

# Assessment of the effects of antihypertensive drugs in patients suffering from hypertension in Kurdistan

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## Abstract

**Background and objectives:** Hypertension is an important cardiovascular disease that carries a high rate of mortality and morbidity if not controlled. Significant complications of untreated hypertension include vascular atherosclerosis, chronic kidney diseases and heart failure. The aim of this retrospective study is to improve practitioners and specialists' practice in the management of hypertension in the Kurdistan region. This study assesses the response of our local patient population to different first line and combination therapies for hypertension to identify the most effective approach. **Methods:** This a retrospective study conducted on 500 patients diagnosed with hypertension consisting of equal numbers of males and females. The sample was randomly chosen using stratified random sampling methods where by patients were finally divided according to the drugs they were prescribed into 5 groups : renin-angiotensin-aldosterone system inhibitors , calcium channel blockers, Diuretics, renin-angiotensin-aldosterone system inhibitors + calcium channel blockers and renin-angiotensin-aldosterone system inhibitors+diuretics. The goal was to achieve a blood pressure of less than 140 mmHg systolic and less than 90 mmHg diastolic, which was maintained for 6 months. The data was inputted into SPSS as categorical variables and analyzed by Chi-square test. **Results:** All the drug groups were significantly effective in bringing the blood pressure to the goal. In relation to mono-therapy calcium channel blockers achieve the goal in (82%) and were the most effective drug group in controlling the blood pressure, whilst renin-angiotensin-aldosterone system inhibitors + calcium channel blockers achieve the goal in (85%) was the most powerful combination for controlling moderate to severe hypertension. All age groups were responding to treatment. **Conclusions:** All the drug groups tested either singly or in combination calcium channel blockers were best for monotherapy, whereas renin - angiotensin - aldosterone system inhibitors + calcium channel blockers were the best effective combination therapy.

**Keywords:** Blood pressure management; Hypertension; Antihypertensive; Kurdistan.

## Introduction

Hypertension (HTN) is defined as raised arterial blood pressure the systolic of 140 mmHg and more and the diastolic of 90 mmHg and more. Hypertension is an important independent risk factor for heart diseases such as coronary heart disease and heart failure; it is one of the main causes of chronic kidney diseases, and a risk factor for stroke especially hemorrhagic type<sup>1</sup>. HTN can be easily detected, and most cases have no underlying detectable cause (primary HTN); the most effective way to reduce the associated risk is to reduce the blood pressure (BP)<sup>2</sup>.

Blood pressure is classified in to the following classes<sup>3</sup>.

1. Normal: 120 mmHg systolic and 80 mmHg diastolic.
2. Prehypertension (120–139) mmHg systolic or (80–89) mmHg diastolic.
3. Stage 1 hypertension (140–159) mmHg systolic or (90–99) mmHg diastolic.
4. Stage 2 hypertension >160 mmHg systolic or >100 mmHg diastolic.

According to National Institute for health and Care Excellence (NICE) guideline HTN is of three

grades<sup>4</sup>. Grade 1 (mild): systolic 140-159- mmHg, diastolic 90-99- mmHg. Grade 2 (moderate): systolic 160-179- mmHg, diastolic 100-109- mmHg. Grade 3 (severe): systolic > or equal 180 mmHg, diastolic > or equal 110 mmHg. BP generally is measured and monitored by the healthcare system doctors or nurses in hospital outpatient departments and, increasingly, in primary care settings. BP can be measured by mercury sphygmomanometer, although electronic device with accurate measuring capacity have been introduced into use. Ambulatory BP monitoring is also being used more often to assess individual's blood pressures outside the clinical setting<sup>2</sup>. A randomized single blind study showed the effectiveness of using home BP monitoring combined with pharmacy care over the Websites learning to improve BP control for patients with essential hypertension<sup>5</sup>. The main idea behind achieving the goal of antihypertensive therapy is to reduce cardiovascular and renal morbidity and mortality, and this goal will be only achieved by control of both systolic and diastolic blood pressure down to the goal. The goal in most of the time and for most of cases is a BP of less 140 mmHg systolic and 90 mmHg diastolic; however, patients with chronic

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kidney diseases and diabetic patients needs more tightly control<sup>3</sup>. In spite of strong health systems, and great funds on management of HTN, the disease is still under diagnosed and under controlled. Furthermore, losses to follow up are high and are responsible for avoidable vascular deaths<sup>2</sup>. The goal levels are actually controversial in certain condition, so that now there is strong evidence to support that the BP goal for persons aged 60 years or older to a is less than 150/90 mm Hg, and hypertensive persons 30 through 59 years of age have 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 its recommended that a BP should be less than 140/90 mm Hg for those groups. The same thresholds and goals are recommended for hypertensive adults with diabetes or no diabetic chronic kidney disease (CKD) as for the general hypertensive population younger than 60 years<sup>6</sup>. There are strong evidences that lowering BP with several classes of drugs, including angiotensin converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), beta-blockers (BBs), calcium channel blockers (CCBs), and thiazide-type diuretics, will all reduce the complications of hypertension. The benefits of the drugs may extend beyond the BP control<sup>3</sup>. Most patients who have moderate and severe HTN will require two or more antihypertensive medications to achieve their BP goals. Addition of a second drug from a different class should be started when use of a one drug in adequate doses cannot achieve the BP goal. When BP exceeds the goal by 20/10 mmHg, two drugs should be used from the most beginning. Now there are two drugs or more which are available in one tablet, this can help in improving the compliance of the patient if ARBs or ACEI can be combined with CCBs or thiazides in different doses to offer a better control of BP<sup>7</sup>. The patient response to a specific drug group is variable, some literature referring to the racial factors affecting the response to antihypertensive drugs, so that it had been shown that Negroes are not responding as Caucasian to ACEI or ARBs<sup>3</sup>. Hydrochlorothiazide is the most commonly used diuretic for the treatment of hypertension and is both used alone and in combination. Thiazide like drugs as chlorthalidone can also be used as diuretic. Recent systematic review and meta-analysis showed that chlorthalidone was indeed superior to thiazide diuretics<sup>8</sup>. Seventh Joint National Committee (JNC 7) and JNC8 suggest to start the patients on thiazide diuretics as the first line of treatment, this is what European hypertension society is also suggesting, on the other hand NICE guide line suggest ACEI or ARBs for patients younger than 55 years provided to not to be Negro, while older patients and Negroes are treated with CCBs or thiazide diuretics<sup>3,6</sup>. ARBs are preferred over ACEI in black patients to be combined with CCBs when they have moderate to severe HTN<sup>7</sup>. Recent evidence supports that in high-

risk group as diabetics or those with chronic kidney diseases ACE inhibitors and ARBs appear to have particular benefits in these diseases and have been recommended in recent clinical practice guidelines<sup>9</sup>, so what could be the best first line treatment and combination treatment for patients of our locality that had hypertension?

### Patients and methods:

The study was retrospective type performed on recorded cases whom are collected from private clinic data base, all patients whom had been diagnosed as hypertensive and whom had no exclusion criteria were included in the study, the patients were from different regions of Iraqi Kurdistan, mainly from Erbil city. Patients recorded from January 2003 till February 2017 were regarded as the population of target, exclusion criteria includes patients failing follow up for any reason, patients with other co morbidities like DM, CKD, and vascular atherosclerotic diseases and patients who stopped the drug or the drug withdrawn because of intolerable adverse reactions. Total numbers of patient were 4200 of different age groups. All of them had been put on life style modification, dietary modification and different antihypertensive drugs (RASI, CCBs, or Thiazides) for cases with mild HTN, and (RASI+CCBs or RASI+Thiazide for moderate and severe HTN), of this population 1500 patients fitted the inclusion criteria. The RASI which were used are Lisinopril in 10 mg daily dose, Valsartan 160 mg daily, Irbesartan 300 mg daily, Candesartan 16 mg daily, Olmesartan 40 mg daily, and Telmisartan 80 mg daily, those received Lisinopril were changed to the ARB type once they developed side effects which was mainly dry cough. The CCBs used by the patients was mainly amlodipine in 5 mg daily dose in the majority of cases, and slow release nifedipine in 20 mg daily dose. The diuretic drugs used were mainly hydrochlorothiazide in 50 mg combined with amiloride hydrochloride 5 mg, in majority of cases or thiazide like drug chlorthalidone 25 mg daily in fewer cases. The combination drugs were Any RASI with 12.5 mg hydrochlorothiazide, or valsartan, olmesartan or telmisartan with 5 mg amlodipine. The 1500 patients were divided in to two main strata according to the gender (700 female patients and 800 male patients), each stratum subdivided in to five groups according to the drug which was used (RASI which includes ARBs and ACEIs), CCBs, diuretics, RASI+CCBs and RASI+Thiazide. The female group were divided to RASI (130), CCBs (135), Diuretics (130), RASI+CCBs (170) and RASI+Thiazide (135) and the male group were divided into RASI (120), CCBs (150), Diuretics (130), RASI+CCBs (200) and RASI+Diuretics (170) From each subgroup and by simple random sampling after putting a code for every case using excel program 50 samples taken, so the groups were as follows:

1. Patients using RASI (50 male and 50 female).

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2. Patients using CCBs (50 male and 50 female).
3. Patients using Thiazide diuretics (50 male and 50 female).
4. Patients using combination of RASI and CCBs (50 male and 50 female).
5. Patients using combination of RASI and thiazide (50 male and 50 female).

The total number of the sample was 500 patients included in to the study. The patients distributed according to age limits in to age class intervals, patients receiving mono-therapy were divided according to age in to those with younger than 55-years and older than 55 years old, these two groups analyzed separately for the most effective drug<sup>7</sup>. Diagnosis of HTN was done by estimation of patients BP in sitting position in both right and left upper limb, by using mercury sphygmomanometer with appropriate cuff sizes, on two different occasions<sup>1, 9</sup>. Follow up done by estimation of left arm (the normal values are for right arm & left arm

BP is normally 10 mmHg higher) BP in sitting position<sup>2, 5</sup>. All patients studied followed up for minimum of 6 months. Any patient with BP of 140 mmHg systolic or more and diastolic of 90 mmHg or more on 2 occasion were regarded as hypertensive. According to BP patients classified into those with mild HTN for whom mono-therapy were started and moderate to severe HTN for whom combination treatment were started<sup>2, 10</sup>. The patients were monthly followed up for 6 months, and BP was recorded on every follow up. Goal definition was BP of less than 140 mmHg systolic and less than 90 mmHg diastolic. The data were inserted in to SPSS program version 10 as categorical variables, the data were presented as bar charts and Chi-square test was used for data analysis, the significance level put at alpha of  $\leq 0.05$ .

### Results

This graph figure 1 shows that all age distributions have been exposed to all drug types, and the differences among them are statistically quite not significant

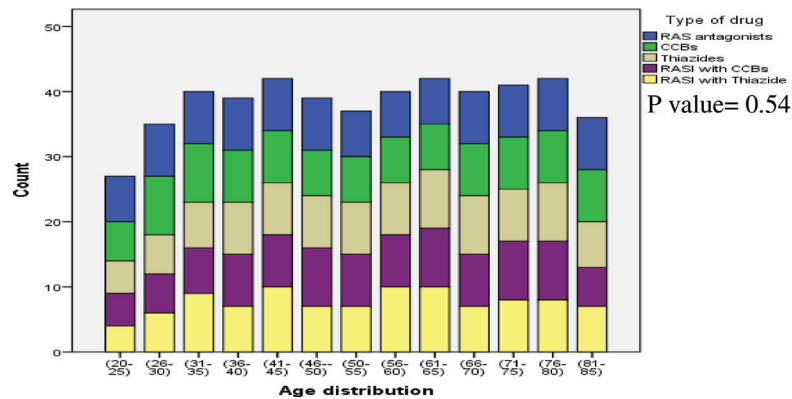


Figure (1): Age distribution of patients receiving different drug types.

This graph shows that all drug types in all age groups are effectively bringing the BP to the target, in age group (46-50) years 50% of them were brought to the target, the differences among the groups are statistically not significant.

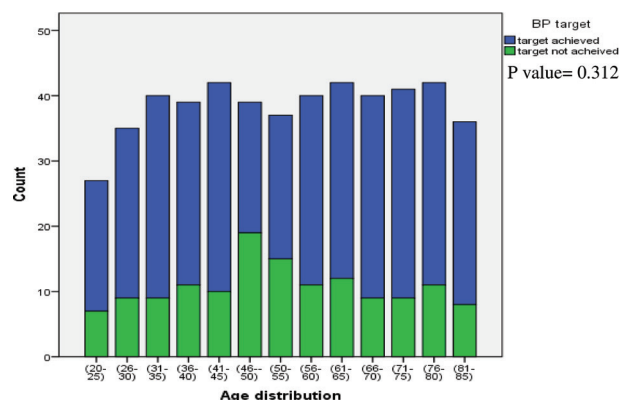


Figure (2): Age distribution among the treatment groups .

All the drug groups are effectively bringing the BP to goal (RASI 61%, CCBs 82%, Thiazide 63%, RASI+CCBs 85% and RASI+thiazide 69%), and the result is significant as shown in this graph

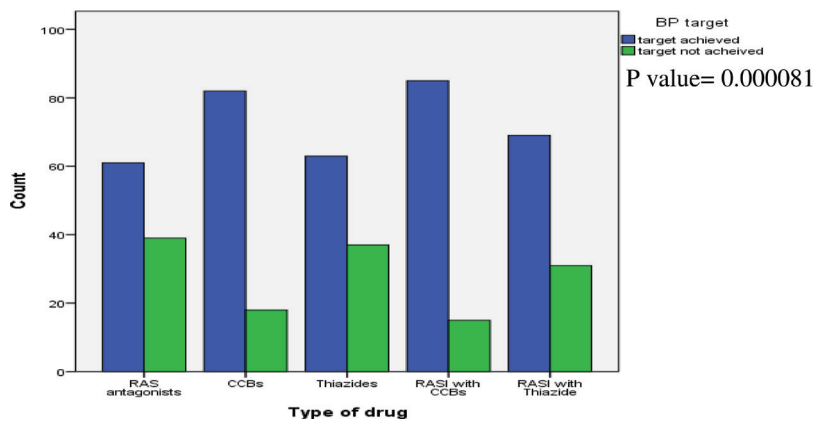


Figure (3): Goal achievement distribution according to the drugs groups.

This graph shows that as mono-therapy CCBs are the most effective antihypertensive in bringing patients to target BP (82% achieved), among the drug groups with highly significant difference. The second effective drug group is diuretics (63% achieved) followed by RASI (61% achieved).

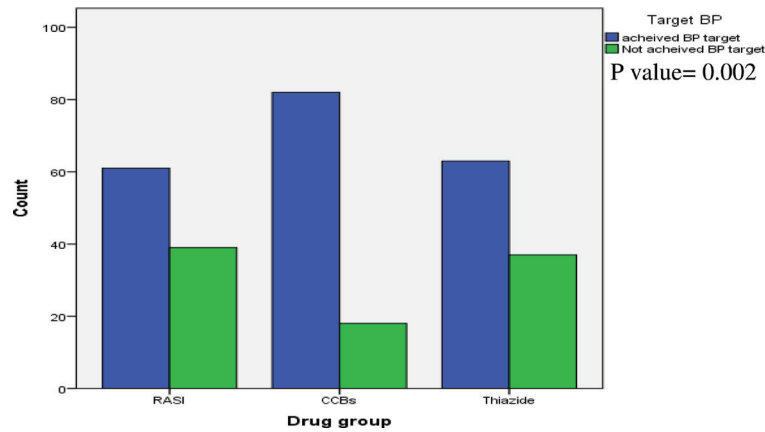


Figure (4): Target blood pressure achievement in patients receiving mono-therapy.

This graph shows that still CCBs are the most effective antihypertensive drug as mono-therapy in bringing BP to goal in patients with 55 year old and younger (80% controlled), compared with RASI (60% controlled ) and diuretics (56% controlled ), the difference is statistically significant. It's noticed that RASI are more effective than diuretics in these group of patients.

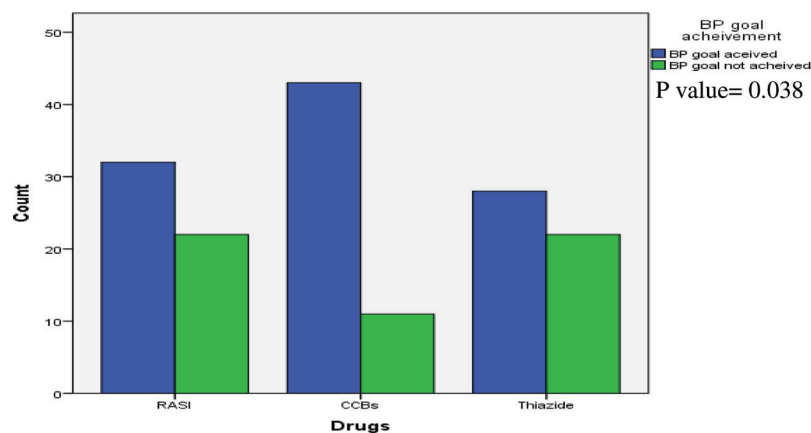


Figure (5): Goal achievement distribution in patients of 55 year old and younger receiving mono-therapy.

Its seen that the most effective combination drugs in bringing BP to target in patients with moderate to severe hypertension is RASI with CCBs (85% of cases controlled) compared with RASI+diuretics (69% controlled ), the difference was significant.

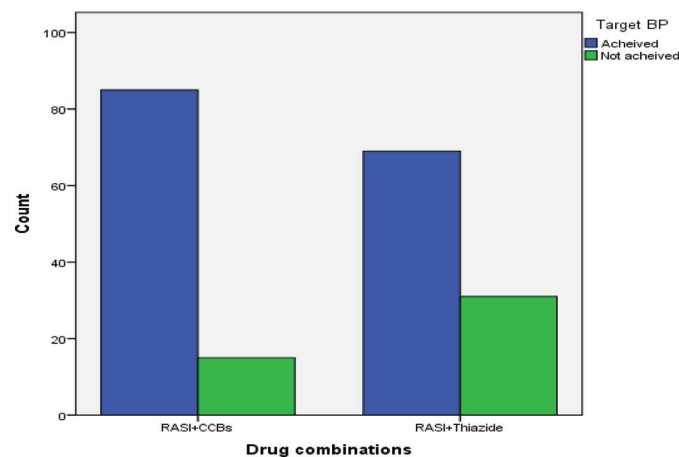


Figure (6): Target blood pressure achievement distribution in patients receiving combination therapy.

This graph demonstrates that RASI is slightly more effective in bringing BP to goal in patients of 55 year old and younger (60%) compared with older patients (59%), but the difference is quite not significant.

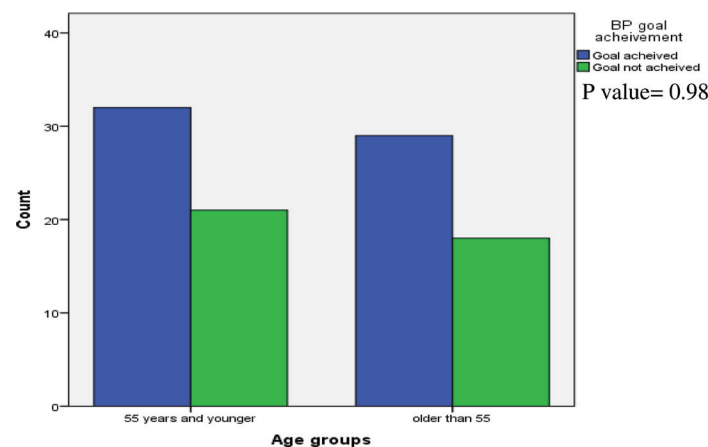


Figure (7): Distribution of target blood pressure achievement in patients of 55 year and younger and patients older than 55 years who received RASI.

### Discussion

Hypertension as a disease carries life threatening complications especially cardiovascular if not properly managed, in the current time the treatment is mainly targeting the BP as a number to bring it bellow 140 mmHg systolic and 90 mmHg diastolic in most of the patients, to achieve this goal many drugs are present, their efficacy is studied widely by many trials, these trial even showed some benefits of some of these drugs beyond BP control, as well as showed some racial factors affecting the response to RASI group of medications<sup>3,5,9</sup>. In our locality, no big trials have been conducted to assess the response of Kurdish patients to different classes of antihypertensive drugs. 500 patients belonging to different age groups (20–85) years have been exposed to three main class of antihypertensive drugs (RASI, CCBs, Thiazide and thiazide like diuretics) as mono-therapy and two commonly used combination therapy (RASI+CCBs and RASI+Thiazide), there

were no significant differences among all age groups exposure to all types of drugs, this can eliminate the effect of age from each group. So the sampling method was stratified sampling that can ensure equal gender participation to exclude any gender effect on the response to different class of drugs.

It's found that all the mono-therapy and combinations are effective in achieving the target BP, in all age groups, although in age group (46–50) years only 50% of patients were brought to control, there were no significant differences between the groups, and there is well known fact in HTN control that 50% of hypertensive patients receiving treatment are controlled (Role of 50 in HTN)<sup>6</sup>, in all the other groups more than 50% of the patients were controlled. All the drug groups in this study were highly significantly and effectively able to control the BP, as mono-therapy CCBs were significantly more effective in controlling the BP, followed by diuretics and RASI. This finding goes with that observed in

many big trials, the VALUE trial reported that the ARB valsartan was not superior to amlodipine in a head-to-head trial, with hydrochlorothiazide added as a second step if needed, the trial showed that CCBs (amlodipine) was superior in controlling the BP, however the RASI (valsartan) was superior in improving the outcome, on the other hand ALLHAT trial showed that diuretics can improve the outcome as RASI and CCBs can do, diuretics may be more effective and since they are more cost effective they should be the first line treatment. ASCOT trial showed that CCBs are more effective in black patients with hypertension, in SYS-EUR trial Treatment initially with nitrendipine (CCB) reduces stroke and cardiovascular events, SHEP trial showed that clothaldione (diuretic) can reduce cardiovascular events but increases the incidence of diabetes mellitus, PROGRESS trial showed that ACEI reduces future strokes, and when indapamide (diuretic) was added further reduction was recorded. So it appears that choosing the first line treatment is controversial, if the BP level is concerned CCBs are more effective, on the other hand if the other benefits of the drugs beyond BP control (pleotropic effect) is concerned RASI look to be more effective<sup>8,11</sup>. In patients of 55 year old and younger CCBs significantly remained the most potent antihypertensive in controlling the BP, followed by RASI and diuretics, the preferred antihypertensive treatment in younger patients are still CCBs<sup>12</sup>, however NICE guideline supports the idea of using RASI inhibitor in patients younger than 55 years, since the role of rennin-angiotensin-aldosterone system in BP elevation compromises with aging<sup>7</sup>, in the current study it was found that RASI are slightly more effective in patients of 55 years old and younger but the difference was not significant at all. ASCOT showed that there are some racial factors affecting the response of patients to RASI as mono-therapy it showed that RASI are less effective in black patients with HTN, in the current study it was shown that RASI are an effective drug in controlling mild HTN<sup>13</sup>. The most effective combination therapy of moderate to severe HTN was found to be RASI+CCBs; they significantly controlled the BP level, compared with RASI+thiazide, ACCOMPLISH trial showed that CCBs+RASI are superior to CCBs+Diuretics in bringing BP to the goal in patients with moderate to severe HTN<sup>11-13</sup>.

### Conclusions

All the drug groups (RASI, CCBs and diuretics) with their combinations are effective in controlling BP in Kurdish patients. As mono-therapy, CCBs are the most powerful drug group in bringing BP to the goal in all age groups. RASI+CCBs are the most effective combination therapy for moderate to severe HTN. It is recommended to perform study on these antihypertensive in patients with co morbidities to assess their efficacy. Longer follow up studies are recommended on the antihypertensive drugs to assess

their pleotropic effects.

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