STUDY OF PRESCRIBING PATTERN OF ANTIHYPERTENSIVE DRUGS IN INDIA: A REVIEW

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ABSTRACT
Hypertension, a leading contributor to the global burden of causes of disease, continues its upward growth trend. In the year 2000 hypertension was estimated to affect almost one billion patients worldwide and the prevalence is predicted to increase by approximately 60% by 2025. Based on clinical evidence and cost-effectiveness, guidelines developed by the Joint National Committee (JNC) in the United States and the National Institute for Health and Clinical Excellence (NICE) in the United Kingdom recommended that diuretics should be the drug of first choice for patients with no compelling indications. However, the results of various studies have shown that adherence to such clinical guidelines and recommendations are not at all uniform; indeed, they have been found to vary by time period and country and by the characteristics of patients and physicians. The primary goal of anti-hypertensive therapy is to prevent morbidity and mortality associated with hypertension. Various drug classes are used in the management of hypertension and they include diuretics, β-blockers, calcium channel blockers, angiotensin converting enzyme inhibitors and angiotensin II receptor blockers. The study of a prescription pattern is in fact, a part of medical audit involving monitoring and evaluation of various prescriptions of medical practitioners to ensure rationality in medical care. This review study therefore envisages evaluation of the pattern, extent, rationality and frequency of use of the antihypertensive drugs in the treatment of essential hypertension for information to the esteemed medical fraternity.

KEYWORDS: Prescription, Hypertension, cost-effectiveness, medical audit.

INTRODUCTION
Hypertension, a leading contributor to the global burden of causes of disease, continues its upward growth trend.1 It is a public health problem and in the year 2000 hypertension was estimated to affect almost one billion patients worldwide and the prevalence is predicted to increase by approximately 60% by 2025 representing an increase from 26.4% in 2000 to 29.2% in 2025 worldwide.2 The situation in India is more alarming. It was reported that of a total of 9.4 million deaths in India in 1990, cardiovascular diseases caused 2.3 million deaths (25%). A total of 1.2 million deaths were due to coronary heart disease and 0.5 million due to stroke.3 It has been predicted that by 2020, there would be a 111% increase in cardiovascular deaths in India. This increase is much more than 77% for China, 106% for other Asian countries and 15% for economically developed countries. Control of the predicted increase in cardiovascular diseases will require modification of risk factors that have two characteristics. First, the risk factors must have a high attributable risk or high prevalence, or both. Second, most or all of the risks must be reversible cost effectively. Blood pressure (BP) is directly associated with risks of several types of cardiovascular disease, and the associations of BP with disease risk are continuous, indicating that large proportions of most populations have non optimal BP values. Moreover, most or all BP-related risk appears to be reversible within a few years with inexpensive interventions. Hypertension is directly responsible for 57% of all stroke deaths and 24% of all coronary heart disease deaths in India. This fact is important because hypertension is a controllable disease and a 2 mmHg population-wide decrease in BP can prevent 151,000 stroke and 153,000 coronary heart disease deaths in India.4 Poor control of this highly prevalent disease can lead to the development of ischemic heart disease, heart failure, stroke and chronic renal insufficiency.5 It is also associated with diabetes mellitus. Hypertension related deaths constitute one third of global mortality cases and there is scientific evidence...
to suggest that such adverse outcomes can be prevented by lowering blood pressure effectively. It is therefore important that once hypertension is diagnosed, a rational anti-hypertensive therapy on a long term basis along with regular follow up is instituted.\[6\] As a result of various clinical trials and studies, a range of clinical guidelines on antihypertensive treatment have been published over the past decade.\[7\] Based on clinical evidence and cost-effectiveness, guidelines developed by the Joint National Committee (JNC) in the United States,\[8\] and the National Institute for Health and Clinical Excellence (NICE) in the United Kingdom,\[9\] recommended that diuretics (particularly thiazide-type diuretics) should be the drug of first choice for patients with no compelling indications. However, the results of various studies have shown that adherence to such clinical guidelines and recommendations are not at all uniform; indeed, they have been found to vary by time period and country and by the characteristics of patients and physicians.\[10\]

The primary goal of anti-hypertensive therapy is to prevent morbidity and mortality associated with hypertension. Many studies have demonstrated that lifestyle modifications and adherence to appropriate drug treatments are sufficient to maintain blood pressure at optimal levels. Various drug classes are used in the management of hypertension and they include diuretics (D), β-blockers (BB), calcium channel blockers (CCB), angiotensin converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARB).\[11\] If a single drug does not adequately control blood pressure, drugs with different modes of action can be combined to effectively lower blood pressure while minimizing toxicity (stepped care). In many cases, 3 or 4 drugs may be necessary. The presence of co-morbid conditions also influences selection of anti-hypertensive drugs because two diseases may be treated with a single drug. Co-morbidities are diseases or disorders that coexist with a disease of interest. Co-morbid illnesses are important because they may delay diagnosis, may influence treatment decisions, are related to complications, alter survival, and confound analysis.\[12\] The widespread use of antihypertensive agents, the public health relevance of hypertension as a risk factor and the costs involved have made this drug class a topic in drug utilization research and ‘evidence-based medicine’ from early on. Moreover, many national medical associations and international organizations aim to promote certain prescribing behaviour by publishing and implementing ‘evidence based’ guidelines.\[13,14\]

The beneficial effects of the optimal control of blood pressure on mortality and cardiovascular morbidity have been confirmed in epidemiological and interventional studies.\[15\] However due to high prevalence of hypertension and the requirement of medications for prolonged periods, the drug treatment cost represents a major issue in health economics. In developed countries, the expenditure on antihypertensive therapy has increased sharply in recent years due to increasing use of the newer and more expensive drugs, such as CCB, ACE and ARB. Furthermore, due to frequent coexistence of hypertension, diabetes mellitus and hyperlipidemia,\[16\] the prescription of drugs to treat the associated conditions further increases the treatment costs of these patients.

A prescription based survey is considered to be one of the most effective methods to assess and evaluate the prescribing attitude of the physicians and dispensing practice of pharmacists.\[17\] It is also important to consider the recommendations of international bodies on hypertension that help to improve prescribing practice of the physicians and ultimately, the clinical standards. A continuous supervision is therefore required through such kinds of systematic audit, which provide feedback from the physician and help to promote rational use of drugs.\[18\] The study of a prescription pattern is in fact, a part of medical audit involving monitoring and evaluation of various prescriptions of medical practitioners to ensure rationality in medical care. This review study therefore envisages evaluation of the pattern, extent, rationality and frequency of use of the antihypertensive drugs in the treatment of essential hypertension for information to the esteemed medical fraternity.

**RECENT INDIAN STUDIES**

Mirza Atif Beg, et al. conducted a drug utilisation study in hypertensive patients by the department of pharmacology in medicine OPD at SGRRIM & HS, Dehradun for 6 months. 645 prescriptions were evaluated for prescribing pattern by using WHO drug use indicators like drug class, dosage form, fixed dose combinations (FDCs) and drugs from National Essential Medicine List 2011. 291(45.12 %) were male and 354(54.88 %) were female patients. Co-morbid conditions associated with Hypertension included Type 2 Diabetes mellitus in 174(26.97%), hypothyroidism in 114(17.67%), Coronary artery disease in 18 (2.79%) and Bronchial Asthma in 14(2.17%) patients. A total of 1828 drugs were prescribed. 697(38.13%) were antihypertensives, in which ARBs were 234(33.57%), ACE inhibitors were 117(16.79%), Beta blockers were 95(13.63%) and CCB were 83(11.91%). Amongst ARBs, the leading drugs were Olmesartan 196(28.12%), Losartan 20(2.86%) and Telmisartan 18(2.58%). Amongst ACE inhibitors the most commonly prescribed drug was Ramipril 84(12.05%) followed by Enalapril 33(4.73%). Atenolol 82(11.76%) was the most commonly prescribed Beta blocker followed by Metoprolol 7(1.04%) and Nebivolol 6(0.86%). Amlodipine 83(11.90%) was the only Calcium channel blocker prescribed. Out of 168 fixed dose combinations, two drug therapies was more common 153(91.07%) than three drug therapy 15(8.93%). The average number of drugs prescribed per prescription was 2.83. Out of 697 prescribed antihypertensives, 225(32.28%) drugs were prescribed from National Essential Medicine List 2011 which included 83(36.88%) Amlodipine, 82(36.44%)...
A prospective, observational study was conducted by Solanki, et al. at Department of Pharmacology in association with Department of Medicine in a Guru Gobind Singh Government hospital, Jammagar for a period of 6 months from Dec 2011-May 2012. The main objective is to evaluate the drug utilization pattern among hypertensive patients and their adverse effects attending medicine OPD in a tertiary care teaching hospital, using WHO drug use indicators. Total of 600 patients were included in the study. Out of 600 patients, 263(43.83%) were male and 337(56.17%) were female. About half of the patients had received two antihypertensive drugs (49.50%), followed by one (33.16%) and three (15.5%) antihypertensive drugs. Patients having diabetes along with hypertension had received two antihypertensive drugs per encounter was 1.86±0.73 with range of 1 to 4. The average number of antihypertensive drugs per encounter was 4.01±1.61 with range of 1 to 10. Among the antihypertensive drugs, enalapril (ACE inhibitor) was the most commonly prescribed drug (79.66%) followed by atenolol (beta blocker) (49.66%), amlodipine (CCB) (33.83%), furosemide (loop diuretic) (17%) and metoprolol (beta blocker) (4.66%). In this study it was found enalapril + atenolol was most commonly prescribed two drug combinations (22%) followed by enalapril + atenolol +amlodipine as most commonly prescribed three drug combinations (8%) followed by enalapril + atenolol + furosemide + metolazone as most commonly prescribed four drug combination (1.66%). Study shows 1785 drugs (74.22%) were prescribed by generic name and 620 drugs (25.78%) were given by brand name. Increasing generic prescribing would rationalize the use and reduce the cost of drugs. Out of 43 drugs used, 32(74.41%) drugs were prescribed from National list of essential medicines of India, 2011 and 33 (76.74%) drugs were prescribed from essential drug list of Gujarat, 2010-11. Use of drugs from the essential drug list should be promoted for optimal use of limited financial resources, to have acceptable safety and to satisfy the health needs of the majority of the population. This study provided a baseline data regarding the prescribing pattern in hypertensive patients. There is a scope for improvement, particularly the under utilization of diuretics and calcium channel blocker in this study. Since hypertension is a common lifelong disorder, prescription cost is one of the major reasons for non-adherence to drug therapy.

Md. Arief et al. conducted a study in the Department of Cardiology at Krishna Institute of Medical Sciences, Hyderabad having duration of 8 months with the objective of evaluating the prescribing pattern of antihypertensive drugs and to identify the factors affecting the implementation and use of the standard...
guidelines and to determine the type of drugs commonly prescribed i.e. either monotherapy or combination drugs. Out of 400 hypertensive patients prescriptions the percentage of males was 59.75% (239 patients) whereas the percentage of females was 40.25% (161 patients). 351 patients received monotherapy and only 49 patients received a combination therapy. In patients receiving monotherapy the rate of prescription of antihypertensives was followed in the order of frequency by ACE-I (38.25%), CCBs (19.25%), Diuretics (13.25%) followed by beta-blockers, ARBs with prescription rate of 6.75% of each. Among combination therapy a 2-drug combination of CCB+ACE-Inhibitors were prescribed to a majority of patients 20 (5%), followed by a combination of Beta-blockers+CCB 14 (3.5%), ACE+Loop-diuretics 11 (1%), CCB+CCB 4 (1%). In this study, it was observed that the physicians had preferred monotherapy more often than the combinations. Thiazide diuretics and the combination drugs were underutilized in this study, despite robust evidence to support their use. As the use of the thiazide diuretics as monotherapy was negligible it increases the burden on the patients.[23]

Rachana PR et al. conducted a retrospective cross-sectional study in tertiary care hospital, Bangalore for three months and utilized 300 prescriptions for the analysis. The main objective was to analyze the current prescription pattern and cost analysis of antihypertensive drugs in hypertensive patients in a tertiary care hospital. The prevalence of hypertension was seen more in males compared to females. Monotherapy (48.94%) was leading trends of antihypertensive therapy followed by fixed dose combination (35.04%) and polytherapy (16.01%). The most frequent antihypertensive class to be prescribed were CCBs (38.59%) followed by beta blockers (24.07%). Among the different classes of antihypertensives Amlodipine (37.3%) was the most prescribed drug followed by Atenolol (19.43%) and Telmisartan (8.03%). In polytherapy beta blockers with CCBs were mostly prescribed (56.66%) followed by beta blockers with ARBs (9.43%). The study was undertaken after the implementation of drug price control order act (DPCO) 2013. According to the DPCO 2013, medication price are calculated taking simple average of all brands which have more than one percent market share. Out of 652 drugs under price control, we found that only seven antihypertensives prescribed by their hospital physicians were included in the DPCO list 2013. These included atenolol, metoprolol, amlodipine, nifedipine, hydrochlorothiazide, losartan and enalapril. The study also analysed the prescription pattern of antihypertensive drugs and found that the prescribing pattern was not totally consistent with the JNC VII guidelines for the treatment of hypertension. Higher percentage of patients (56.66%) was found to be on polyphterapy. The DPCO 2013 has overcome the problem of fixation of prices of drugs.[24]

Kaur et al. conducted a descriptive drug utilization study on randomly selected 297 prescriptions of hypertensive patients attending the medical OPD at tertiary care hospital, Govt. Medical College Jammu for a period of 6 months to find out the prescribing pattern of usage of antihypertensive drugs. Higher proportion of males was found as compared to females (38.7% males and 31.88% females respectively). Type 2 diabetes mellitus was the most common co morbidity observed in the patients (40%). Commonly prescribed anti hypertensive group of drugs in decreasing order of frequency were; ACE inhibitors and CCBs followed by beta-blockers, ARBs and diuretics. Ramipril, Amlodipine, Atenolol, Losartan and Hydrochlorothiazide were the leading drugs in the respective groups. A slightly more than half of patients studied (55.6%) were prescribed combination therapy CCBs, diuretics and ACE inhibitors were most commonly prescribed as single agents whereas most commonly prescribed combination comprised of CCB and ACE inhibitors. Most of the drugs were in accordance with WHO essential drug list with the exception of ACE inhibitors where ramipril was more frequently prescribed as against enalapril. JNC-VII guidelines stipulate that thiazide diuretics should be used as initial therapy for most patients with uncomplicated hypertension either alone or in combination with drugs from other classes. As diuretics are known to enhance the anti-hypertensive efficacy of multidrug regimen, they can be useful in achieving BP control and are most cost effective than other anti- hypertensive agents. Despite these recommendations, diuretics were found to be prescribed less often to patients as single drug treatment in this study; however, as combination therapy, it was second only to CCBs (42.3%). Similarly, prescription of beta blockers was also not found to be consistent with recommendations of JNC VII.[25]

Reshma S. R et al. conducted a cross sectional study in an outpatient and inpatient Department of General Medicine at JJM Medical College Hospital, Davangere. Data was collected for duration of 3 months. Analysis of prescribing pattern of antihypertensives in geriatric and non geriatric Individuals was the main objective. Total of 210 prescriptions were analyzed. The no. of males 118(56.19%) and no. of females 102(43.81%) were nearly equal. Out of 81 prescriptions in non geriatric hypertensive individuals 34% received CCBs, 21% beta blockers, 11% ACE inhibitors, 8% ARBs and 12.5% fixed dose combination of angiotensin receptor blocker and hydrochlorothiazide. Rest of 129 geriatric patients 23% had CCBs, 20% beta blockers, 17% ARBs, 9% ACEs and 15% fixed dose combination of ARBs and hydrochlorothiazide. Other antihypertensives prescribed include clonidine and different FDCs such as Amlodipine + Hydrochlorothiazide, Olmesartan + Amlodipine, Ramipril + Hydrochlorothiazide, Telmisartan + Amlodipine, Amlodipine + Atenolol, Losartan + Hydrochlorothiazide etc. In this study, the prescribing pattern does not differ depending on the age of the individual rather it depends on duration and severity of illness and co morbid conditions. Calcium antagonists are commonly prescribed drugs in both
geriatric and non-geriatric individuals. ARBs alone or in combination with hydrochlorothiazide are increasingly prescribed in geriatric individuals.[26]

A retrospective, cross-sectional analysis of prescriptions of antihypertensive cases admitted in Medicine in-patient wards of S. Nijalingappa Medical College and HSK Hospital and Research Centre was conducted by Anand et al. during the period of January 2012 to June 2012. A total of 214 patients with essential hypertension were screened. In the overall utilization pattern, CCBs (49%) were the most commonly prescribed drugs followed by diuretics (43.5%), ACE inhibitors (29.5%), beta blockers (29%), ARBs (21%), alpha-adrenergic blockers (2%) and central sympatholytics (2%); the leading drugs being Amlodipine, Hydrochlorothiazide, Enalapril, Atenolol, Losartan, Prazosin and Clonidine in the respective groups. In this study, two-drug combinations were mostly prescribed (67.7%), followed by three-drug combinations (27.5%) and four drug combinations (4.9%). In two-drug combinations, a diuretic with angiotensin receptor blocker (29.5%) was most commonly prescribed followed by a β-blocker with a calcium channel blocker (22.1%). 51% of patients were on multiple drug therapy, the most favored fixed drug combination being diuretics with angiotensin receptor blockers (25.4%). Among the hypertensive cases with co-existing diabetes mellitus type II, the most prescribed class of drugs was diuretics (43.8%) followed by ACE inhibitors (40.4%).[27]

A prospective study was conducted by T Janagan et al. to establish the antihypertensive drug prescription pattern in hypertensive patients with associated Type 2 Diabetes mellitus who were attending as outpatient in general medicine department at SRI Muthukumarman Medical College & Research Institute over a period of 3 months. The total of 130 patients were screened. 85 patients who met with inclusion criteria were selected. Out of 85 patients selected 52 were male (61%) and 33 were female (39%). The patients receiving combination antihypertensive agents (76.3%) were more than those receiving monotherapy (24.7%). The ACE inhibitors are the most commonly used drug both as a monotherapy and in combination therapy. In patients receiving monotherapy, ACE Inhibitors (52.3%) were commonly prescribed class followed by ARBs (23.8%), Cardioselective Beta blockers (09.5%), CCBs (09.5%) and Diuretics (04.7%). In combination therapy, ACE inhibitors with Thiazide diuretics (34.3%) are the most commonly prescribed combination followed by ARBs with Thiazide diuretics (26.5%), ARBs with Beta blockers accounts for about 9.3%. The three drug regimen of ACE inhibitor with Thiazide diuretic and Beta blockers were prescribed in 6.2% of the treatment population. The prescription pattern was found to be in concordance with the Joint National Committee (JNC7) recommended therapy for hypertension associated with Diabetes mellitus.[28]

Kuchake VG. et al conducted an observational and prospective study at Indira Gandhi Memorial Hospital, Shirpur, Maharashtra in India over the 6 months periods. The objective of this study was to evaluate the prescribing pattern and drug utilization of antihypertensive medications in uncomplicated hypertension. Total 5025 out patients visited the medicine ward of hospital, among them, 510 patients were diagnosed with hypertension of which 244 had uncomplicated hypertension. The present prospective study observed that hypertension was more prevalent in males than in females. Overall, 150(61.48%) patients were treated with a single anti-hypertensive drug, among them, 81(54.0%) patients were treated with CCBs, 37(24.67%) were treated with β-blocker, 17(11.33%) with ARBs, 9(6.0%) were treated with ACEIs and 6(4.0%) treated with diuretic. 94 (38.52%) patients were treated with anti-hypertensive drug combinations. Among them 59, (62.78%) were treated with two drugs, 31(32.98%) with three drugs and 4(4.25%) were treated with 4 drugs. The CCBs with β-blocker was the most frequently prescribed two-drug combination in overall.
population followed by ARB with Diuretic. In view of often costly drugs for long term treatment, it is necessary that monitoring of their use, its co-relationship with clinical outcomes and quality of life is essential to ensure the optimal use of health care resources. It is found from the study that the prescription of diuretics in hypertension is comparatively low whereas the calcium channel blockers are widely prescribed. The overall findings of the study show that there is need for further improvement in the prescription pattern of antihypertensives.\(^{30}\)

Drug utilization data of 500 hypertensive patients, attending medicine Out Patient Department of Punjab Institute of Medical Sciences Hospital from October 2010 to March 2011 was collected from 24 hour hospital pharmacy by Bajaj J.K., et al. The study was conducted to analyze the prescription patterns of antihypertensive drugs and adherence to JNC VII guidelines in a North Indian tertiary care hospital. 210 patients (42%) were males & 290(58%) were females indicating 16% higher prevalence of hypertension in female population. Diuretics was the most commonly prescribed group of antihypertensive drugs in 53.4% patients, followed by ARBs in 42.6%, beta blockers in 38.6% & CCBs in 26.4% patients. Out of diuretics, thiazides group was the most commonly used (40.4%), 42.6% patients received monotherapy and rest 57.4% combination therapy. 37% of total patients received two drugs, 17.2% three drugs & 3.2% received four or more drugs. Fixed Dose Combinations (FDCs) are quite frequently used in treatment of hypertension. 41.6% of all prescriptions had FDCs. Main limitation of drug utilization studies is the lack of detailed patient records for justifying the prescribed drugs based on grade of hypertension, presence of complications and previous drug therapy.\(^{31}\)

V Pavan et al conducted a prospective study of six months duration in 360 patients at Sathya Hospital (Vanamala Clinic), Warangal. The data collected were analyzed for the Prescribing patterns of antihypertensive drugs and demographic profile of the patients suffering from hypertension. The patients enrolled in the study were grouped based on the number of antihypertensive drugs prescribed. Out of 360 patients during study period, 59% were male and 41% were female. The results revealed that, maximum number of patients 174(48.3%) underwent Dual therapy, followed by 109(30.2%) monotherapy, 47(13%) of the patients with Triple therapy and 30 (8.3%) of the patients were treated with more than 3 drugs. Out of 109 patients who underwent monotherapy for the treatment of hypertension, 46 (42.2%) of the patients were prescribed with ARBs, followed by 24(22.0%) with CCBs, 18(16.5%) of the patients with ACE inhibitors, 12 (11.0%) of the patients with diuretics and 9 (8.2%) of the patients with β-blockers. Out of 174 patients in whom two antihypertensives were prescribed, 124 (71.3%) of the patients were prescribed with a combination of Diuretics and ARBs followed by 26(15%) of patients with Diuretics and ACE I and 8 (4.6%) of the patients treated with Diuretics and β blockers. Out of 47 patients treated with triple therapy maximum number of patients were treated with Diuretics in combination with ARBs, ACE I, α-blockers, (21.2%) of the patients were prescribed with Diuretics along with ARBs and β-blockers, followed by 9(19.1%) of the patients prescribed with a combination Diuretics + ARBs + ACE I and Diuretics + ARBs + CCBs respectively. This indicates that Diuretics is used as first line therapy which complies with JNC VII guidelines. Counseling and educating the patient on the importance of diet and exercise in the management of hypertension are of vital importance.\(^{32}\)

A prospective study was conducted by Sindhu et al in multi specialty hospital in southern Indian state of Andhra Pradesh from June 2012 to September 2012 from a prospective series of 205 patients of either sex by scrutinizing the outpatient cards and laboratory reports of inpatients attending the hospital. The aim of study was to provide incite in to the prescriptive patterns of antihypertensive drugs in a south Indian super-speciality hospital. Out of 205 patients recruited for the present study, 127(61.95%) were males and 78(38.04%) were females, 78(38.04%) were found to be on monotherapy. Among 78 patients, 38(48.7%) were found to be treated with CCBs, followed by 22(28.2%) were treated with ARBs, 8(10.25%) of patients with ACE inhibitors, 6(7.69%) of patients with beta blockers, 4(5.12%) of the patients with diuretics. Among 115 patients given dual therapy, 73(63.4%) of the patients were found to be treated with a fixed dose combination ARB+ Diuretic followed by β-blocker+ CCBs i.e 10.43%. Multiple therapies were given only among 12 patients with Diuretics+ARBs+CCBs being the mostly prescribed combination (33.3%). In hypertensive patients with coexisting diabetes ACEI are the mostly prescribed class of anti-hypertensives (50.6%). The results revealed that out of 205 patients included in the study, 97(47.31%) patients had single co-morbid condition and 33(16.09%) patients had multiple co-morbidities whereas 75(36.58%) patients had no co-morbid condition. Out of 97 patients with single co-morbidity, 60(61.85%) of the patients had Diabetes Mellitus followed by IHD in 12(12.37%) patients and among the patients with coexisting diabetes, ACEIs are found to be mostly prescribed class of drugs (50.6%), along with a combination of diuretic or a CCB. The study revealed that the prescription of antihypertensive medication is according to JNC guidelines, except monotherapy of diuretics.\(^{33}\)

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