PRESCRIBING PATTERN OF ANTIHYPERTENSIVE DRUGS IN A TERTIARY CARE HOSPITAL: A REVIEW

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Abstract

Hypertension is one the leading cause of mortality in various developing countries like India. For the effective management of this lifestyle disorder a rational approach & measures are required to be taken by the health care professionals. In order to achieve this, prescription pattern analysis is a powerful tool which elaborated the trends of prescribing and their evaluation in reference to the standard treatment guidelines by the various health agencies. An ample of studies focusing on prescribing patterns of antihypertensive drugs was reviewed in this article. It has been concluded that most of the studies were showing that monotherapy including ACEIs (Angiotensin converting enzyme inhibitors) was first choice antihypertensive treatment. Additionally, ARBs (angiotensin receptor blockers) were the second most preferred class followed by CCBs (calcium channel blockers), Diuretics and BB (beta blockers). However, most of the studies have shown that the prescribing trends were according to the recommended guidelines but JNC 8 guidelines were not being completely followed. Due to persistent clinical challenges in the management of hypertension, we still require additional care & monitoring of the treatment patterns. So adoption of a rational approach aligned with standard treatment guidelines is essential which will not only fill the gaps in the clinical practice but also help in complete & effective management of this illness.

Keywords: Hypertension, Prescription pattern, ACEIs, ARBs, CCBs, BBs, JNC 8 guidelines.

Introduction

A hemodynamic vascular disorder called hypertension is aligned with a rise in vascular resistance in periphery that can results into development of various cardiovascular morbidities like renal failure, MI (Myocardial Infarction), strokes and death, in case it is not properly diagnosed and treated rationally on early basis. (Sever *et al.,* 2011, Gradman *et al.,* 2010). There are myriad of factors found to be associated with hypertension i.e. genetic and environmental factors are closely related to its development as activation or inhibition of various processes involved in the maintenance of normal blood pressure regulated by these two factors. (Sever *et al.,* 2011; Gradman *et al.,* 2010; Yang *et al.,* 2010; Neutel *et al.,* 2008).

Additionally, dietary factors and sedentary lifestyle also throw in to the genetic predilection, while environmental factors include smoking, obesity and alcoholism, are making the hypertension a preventable cause of morbidity and mortality due to this lifestyle illness (Sever *et al.,* 2011). All over the globe, plethora of guidelines have been formulated for an effective management for hypertension, and these guidelines are considered as a standard for health care professionals in complete diagnosis, prevention & management of this illness. It has been seen that a number of clinicians especially primary care physicians prefer to prescribe the drugs according to their own evidence based clinical practice experience rather than following the guidelines. put into practice with their prescriptions in the management of hypertensive patients according to their evidence based clinical practice. Therefore a rational approach can be developed to make hypertensive treatment more effective by analyzing these guideline-based prescribing patterns of antihypertensive drugs (Peltzer *et al.,* 2013).

Hypertension is usually considered as a complex condition involving an ample of factors, those interacts with other mechanisms and acts on several physiological systems responsible of management of BP. Firstly, RAAS has proven to be one of the prime mechanisms possessing a central role in the management of normal level of blood pressure and vascular resistance. This system facilitates the rennin secretion which further controls the renal sodium excretion, water retention and plasma volume by feedback mechanism. Angiotensin II is the major determinant of this system because it has direct vasoconstrictor effect. Another mechanism is the neural control of blood pressure involving balance approach of sympathetic and parasympathetic nervous system. RAAS in conjugation with sympathetic nervous system collectively regulate some contributing factors like blood pressure, intravascular volume, systemic vascular resistance and cardiac output, responsible for hypertension. The rational approach for hypertension management involves the combination of different drug categories to achieve the target more rapidly and effectively (Schellack *et al.,* 2015) **(Fig.1).**

Guidelines and Treatment (Table. 1)

JNC 7 guidelines published in 2003 includes the following important highlights:

- Systolic Blood Pressure ≥140 mmHg is considered to be a more vital cardio vascular disease risk factor than DBP in patients aged ≥50 years.

- Beginning at 115/75 mmHg, each increment of 20/10 mmHg blood pressure doubles.

- Prehypertensive individuals need to implement lifestyle modification interventions to reduce the likelihood of disease progression.

- For the hypertension without any complication, thiazide diuretics need to be included in drug treatment chart, either as monotherapy or in combination with other antihypertensive (JNC 6th report., 1997; Nicole et al., 2015).

- Initial treatment algorithm should include more than two drugs, one of which should include a thiazide diuretic, especially when the hypertension is complicated by other high-menace conditions like CKD (chronic kidney disease) and type 2 diabetes (Vidt et al., 2003; JNC 6th report 1997, Nicole et al., 2015).

According to the latest JNC 8 guidelines published on hypertension, the control of the systolic as well as diastolic blood pressure according to the age and the co morbidities associated with it. These recent guidelines emphasize on the secure use of the angiotensin receptor blockers (ARBs) and angiotensin converting enzyme inhibitors (ACEIs). There are some significant changes those have been made in JNC 8 guidelines in comparison to JNC 7 such as (Arief, et al., 2013).

- In case of patients of age ≥60 without any co morbidity like type 2 diabetes or CKD the blood pressure goal is <150/90 mmHg.

- The patients having age group 18-59 years without any co morbidity and the patients of age ≥60 with co morbidities like type 2 diabetes or CKD, the BP goal has become <140/90 mmHg.

- JNC 8 says the 1st line treatment of hypertension should be confined to only these four categories of drugs: Calcium channel blockers (CCBs), Thiazide diuretics, ACEIs and ARBs.

- 2nd and 3rd line treatments require including high doses or combination therapy of ARBs, ACEIs CCBs and thiazide type diuretics.

- The drugs like beta blockers, alpha blockers, centrally acting adrenergic agonists, direct as well as peripheral vasodilators, loop diuretics and aldosterone antagonists have been given the status of later-line drugs.

- Initial therapy for African without CKD should be CCB and thiazide diuretics instead of ACEIs.

- All the patients with CKD must be treated with ARBs and ACEIs either as 1st line therapy or addition to 1st line therapy despite their ethnic background.

- ARBs and ACEIs require not to be used on same patient as an additive therapy.

- Instead of ARBs or ACEIs the drug categories including CCBs & thiazide type diuretics are the 1st line drugs for the patients age >75 and having impaired kidney functions as there is risk of increased creatinine and hyperkalemia which additional deteriorate the renal function (Arief, et al., 2013). **(Fig. 2)**

Apart from the pharmacological treatment JNC 7 and JNC 8 guidelines it is suggested that the lifestyle changes play a crucial role in effective management of hypertension. These contains implementation of weight control measures, dietary Approaches to Stop Hypertension (DASH) eating plan, less salt intake and minimum 30 minutes of aerobic exercise daily by the patients. Additionally, limiting the alcohol intake and quitting the smoking also reduces the cardiovascular risk.

Prescribing Pattern Evaluation of Antihypertensive Drugs

According to a study conducted by Mohammad Arief and Harika B et al., it has found that the physicians prefer to prescribe monotherapy over the combination therapy and prils were the most frequently prescribed category in diabetic hypertensive patients as this class prevents the occurrence of other diabetic complications such as diabetic nephropathy, diabetic retinopathy & diabetic neuropathy. It has also seen that only two drug combinations were prescribed mostly and there were no three or four drug combination prescriptions thiazide diuretics were negligibly prescribed, it poses a financial burden on the patients (Shrivastav et al., 2018). ARBs were the most frequently prescribed class of antihypertensive together with their combinations along with diuretics. Further calcium channel blocker & angiotensin converting enzyme inhibitors followed by beta blocker (BB) and followed by its combination with calcium channel blocker were preferred. Most frequently used drug was olmesartan (ARB). In a study two drug combinations were used in 63 patients (30.28 %) and concluded that ARBs are the most preferred drug in hypertension (Shrivastav et al., 2018). Gupta et al states that with the increasing age, males become more prone to the development of hypertension than females. They concluded that CCBs as monotherapy are being most frequently prescribed drug treatment for hypertension. Also the diuretics found to be most commonly prescribed drug class in combination (Gupta et al., 2018).

Treatment patterns of antihypertensive medications in a study has shown that both mono-therapy and combination therapy of ACEI and CCB were the topmost priority of health clinicians. Diuretics were underutilized according to the findings of this study (Yazie et al., 2018). Kuchake et al. have found from their study that diuretics were least prescribed whereas CCBs were extensively prescribed. They also state that there is no scope of improvement in the prescription pattern of antihypertensive (Kuchake, et al., 2009). A study conducted by Rajeev Mishra et al. has revealed that calcium channel blockers were the most commonly prescribed drugs, followed by ACEIs and ARBs as a monotherapy. In CCBs, most commonly prescribed drug was amlodipine. Telmisartan was most commonly prescribed in ARBs. In associated risk factors and co morbid conditions, combination therapy was prescribed. Criteria for the selection of drugs according to the NICE guidelines should be kept in mind during prescription of antihypertensive drugs (Mishra et al., 2017).

Das et al. has shown that most of the hypertensive patients with type 2 diabetes require combination drug therapy to control it. According to the ADA or JNC recommendations, maximum number of patients were on ACEIs/ARBs. It also has been found that the 37% of patients achieved a good control on hypertension but diabetic patients had lesser chance to control this (Das et al., 2015). According to an another study Ang II (Angiotensin II) receptor blockers and calcium channel blockers were found to be the most commonly prescribed drugs either alone or as

combination therapy with other antihypertensive classes for efficient manage of BP in various co morbid conditions. In this case monotherapy was first approach than combination therapy. In addition to this, these two classes of drugs reduce the complications associated with hypertension. For patients with different compelling indications, trends in antihypertensive drugs prescribing were according to the JNC 7 recommendations (Rajasekhar *et al.*, 2016). A study concluded that majority of the clinicians (47%) considered the thiazide diuretics as first choice among various antihypertensive classes for the treatment of hypertension. ACEIs were the commonest used class as a single agent (55.7%) or in combination with other classes. The frequently used combinations were ACEIs/ thiazides, ACEI/ CCBs and CCBs/ thiazides (Ibrahim *et al.*, 2017).

In severe cases CCBs, especially amlodipine, followed by angiotensin receptor blocker, telmisartan was the top most prescribed combination therapy. Apart from this classes like ARBs (telmisartan) with diuretics such as hydrochlorothiazide were also prescribed. This prescribing pattern of antihypertensives followed the Joint National Committee 7 guidelines. Amlodipine as monotherapy designated to be the most frequently prescribed drug in case of geriatric population suffering from hypertension with type 2 diabetes mellitus. Among antihypertensive multidrug choices, Telmisartan along with Hydrochlorothiazide was found to be most preferable (Philip *et al.*, 2016).

Uncomplicated essential hypertension was treated with monotherapy of ARBs and CCBs as 1st choice among other antihypertensives followed by ACEIs. Age is the major factor that calculates the therapeutic administration i.e. young patient population compared adolescent population (20–40 years) was treated less aggressively while using monotherapy. Intensity of treatment depends on the other co morbidities and generally increases with the progression of these conditions. (Pyarelal *et al.*, 2015) It has been seen that again ARBs (58%) together with CCBs (50%), beta blockers (15%) and diuretics (14%) were most preferable classes among antihypertensives. From the total population 68% received monotherapy while remaining 32% received combination therapy. In this study they have found that JNC 7 guidelines were not followed accurately while prescribing the different antihypertensive drug categories (Kalamdani *et al.*, 2014).

Ethiraj dhanaraj et al., has found that ARBs and ACEI were the regularly prescribed drug categories. After these two classes, others like beta-blockers, diuretics and calcium channel blockers were followed, either as monotherapy or as poly therapy. This study included the patients those were on combination therapy. Among all, beta-blockers (14%) were least prescribed followed by diuretics (27%), CCBs (29%), ARBs (52%), and ACEIs (59%). However, prescribing pattern was following the evidence-based guidelines (Dhanaraj *et al.*, 2012). *Datta et al*. have found that the drug classes like thiazides & ACEI/ARB were used sub optimally. CCBs were the most prescribed antihypertensive class. Considering the monotherapy, amlodipine was found to be the most extensively prescribed antihypertensive. The classes like ACEI/ARBs were moderately prescribed and single drug therapy was preferred over multidrug therapy. According to the findings of this study, it was concluded that the prescribing practice in case of antihypertensive drugs, was

aligned with the standard guidelines for the proper treatment of hypertension (Datta *et al.*, 2016).

The prescribing pattern depicted in another study has revealed that diuretics were highly prescribed drug category. After this, the prescribing frequency for drugs like ARBs, BBs, CCBs and ACEI decreases when we move from ARBs to ACEI. However, proportion of the patients received monotherapy was higher than combination therapy and 41.6% received fix dose combination. In this study, antihypertensive were prescribed rationally according to the JNC guidelines (Bajaj *et al.*, 2012). However it has been seen that for the initial stage hypertension single therapy is being considered to be more beneficial including CCBs as 1st preference. Focussing on the multi-drug therapy, diuretics plus ARBs combination was preferred over others, which is also recommended by the JNC. Comparing with the monotherapy, a significant proportion of antihypertensive patients were on polytherapy (Rachana *et al.*, 2014). Further in the study conducted by *Amruth et al.*, it has demonstrated that the majority of antihypertensive population was treated with diuretics prescribed drugs of classes were diuretics chased by ARBs, CCBs, BB's and ACE-Inhibitors. In case of hypertensive patients without other co-morbidities like type II diabetes or CKD, ACEIs were 1st line of treatment. To moderate the cardiovascular complications in geriatric patients, CCBs along with diuretics were used (Amruth *et al.*, 2015). In the *Cidda et al*, demonstrations, ARBs was most commonly prescribed antihypertensive class. The trend in prescribing of antihypertensive drugs was satisfying the algorithm given in JNC-VII guidelines for hypertension (Cidda *et al.*, 2017).

In a study conducted at Andaman Nicobar Islands Institute of Medical Sciences (ANIIMS) it has been seen that combination therapy was preferred by the physicians of the ANIIMS for hypertension. Diuretics were the regularly prescribed antihypertensive drug as per the guidelines. Most of the physicians are well-known about the JNC 8 guidelines but were not admiring them as 7.1% prescriptions were irrational (Dinesh *et al.*, 2017). Study by Juno J. Joel et al. has revealed that CCBs were most extensively prescribed antihypertensive class hypertension. Drug combination of amlodipine and atenolol was maximally prescribed among combination drug therapies (Joel *et al.*, 2015).

Due to persistent clinical challenges in the management of hypertension, we still require additional care & monitoring of the treatment patterns. From the recent years, an ample of regulatory guidelines has come into practice which includes both monotherapy & combination therapy approaches according to the type & frequency of the disease. It has been seen that the treatment pattern across the different parts of world shows variations due to difference in clinical practices. For instance, in some cases diuretics are prescribed as initial treatment while in other areas the classes like ACEI/ ARBs/CCBs are preferred as monotherapy or combination therapy.

From the government aspect, it is necessary for the policy makers to consider management & treatment of hypertension as one of the national policy in order to prevent the mortality & morbidity in the population suffering from this lifestyle disorder. A rational approach toward this includes the proper compliance from the healthcare professionals in every clinical aspect like diagnosis,

treatment, monitoring & follow up therapy. Additionally the consideration of the regulatory guidelines by the prescribers while selecting, changing or maintaining the hypertensive therapy is also an integral part of the this strategy. In hypertensive patients, existence of various other comorbid conditions like diabetes, CKD and lipid disorders need to be carefully taken into account while putting any drug or therapy to their treatment plan for an effective control & management of this condition. It has been generally seen that despite availability of these noble guidelines, inconsistency exists in treatment approach which results in personalization of treatment according to the particular patient response & their characteristics. In various undeveloped countries like India, more rational & systematic clinical studies are required for accurate evaluation of the prescribing patterns of antihypertensive drugs (Jarari1 et al., 2015).

It has been seen that Malaysian healthcare professionals adhere to the prescribing guidelines up to a great extent in case of hypertensive patients without any complication but not in case of hypertensive with co-morbid conditions like diabetes. Hence, thiazide diuretics are required to be at the top of prescribing list because they are well tolerated and inexpensive. In addition to this a number of studies have claimed that thiazide diuretics also minimize the risk of cardiovascular events. Also, ACEI possess the cardio as well as Reno protective properties, thus they should be preferred over other conventional treatment options. For instance, perindopril, is a relatively more economical & efficient drug of this class which ought to be prescribed on regularly. However, the cost of hypertensive treatment with diuretics or beta blockers is more cost effective than the classes like ARBs/ACEI (Abdulameer et al., 2012). All across the world JNC 7 & 8 guidelines, South African standard treatment guidelines, essential medicine list & South African hypertension guidelines are being followed by the healthcare professionals for the diagnosis, maintenance & treatment of the hypertension. Initially, thiazide diuretics are still believed to be the most effective & reliable class for hypertension treatment and other drugs are added to the treatment as per the severity of the patient and clinical need (Schellack et al., 2015).

Conclusion

From the extensive studies enlisted in this article it has been found that the monotherapy in the treatment of hypertension included ACEI as first choice followed by ARB, CCB, Diuretics and BB for the treatment of hypertensive patients with or without other co-occurring conditions like diabetes or CKD. Multiple therapies used ARBs plus CCB as most preferred combination in the treatment of patients having hypertension along with other co morbidities. Likewise it has been concluded that in majority of the studies the prescribing trends of antihypertensive drugs was according to the JNC guidelines. However, JNC 8 recommendations were not being followed completely by the healthcare professionals.

Conflict of Interest

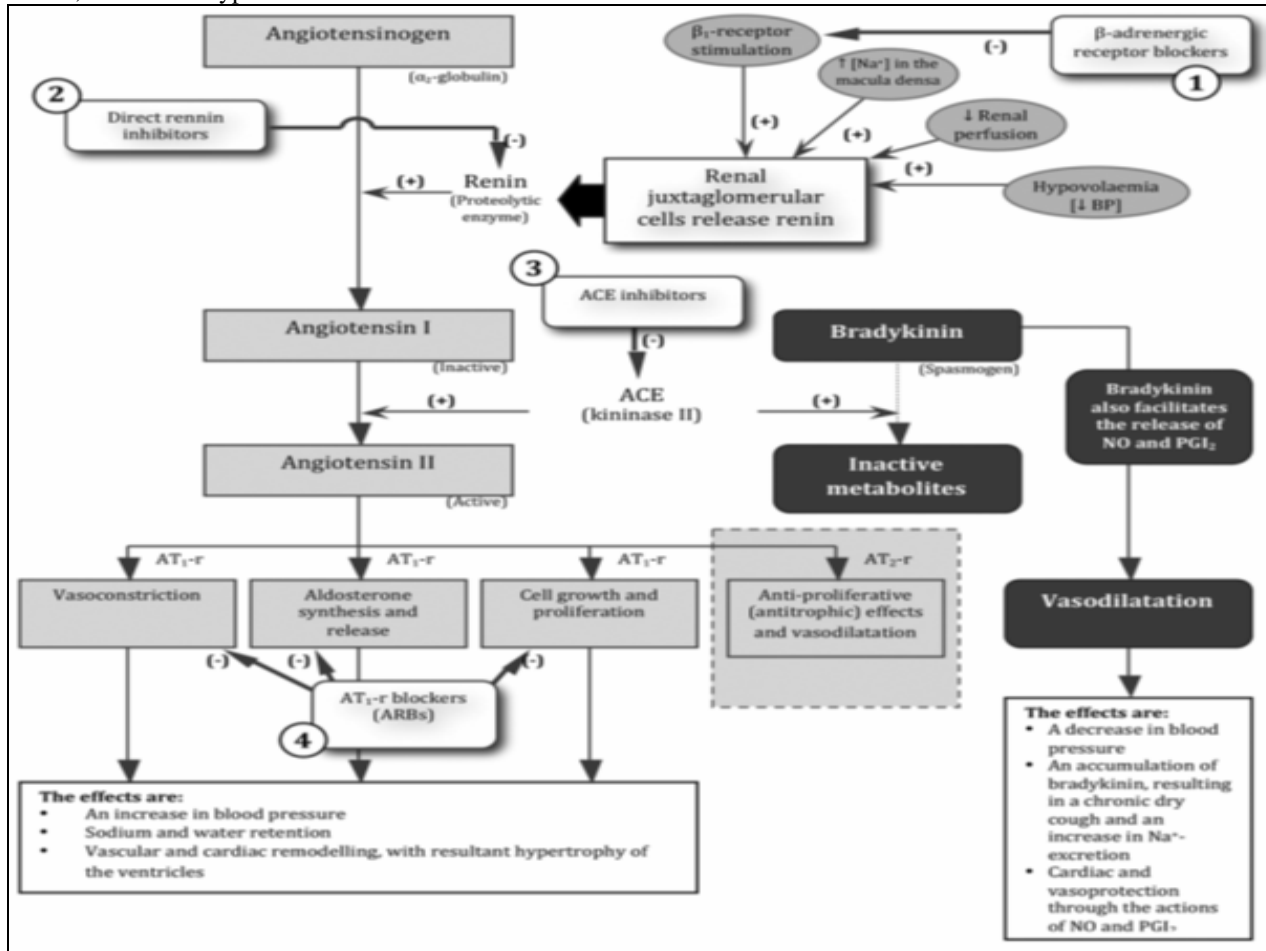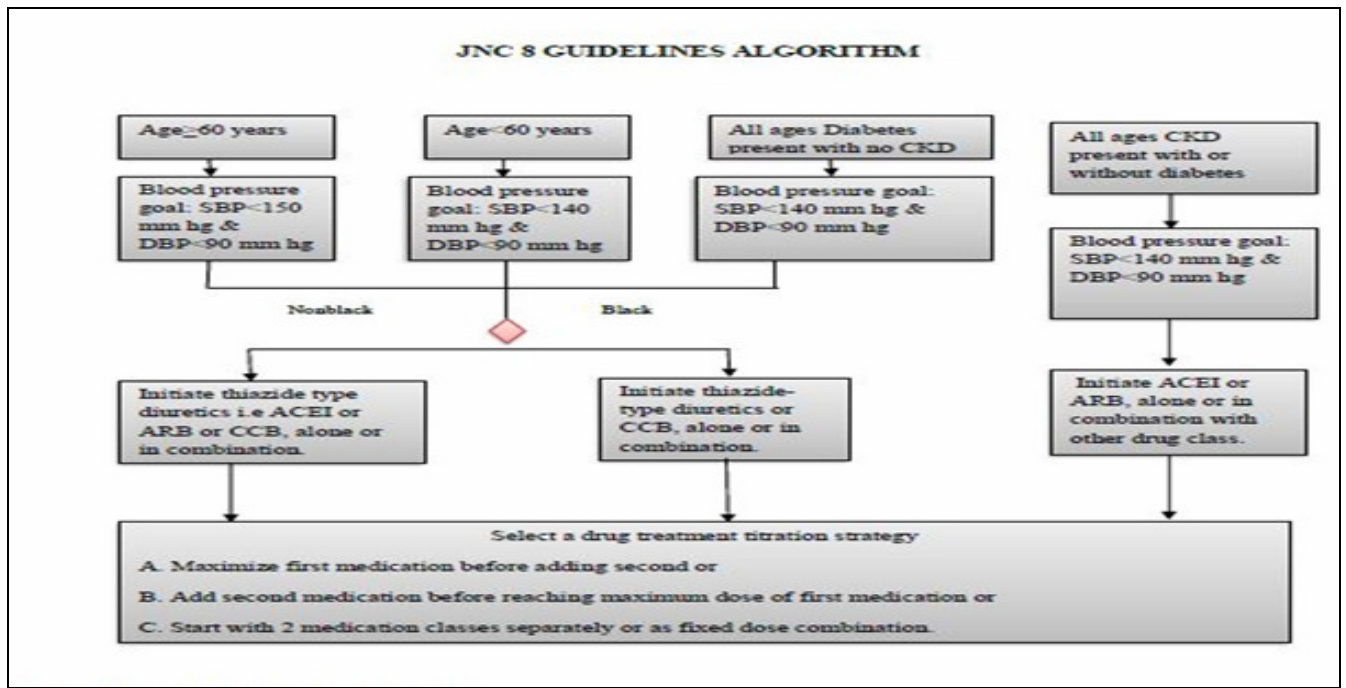The authors declare that they have no conflict of interests.

Fig. 2 : Guidelines by Joint National Committee on Treatment of hypertension.

JNC 8 GUIDELINES ALGORITHM

Table 1: Classification of Hypertension according to JNC 7 guidelines.

BP Classification	SBP MMHG	DBP MMHG	Lifestyle Modifications	Initial Drug Therapy	
				Without Complications	With Complications
Normal	<120	And <80	Encourage	No drug indicated for hypertension	Drugs for undeniable indications
Pre-hypertension	120-139	Or 80-89	Yes	Thiazide type diuretics for most. May consider ARB, ACEI, CCB, BB, or combination	Drugs for undeniable indications. Other antihypertensive drugs (ACEI, ARB, CCB, Diuretics, BB) as needed.
Stage 1 Hypertension	140-159	Or 90-99	Yes	Two drugs combination for mainly (Usually ARB or ACE or BB or CCB and thiazide type diuretics)	
Stage 2 Hypertension	≥160	Or ≥100	Yes		

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Figure Caption

Figure 1: ACE: angiotensin-converting enzyme, ARBs: angiotensin-receptor blockers, AT1-r: angiotensin II type 1 receptor, NO: nitric oxide, PGI2: prostacyclin. RAAS mechanism presenting the action of the angiotensin II -receptor blockers, β-adrenergic receptor blockers, the direct renin inhibitors and the ACEIs (Schellack *et al.,* 2015, Chobanian *et al.,* 2000).