points decreased by 37% (P = .004) and allcause mortality by 39% (P = .003). At the rates observed in the placebo group, treatment of 1000 Chinese patients for 5 years could prevent 39 strokes, 59 major cardiovascular complications, or 55 deaths [52].Nitrendipine-based antihypertensive therapy is particularly beneficial in older patients with diabetes and isolated systolic hypertension.

ALPHA BLOCKERS

Alpha blockers lower blood pressure by inhibiting the alpha receptors of arterial smooth muscle. Agents of this class include doxazosin, prazosin, and terazosin. All are primarily used as add-on therapy in unresponsive patients and in men with benign prostatic hyperplasia, and can cause orthostatic hypotension. Direct Vasodilators Patients with refractory hypertension may be helped by direct vasodilators like hydralazine or minoxidil, whichn directly dilate the vascular smooth muscle. Minoxidil is considered the more potent, but has more adverse events including serositis, hirsutism, and edema [53].

JNC VII

In 2003 the National High Blood Pressure Education Program presented the complete Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. Like its predecessors, the purpose is to provide an evidence-based approach to the prevention and management of hypertension. The key messages of this report are these: in those older than age 50, systolic blood pressure (BP) of greater than 140 mm Hg is a more important cardiovascular disease

(CVD) risk factor than diastolic BP; beginning at 115/75 mm Hg, CVD risk doubles for each increment of 20/10 mm Hg; those who are normotensive at 55 years of age will have a 90% lifetime risk of developing hypertension; pre-hypertensive individuals (systolic BP 120–139 mm Hg or diastolic BP 80–89 mm Hg) require health-promoting lifestyle modifications to prevent the progressive rise in blood pressure and CVD; for uncomplicated hypertension, thiazide diuretic should be used in drug treatment for most, either alone or combined with drugs from other classes; this report delineates specific high-risk conditions that are compelling indications for the use of other antihypertensive drug classes (angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, beta-blockers, calcium channel blockers); two or more antihypertensive medications will be required to achieve goal BP(140/90 mm Hg, or 130/80 mm Hg) for patients with diabetes and chronic kidney disease; for patients whose BP is more than 20 mm Hg above the systolic BP goal or more than 10 mm Hg above the diastolic BP goal, initiation of therapy using two agents, one of which usually will be a thiazide diuretic, should be considered; regardless of therapy or care, hypertension will be controlled only if patients are motivated to stay on their treatment plan. Positive experiences trust in the clinician, and empathy improve patient motivation and satisfaction. This report serves as a guide, and the committee continues to recognize that the responsible physician's judgment remains paramount [54]

JNCVIII

Hypertension is the most common condition seen in primary care and leads to myocardial infarction, stroke, renal failure, and death if not detected early and treated appropriately. Patients want to be assured that blood pressure (BP) treatment will reduce their disease burden, while clinicians want guidance on hypertension management using the best scientific evidence. This report takes a rigorous, evidence-based approach to recommend treatment thresholds, goals, and medications in the management of hypertension in adults. Evidence was drawn from randomized controlled trials, which represent the gold standard for determining efficacy and effectiveness. Evidence quality and recommendations were graded based on their effect on important outcomes. There is strong evidence to support treating hypertensive persons aged 60 years or older to a BP goal of less than 150/90 mm Hg and hypertensive persons 30 through 59 years of age to a diastolic goal of less than 90 mm Hg; however, there is insufficient evidence in hypertensive persons younger than 60 years for a systolic goal, or in those younger than 30 years for a diastolic goal, so the panel recommends a BP of less than 140/90 mm Hg for those groups based on expert opinion. The same thresholds and goals are recommended for hypertensive adults with diabetes or non-diabetic chronic kidney disease (CKD) as for the general hypertensive population younger than 60 years. There is moderate evidence to support initiating drug treatment with an angiotensin-converting enzyme inhibitor, angiotensin receptor blocker, calcium channel blocker, or thiazide-type diuretic in the nonblack hypertensive population, including those with diabetes. In the black hypertensive population, including those with diabetes, a calcium channel blocker or thiazide-type diuretic is recommended as initial therapy. There is moderate evidence to support initial or add-on antihypertensive therapy with an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker in persons with CKD to improve kidney outcomes. Although this guideline provides evidence-based recommendations for the management of high BP and should meet the clinical needs of most patients, these recommendations are not a substitute for clinical judgment, and decisions about care must carefully consider and incorporate the clinical characteristics and circumstances of each individual patient [55].

Antihypertensive Medication	Initial Daily Dose, mg	Target Dose in RCTs Reviewed, mg	No. of Doses per Day
ACE inhibitors			
Captopril	50	150-200	2
Enalapril	5	20	1-2
Lisinopril	10	40	1
Angiotensin receptor blockers			
Eprosartan	400	600-800	1-2
Candesartan	4	12-32	1
Losartan	50	100	1-2
Valsartan	40-80	160-320	1
Irbesartan	75	300	1
β-Blockers			
Atenolol	25-50	100	1
Metoprolol	50	100-200	1-2
Calcium channel blockers			
Amlodipine	2.5	10	1
Diltiazem extended release	120-180	360	1
Nitrendipine	10	20	1-2
Thiazide-type diuretics			
Bendroflumethiazide	5	10	1
Chlorthalidone	12.5	12.5-25	1
Hydrochlorothiazide	12.5-25	25-100[a]	1-2
Indapamide	1.25	1.25-2.5	1

Abbreviations: ACE,angiotensin-converting enzyme; RCT,randomized controlled trial.

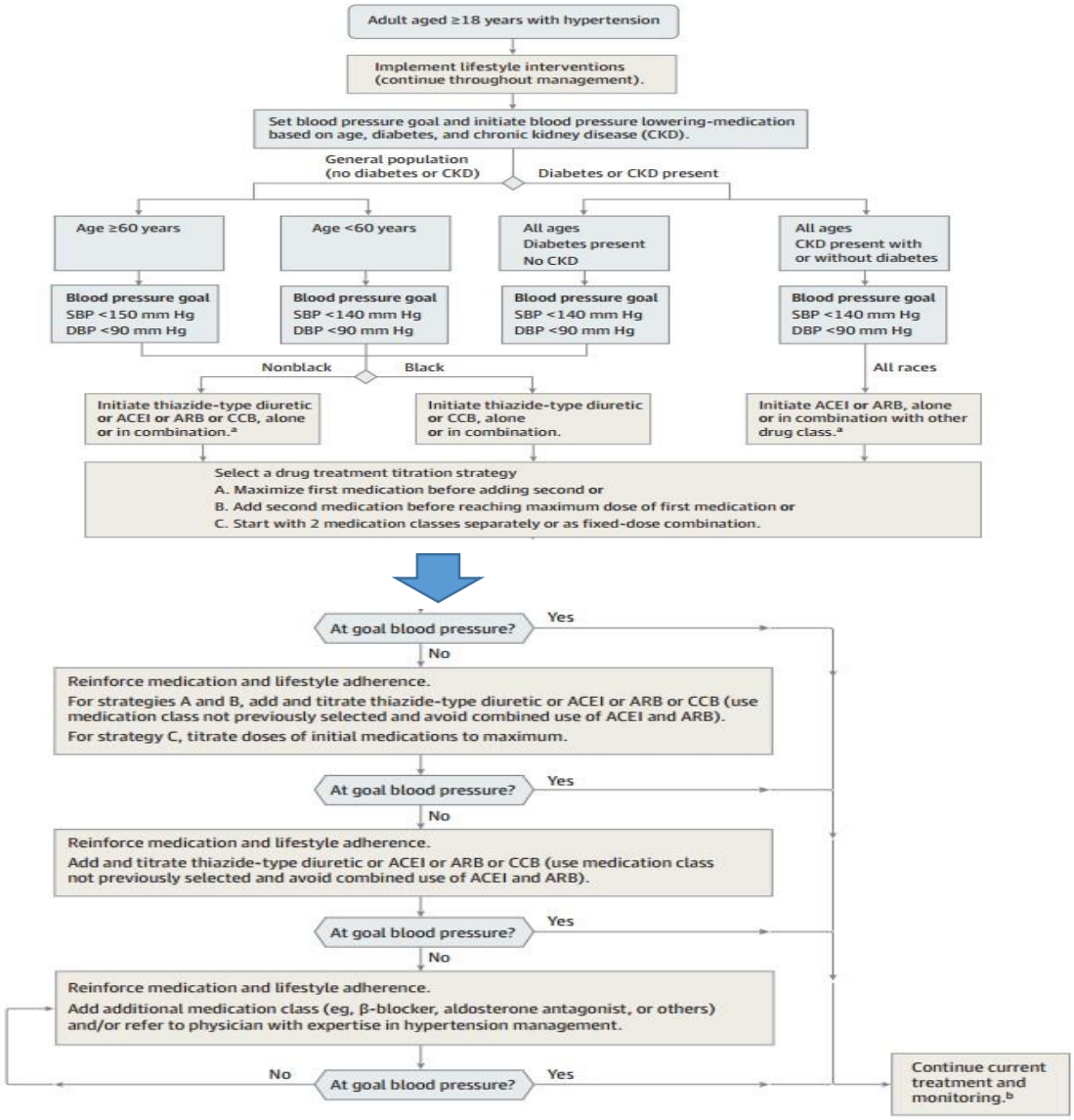


Figure. 2014 Hypertension Guideline Management Algorithm (JNC VIII)

Rationale of Study:
Systolic blood pressure (SBP) is known to be a more important independent cardiovascular risk factor than diastolic blood pressure (DBP) in elderly patients; a high incidence of two types of systolic hypertension is observed, sustained essential hypertension with a disproportionate increase in systolic pressure and isolated systolic hypertension. This kind of work will be able to explore the pattern of treatment and available resources for the management of such illness in elderly patients in India.

Methodology PLACE OF STUDY
The study was conducted at Hakeem Abdul Hameed Centenary Hospital, Jamia Hamdard, New Delhi – 110062, India.

STUDY DESIGN
It was a single Centre, prospective, observational study on Gram-negative severe sepsis/septic shock patients.

STUDY DURATION
This study was conducted over a period of 36 months from August- 2019 to April -2022.

SAMPLE SIZE
The prevalence of hypertension of 27.5%, in Delhi [56],by the previous literature. A minimum of 165 subjects was required with CI (confidence Interval) of 95% at 10% absolute precision. Sample size was calculated by n-Master (2.0) software.

Sample size

Precision	95% CI
10%	≥165

INCLUSION CRITERIA
a) Elderly patients male ≥50 yr and female ≥ 45yr
b) Patients with > 140/90 mm of Hg
c) All menopausal female with BP > 140/90 mm of Hg
d) Systolic blood pressure >140 mm of Hg
e) Patients who are agree to give the consent will be included

EXCLUSION CRITERIA
a) Patient with age of < 50 yr and female < 45yr (or non-menopausal)
b) Patients with ≤ 140/90 mm of Hg
c) Those patients who will not agree to give his consent
d) Patients with other chronic diseases

VISCRAL ADIPOSITY INDEX CALCULATION
FEMALES: VAI= [WC/36.58+ (1.89X BMI)] X (TG/0.81) X (1.52/HDL)
MALE: VAI= [WC/39.68+ (1.88 X BMI)] X (TG/1.03) X (1.31/HDL)

GFR CALCULATION

$$eC_{Cr} = \frac{(140 - \text{Age}) \times \text{Mass (in kilograms)} \times [0.85 \text{ if Female}]}{72 \times \text{Serum Creatinine (in mg/dL)}}$$

DATA COLLECTION
The study was conducted after approval from the Institutional Dean & Principle of HIMSR & HAHC-HOSPITAL. Informed consent form for participation was collected from patient prior to data collection. A data collection sheet was used to collect study specific data.

The data was collected using various data sources as mentioned below. Sources of data:
a. OPD/IPD/MICU visiting patients
b. Personal interview with patients or his/her attendant
c. Medical prescribing records.
d. Patient's medication profile/treatment chart.
e. Laboratory investigation reports (if available)

The data was documented in a properly designed case record form (CRF), in which all the essential particulars/findings were added which can be documented after review of patient's data.

STATISTICAL CONSIDERATION

The data had been maintained in a database prepared in excel. The data was divided various subheadings- demographics, anti-hypertensive drugs prescribed, calculated GFR and VAI.. Descriptive statistics was used to describe the variables in terms of frequency, percentage, mean and Standard Deviation. Logistic regression analysis and independent t-test were used to determine the variables associated with mortality. SPSS v.20.0 statistical software was used to analyze the variables. A probability value (p-value) of <0.05 was considered as statistically significant. All outcome events were recorded and summarized individually.

WORK FLOW PLAN OF WORK

After confirmed diagnosis of hypertension about 200 patients from OPD who are willing to give his/her consent will be included (men ≥ 50 yr and women ≥ 45 yr)

All Demographic information will be recorded for each patient

Drugs prescribed to each patient alone or in combination with all relevant information will be noted

GFR and VAI will be calculated by using the standard formula

Patients will be segregated in individual groups on the basis of different medications prescribed to them

Single Follow up information will be recorded after standard time period (1 month aprx.)

Blood pressure recorded during follow-up and change in medication also recorded.

Various comparisons will be made with regard to changes in SBP vs different drug groups

Appropriate Statistical calculation will be made by using excel & IBM SPSSv20 software to check the significance of the data

Results

Total number of patients enrolled was 230 and follow up taken of 220 patients (9 were drop out and 1 died due to diabetic complications). Patient participation was strictly abided by the provisions of inclusion and exclusion criteria and informed consent form (ICF) required before their admission in the study.

MONO DRUG THERAPY

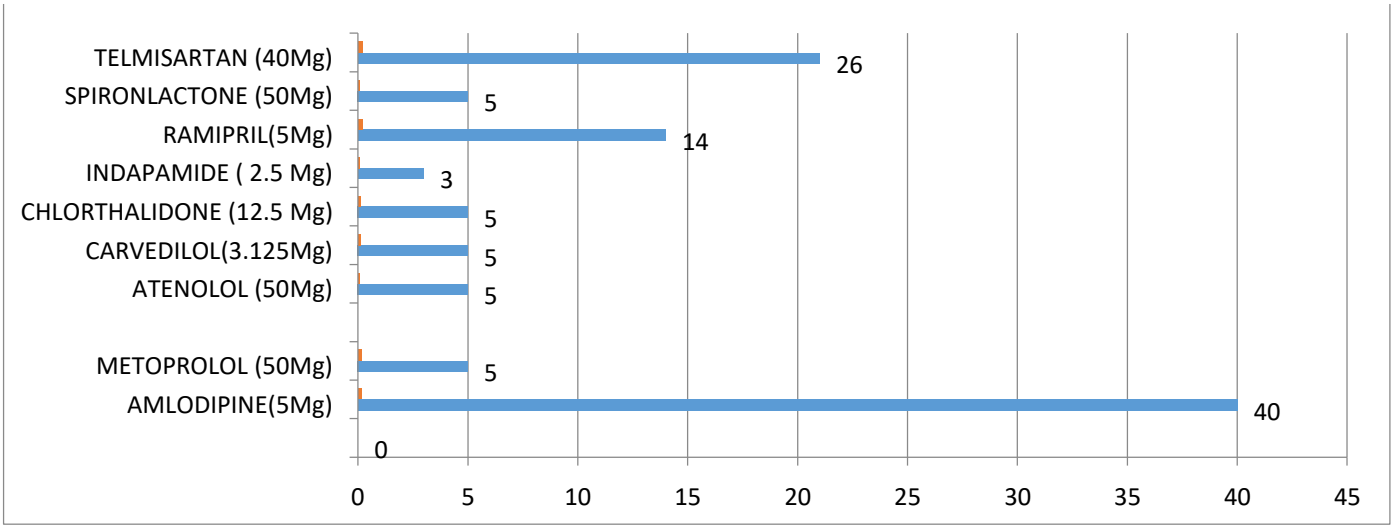
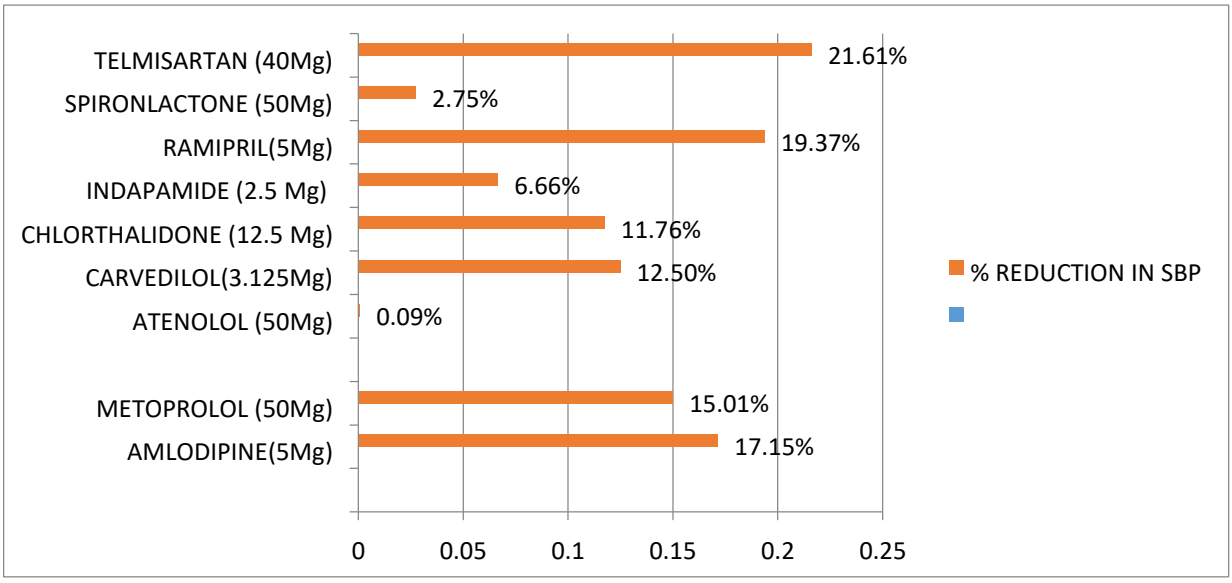


Table no: 27 Hyptension single drug therapy

DRUGS	NO OF PATIENTS (%)	PRE SBP MEAN	POST SBP MEAN	% REDUCTION IN SBP
TELMISARTAN (40Mg)	26 (11.81%)	176.5238	138.3636	21.61%
RAMIPRIL(5Mg)	14 (6.36%)	182	146.75	19.3681%
AMLODIPINE(5Mg)	40 (18.18%)	173.21	143.5	17.154 %
METOPROLOL (50Mg)	5 (2.27%)	176.5	150	15.014%
CARVEDILOL(3.125Mg)	5 (0.90%)	160	140	12.5%
CHLORTHALIDONE (12.5Mg)	5 (0.90%)	170	150	11.76%
INDAPAMIDE (2.5 Mg)	3 (0.45%)	150	140	6.66%
SPIRONLACTONE (50Mg)	5 (2.27%)	182	177	2.747%
ATENOLOL (50Mg)	5 (2.27%)	169.33	168.5	0.09 %
TOTAL	95 (43.18%)			

MONOTHERAPY GIVEN TO THE PATIENTS

REDUCTION IN SYSTOLIC BLOOD PRESSURE BY MONOTHERAPY



This study reveals that among the single drug therapy telmisartan (40mg) shows 21.61% reduction in systolic blood pressure followed by ramipril (5mg) shows 19.3% reduction, amlodipine (5mg) shows 17.15% reduction, metoprolol (50mg) shows 15.01% reduction & carvedilol (3.125mg) shows 12.5% reduction.

TWO DRUG THERAPY

Table no: 1

CLASS OF DRUGS	NO OF PATIENTS (%)	PRE SBP MEAN	POST SBP MEAN	% REDUCTION IN SBP
α1 & β1 BLOCKER + THIAZIDE	7	178.6	130	27.21%
CCB+ DIURETICS	8	191	140	26.7%
CCB+ β1 BLOCKER	19	177.0588	133.5	24.57%
ARBS + CCB	31	176.0625	142.5	19.03%
THIAZIDE + ARBS	25	173.2727	140.6	18.72%
TOTAL	90			

This study reveals that among the dual drug therapy α1 & β1 blocker + diuretic shows 27.21% reduction in systolic blood pressure followed by CCB+ diuretics shows 26.7% reduction, CCB+ β1 blocker shows 24.57%reduction, ARBS + CCB shows 19.03% reduction & thiazide + ARBS shows 18.72%reduction.

TRIPLE DRUG THERAPIES

Table no: 2

DRUGS	NO OF PATIENTS (%)	PRE SBP MEAN	POST SBP MEAN	REDUCTION IN SBP (%)
CCB+β1 BLOCKER + ARBs	8	184	140	23.91%
CCB+ ACE + DIURETIC	4	162	127	21.60%
ARBs + DIURETIC + CCB	10	175.33	150	14.44%
DIURETIC+DIURETIC+α1&β1BLOCKER	4	180	155	13.88%
CCB+α2agonist+DIURETIC	4	175	170	2.85%
TOTAL	30			

This study depicted that among the triple drug therapy CCB+ β1 blocker + ARBs shows 23.91% reduction in systolic blood pressure followed by CCB+ ACEI+ diuretic shows 21.60% reduction,

ARBs + Diuretic + CCB shows 14.44% reduction and diuretic +diuretic + α1 & β1 blocker shows 13.88%reduction

FOUR DRUGS THERAPY

Table no: 3

DRUGS	NO OF PATIENTS (%)	PRE SBP MEAN	POST SBP MEAN	%REDUCTION IN SBP
ACEI+ CCB+DIURETICS + β1 BLOCKER	5	177.5	157	11.54%

This study reveals that the four drugs therapy ACEI+ CCB+ diuretics + β1 blocker shows 11.54% reduction in systolic blood pressure.

DISCUSSION

Uncontrolled or poorly controlled systolic hypertension is a major risk factor for cardiovascular morbidity and mortality in the elderly population (WHO, 2004). Proper controlled of SBP by using appropriate medicine may improve the quality of life and productivity of the elderly population.

Single drug therapy

This study reveals that among the single drug therapy telmisartan (40mg) shows 21.61% reduction in systolic blood pressure followed by ramipril (5mg) shows 19.3% reduction, amlodipine (5mg) shows 17.15% reduction, metoprolol (50mg) shows 15.01% reduction & carvedilol (3.125mg) shows 12.5% reduction. ACE inhibitors and ARBs, via different mechanisms, interfere with the renin-angiotensin-aldosterone system (RAAS). ACE inhibitors block the conversion of the peptide angiotensin I to angiotensin II (a potent vasoconstrictor), and whereas ARBs directly occupy angiotensin II subtype 1 receptors. These classes of drugs are considered safe and equally effective [35] (Chobanian AV et al., 2003 & The ONTARGET Investigators., 2008). Multiple clinical trials have demonstrated the efficacy of ACE inhibitors in hypertensive patients, and there are compelling indications for their use post MI, and in patients with heart failure, diabetes, chronic kidney disease, and stroke. CCB (Nitrendipine) based antihypertensive therapy is particularly beneficial in older patients with diabetes and isolated systolic hypertension[57]. Weber et al., 2014 has documented in ASH/ISH hypertension guidelines that ARB or ACE inhibitor are first line single drug therapy in white and other non-black patients younger than 60 years and in white and other non-black patients ≥60 yr , CCBa or thiazide diuretic is first line single drug therapy. The rationale for thiazidetype diuretics as the preferred first-line treatment for uncomplicated hypertension is based on randomized trials such as ALLHAT (Research Group the ALLHAT Officers and Coordinators, 2002) [58].

Dual drug therapy

This study reveals that among the dual drug therapy carvedilol + diuretic shows 27.21% reduction in systolic blood pressure followed by CCB+ diuretics shows 26.7% reduction, CCB+ β1 blocker shows 24.57%reduction, ARBs + CCB shows 19.03% reduction & thiazide + ARBS shows 18.72%reduction. According to Kenneth Jamerson et al., 2008 the ACE inh+ CCB (benazepril–amlodipine) combination was superior to the ACE inh+ Diuretic (benazepril–hydrochlorothiazide) combination in reducing cardiovascular events in patients with hypertension who were at high risk for such events. Weber et al., 2014 has documented in ASH/ISH hypertension guidelines that ARBs/ACE inhibitor + CCB/thiazide diuretic are first line dual drug therapy for white and other non-black patients ≥ 60 yr. James Paul et al., 2014 has revealed that in dual drug therapy thiazide-type diuretic + CCB or thiazide-type diureticor ACEI/ARBs/CCB, is first line drug therapy for black and non-black patients and ACEI + ARBs for all race patients [59]. E A Karpanou et al., 2006 has revealed in his study that antihypertensive medications used in everyday practice, PP decrease may be achieved best with ARBs and calcium antagonists [60]. In our study combination of two drugs provides over all better control

of systolic hypertension as compared to monotherapy in elderly population. S S Franklin et al., 2008 has also documented that initial combination therapy with a renin-angiotensin system (RAS) inhibitor and diuretic has the potential to rapidly and effectively reduce BP across a range of baseline BPs, with a comparable adverse event profile to monotherapy [44].

Triple drug therapy

In the triple drug therapy CCB+ β1 blocker + ARBs showed 23.91% reduction in systolic blood pressure followed by CCB+ ACE inh + diuretic (21.60% reduction) and ARBs + diuretic + CCB shows 14.44% reduction. Weber et al., 2014 has documented in ASH/ISH hypertension guidelines that ARBs/ACEI + CCB/thiazide diuretic + Combination of CCB + ACEI/ARB + thiazide diuretic are first line triple drug therapy for white and other non-black patients ≥ 60 yr. James Paul et al., 2014 has recommended that starting therapy with ≥2 drugs when SBP is >160 mm Hg and/or DBP is >100 mm Hg, or if SBP is >20 mm Hg above goal and/or DBP is >10 mm Hg above goal. If goal BP is not achieved with 2 drugs, select a third drug from the list (thiazide-type diuretic, CCB, ACEI, or ARB), avoiding the combined use of ACEI and ARB. Titrate the third drug up to the maximum recommended dose [61].

Four drug therapy

This study depicts that the four drugs therapy ACEI + CCB+ diuretics + β1 blocker shows 11.54% reduction in systolic blood pressure. Sarafidis P et al., 2008 has concluded that if systolic blood pressure ≥ 20 mmHg above goal BP and is not controlled by triple drug therapy then start renin-angiotensin system based combination therapy (ARBs + ACEI) + chlorthalidone/CCB + β1 blocker (carvedilol/ nebivolol)/ aldosterone receptor blocker (if obese) is the first line treatment for resistant hypertension [62].

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