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To Cite:
Alakhali KM, Alshami AS, Al-dahbali AA, Mohammed SFK. Prescribing pattern of antihypertensive agents in patients with Type 2 Diabetes patients visiting governmental hospital in Yemen capital city, Sana'a. *Drug Discovery* 2024; 18: e13dd1985
doi: https://doi.org/10.54905/dissi.v18i41.e13dd1985

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Peer-Review History
Received: 12 March 2024
Reviewed & Revised: 16/March/2024 to 20/May/2024
Accepted: 23 May 2024
Published: 27 May 2024

Peer-Review Model
External peer-review was done through double-blind method.

Drug Discovery
pISSN 2278–540X; eISSN 2278–5396

DISCOVERY SCIENTIFIC SOCIETY

Prescribing pattern of antihypertensive agents in patients with Type 2 Diabetes patients visiting governmental hospital in Yemen capital city, Sana'a

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ABSTRACT

Background: The prevalence of hypertension has been observed to be high among individuals diagnosed with type 2 diabetes mellitus. Furthermore, the coexistence of both illnesses has been linked to an elevated susceptibility to cardiovascular problems. Hence, it is imperative to ensure adequate blood pressure regulation using suitable antihypertensive medication. This study aims to evaluate the prescription patterns of antihypertensive medicines among patients diagnosed with Type 2 diabetes mellitus in the capital city of Yemen, Sana'a. *Method:* A two-month prospective study was undertaken in Sudanese government hospitals. We obtained the antihypertensive prescriptions from patients receiving care at the outpatient department of general medicine. The study excluded pregnant women, non-diabetic patients, and patients under the age of 35. *Results:* In terms of prescription frequency, the rennin angiotensin-aldosterone system (ACE-I/ARBS) was the most commonly prescribed medication (48%), followed by beta-blockers (41%), calcium channel blockers (5.4%), and thiazide diuretics (5.4%), regardless of whether they were used alone or in combination. Because our patients had cardiovascular problems, combination therapy was more prevalent than monotherapy (87.3% vs. 12.7%). Lisinopril was widely utilized. Furthermore, the study frequently employed ARBs, which are advantageous for patients with both hypertension and diabetes mellitus. It is advisable to utilize ACEI or ARBs as the initial treatment option due to their renal protective impact. *Conclusion:* The prescribing pattern adhered to the JNC 8 guideline, which is an international standard. The use of the RAAS system as a first-line agent is advocated due to its demonstrated efficacy in kidney protection.

Keywords: Hypertension, diabetes, antihypertensive drugs, governmental hospitals, anti-diabetics

1. INTRODUCTION

Diabetes and hypertension are significant challenges in the field of global health (Wild et al., 2004). The World Health Organization estimates that by 2025, diabetes will affect around 300 million individuals, while hypertension will affect 1.5 billion people (Kearney et al., 2005). The primary risk factors for cardiovascular problems are hypertension and diabetes mellitus (El-Hazmi and Warsy, 2001). Hence, it is critical to consider blood pressure management in conjunction with other concurrent cardiovascular risk factors. The prevalence of hypertension (HTN) is significant, and the prescription of antihypertensive medications is on the rise, increasingly associated with comorbidities like diabetes, hypercholesterolemia, and cardiovascular disease. Diabetes mellitus (DM) and hypertension (HTN) frequently co-occur, with a higher prevalence in older individuals.

Hypertension is about twice as prevalent in those with DM as it is in those without (8%) (McInnis et al., 2008). Nevertheless, research regularly shows that the majority of diabetic patients fail to attain the recommended levels of blood pressure regulation, with the majority having a blood pressure reading exceeding 140/90 mmHg (Berlowitz et al., 2003). If ACE-I is not well tolerated, the Hypertension Management Guidelines suggest using either an ACE-I or an ARB. If blood pressure targets are not met, it is recommended to administer a thiazide diuretic to individuals with a glomerular filtration rate (eGFR) of more than 30 or a loop diuretic to those with an estimated GOF FR of less than 30. Several studies have shown evidence of the advantageous impacts of beta blockers and calcium channel blockers in individuals with diabetes and hypertension.

2. MATERIALS AND METHODS

Study design

A cross-sectional survey design was utilized in this research study, which was conducted at the government Hospital in Sanaa, Yemen, from September 1, 2022, to November 30, 2022.

Sampling Size

We conducted this study on patients who visited a government hospital in Yemen, specifically examining the incidence of prescribing patterns for antihypertensive agents among patients diagnosed with type 2 diabetes. The study included a cohort of 110 individuals diagnosed with both hypertension and type 2 diabetes mellitus.

Study Instrument and Data Collection

We conducted a prospective cross-sectional study to collect data. Furthermore, the data for this study were obtained using a snowball nonrandom sampling technique until the desired sample size was achieved. Furthermore, the data that has been gathered encompasses many demographic factors such as age, gender, nationality, weight, marital status, the existence of additional co-morbidities, and the prescribed medication for hypertension and diabetes mellitus, including the prescribed dosage, frequency, and form. Individuals without hypertension and diabetes under the age of 35 are excluded from the study. The study required written consent from all participants and guaranteed the protection of their identities.

The survey comprised four sections: demographics, prescription single agent pattern, and antihypertensive drug combination pattern. The demographic segment examined variables such as age, gender, nationality, body weight, and marital status. The second segment examines the pattern of prescribed single agents, consisting of four questions designed to assess participants' awareness of antihypertensive agents. The third part of the study focuses on the pattern of usage of antihypertensive drug combinations, specifically highlighting the combination of anti-diabetic drugs. For example, the use of metformin combined with glibenclamide and metformin sitagliptin medications, as well as the existence, frequency, and duration of antihypertensive groups throughout the last two-month period, might be examined.

Ethical Considerations

The present study received approval from the Ethics Regional Committee of Lebanon International University in Yemen, as well as from the management of the community pharmacies (REC#2022-07-85). Additionally, we provided comprehensive information to all participants and obtained their written informed consent prior to their involvement in the study.

Statistical Analysis

The analysis of the data was conducted utilizing Microsoft Excel. We represented continuous variables as the mean (standard deviation), and categorical variables as the frequency.

3. RESULTS

The study included a total of 110 individuals, all of them had a predominance of 15 years or more and were diagnosed with hypertension and type 2 diabetes mellitus. The majority of participants (66%) were male (Table 1).

Table 1 Frequencies of gender.

Gender	No. of Sample	Sample (%)
Male	73	66
Female	37	34
Total	110	100

Table 2 and Figure 2 reveal that the average age of the study's patients was 61 years. Additionally, a majority of the patients (58%) fell within the age range of 56 to 65 years. There was a range of ages among the patients, with the majority (33%) being males between the ages of 56 and 65. The data indicates that 20% of the respondents were female. Additionally, an equal percentage of respondents (2%) between the ages of 35 and 45 reported using antihypertensive drugs. Among males aged 46–55, 14% claimed to use medicinal agents, compared to 8% for females. However, less than 5% of participants aged 75 years and older reported using antihypertensive medication. None of the females in the same age group reported using any medications.

Table 2 Frequencies of antihypertensive agent across age groups.

Age group	Male	Female	Total
35 years to 45 years	2 (2%)	2 (2%)	4 (4%)
46 years to 55 years	15 (14%)	9 (8%)	24 (22%)
56 years to 65 years	36 (33%)	22 (20%)	58 (53%)
66 years to 75 years	15 (14%)	4 (4%)	19 (18%)
>75 years	5 (5%)	0	5 (5%)
Total	73 (68%)	37 (34%)	110 (102%)*

*It added up to more than 100% because of approximation.

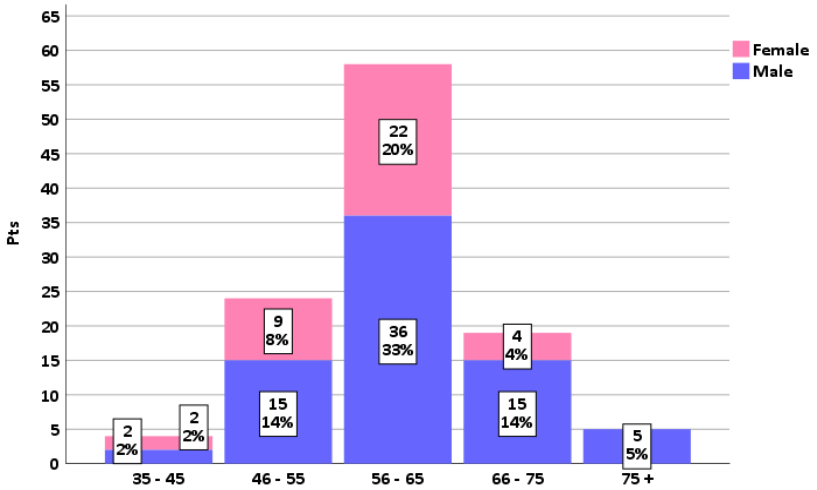

Figure 2 Frequencies of antihypertensive agent across age groups

The results of this study indicate a statistically significant disparity in the treatment of hypertension between male and female participants in the antihypertensive groups. A significant proportion of patients, particularly males, exhibit a preference for the administration of angiotensin-converting enzyme inhibitors (ACE inhibitors) as their initial therapeutic approach. Furthermore, Table 3 and Figure 3 indicate that an equal proportion of individuals of both genders utilize calcium channel blockers.

Table 3 Statistics of antihypertensive groups across gender.

S. No	Antihypertensive Agents	No. Male	No. Female	Total
1	ACE-I/ARBs	72 (33%)	34 (15%)	106 (48%)
2	β-Blockers	62 (28%)	28 (13%)	90 (41%)
3	CCB	6 (3%)	6 (3%)	12 (6%)
4	Thiazide diuretic	9 (4%)	3 (1%)	12 (5%)
	Total	149 (68%)	71 (32%)	220 (100%)

[Angiotensin Converting Enzyme Inhibitors (ACE-I), Angiotensin Receptor Blockers(ARBs), Beta Blockers (β- Blockers), Calcium channel blockers (CCB)].

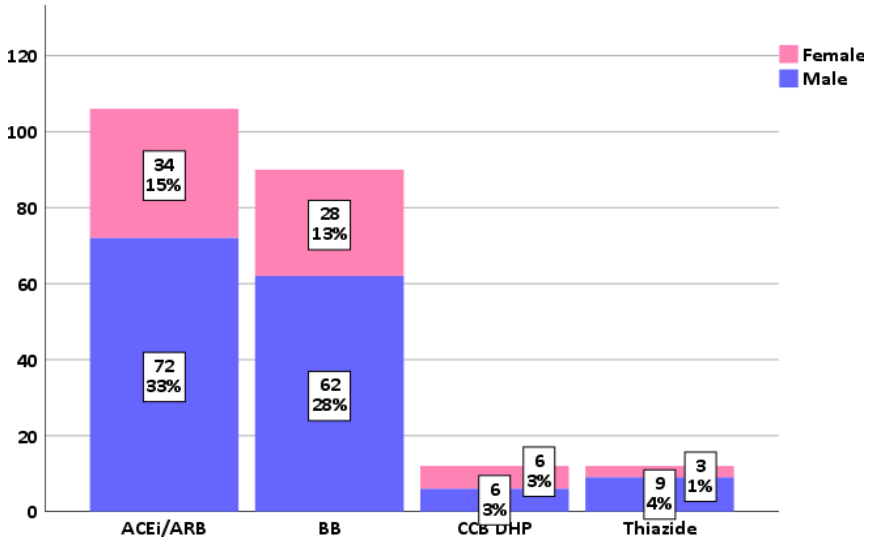

Figure 3 Statistics of antihypertensive groups across gender.

The frequency and percentage of prescription medicines for angiotensin-converting enzyme inhibitors (ACE-I) and angiotensin receptor blockers (ARBs) are described in (Table 4 and Figure 4). ARBs serve as options in cases where ACE-I inhibitors are not well-tolerated. Among ACE-I medications, lisinopril was the most commonly prescribed, accounting for 71 (93%), whereas losartan was the most commonly prescribed drug among ARBs, accounting for 27 (90%). Subsequently, treatment with beta-blockers (BB) was suggested. Bisoprolol had the highest prescription rate, recorded at 86%. Furthermore, a majority of the respondents exhibit a preference for beta-blocker medications over angiotensin-converting enzyme inhibitors.

In contrast, calcium channel blockers (CCB) and thiazide diuretics exhibited the lowest rates of prescription, with each medication accounting for a mere 5.4% of prescriptions. The only medication prescribed by the CCB was amlodipine, while the only medication prescribed by the diuretic was hydrochlorothiazide. Furthermore, a significant disparity was observed between lisinopril and ramipril in terms of their efficacy as medications for hypertension. Furthermore, a majority of the individuals who responded to the treatment expressed a preference for beta-blocker treatments over angiotensin-converting enzyme inhibitors. On the contrary, the lowest proportion of participants employed thiazide diuretics.

Table 4 Frequencies and percentages of antihypertensive agents

S. No	AntihypertensiveClass	Drug	Number of Prescriptions	Percentage %
1	ACE-inhibitor	Lisinopril	71	93
		Ramipril	5	7
Total			76	100
2	ARBs	Losartan	27	90
		Candesartan	2	7
		Valsartan	1	3
Total			30	100
3	β-Blockers	Bisoprolol	77	86
		Carvedilol	13	14
Total			90	100
4	CCB	Amlodipine	12	100
Total			12	100
5	Thaizaidediuretic	Hydrochlorothiazide	12	100
Total			12	100
Total No. of prescriptions			220	100

[Angiotensin Converting Enzyme Inhibitors (ACE-I), Angiotensin Receptor Blockers(ARBs), Beta Blockers(β-Blockers), Calcium channel blockers (CCB)].

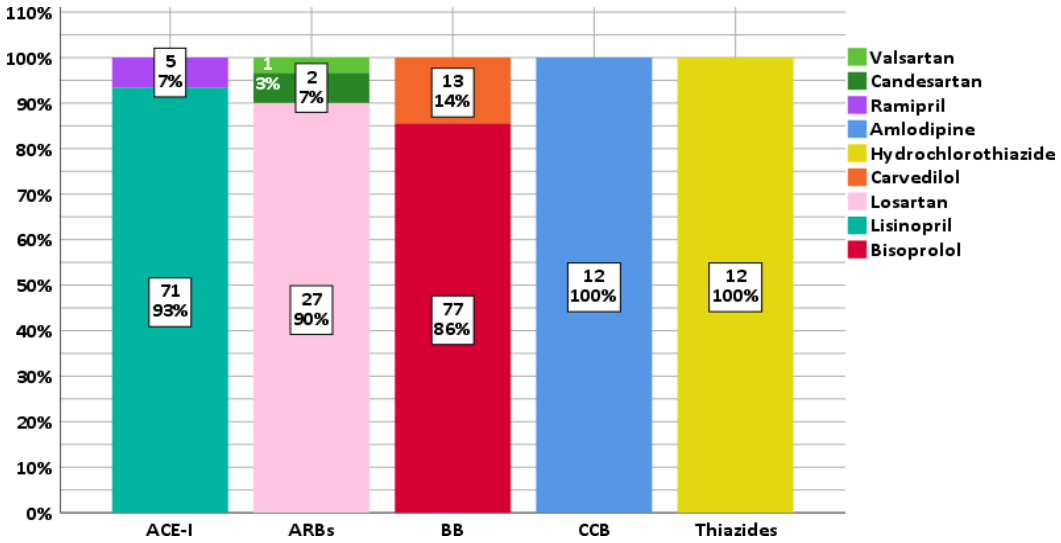

Figure 4 Frequencies and percentages of antihypertensive agents.

Table 5 presents the frequencies and percentages of antihypertensive groups, as well as the number of patients who utilized the class of monotherapy. The data shows that of the 14 patients undergoing monotherapy for hypertension treatment, 11 (10%) received ACE-I prescriptions, while 3 (2.7%) received ARB prescriptions.

Table 5 Frequencies and percentages of antihypertensive groups (n=14,12.7%).

S. No	Antihypertensive Class	Number of prescriptions	Percentage
1	ACE-I	11	79
2	ARBs	3	21

[Angiotensin Converting Enzyme Inhibitors (ACE-I), Angiotensin Receptor Blockers (ARBs)].

Table 6 & Figure 5 illustrates the distribution of antihypertensive drug combinations, emphasizing the importance of patients with a two-drug combination compared to those with a three-drug combination. We found ACE-I+ B-blockers to be the most effective combination for treating hypertension, followed by ARBs and B-blockers. However, only a small proportion of the respondents utilized a combination of ARBs and diuretics, whereas the combination of ARBs, B-blockers, and diuretics was the most common among patients who underwent triple therapy. Only 1% of the patients employed a combination of four drugs.

Table 6 Pattern of use of antihypertensive drug combinations (n=96,87.3%).

Drug combination	No of prescriptions	Percentage
2 Drug combination	n=83	75.4
ACE-I + β-Blockers	59	71
ARBs + β-Blockers	15	18
β-Blockers + CCB	4	5
ACE-I + CCB	3	3.6
ARBs + diuretics	2	2.4
3 Drug combination	n=12	10.9
ARBs + β-Blockers + diuretics	8	67
ACE-I + β-Blockers + CCB	3	25
ARBs + CCB + diuretics	1	8
4 Drug combination	n=1	1%
ACE-I + β-Blockers + CCB + Diuretics	1	100

[Angiotensin Converting Enzyme Inhibitors (ACE-I), Angiotensin Receptor Blockers(ARBs), Beta Blockers(β-Blockers), Calcium channel blockers (CCB)]

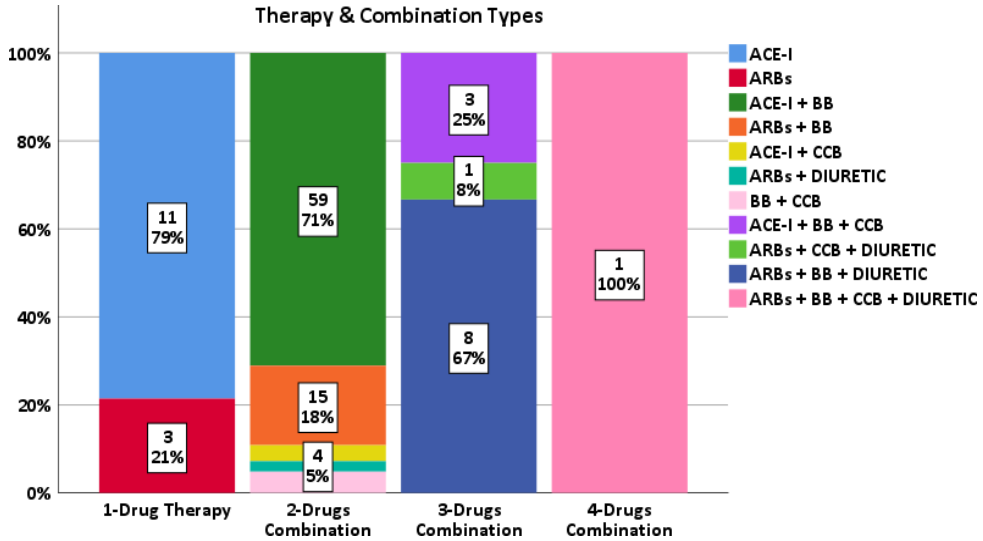

Figure 5 Frequencies and percentages of antihypertensive groups

Table 7, along with Figure 6, summarize the description of anti-diabetic medicines. This study included all participants diagnosed with type 2 diabetes mellitus. Metformin, either alone or in combination, is the most frequently prescribed medication for diabetic patients with hypertension. Patients administered single drugs to nearly half (46.4%), metformin to 47.5%, and a combination of insulin to 44.3%. We observed that an equal number of patients used Sitagliptin Glibenclamide. Additionally, the smallest proportion of patients (1%) utilized empagliflozin.

Table 7 Pattern of prescribed single agent for DM (n=61, 55%).

S. No	Name of drug	Number of prescriptions	Percentage
1	Metformin	29	18
2	Mixture insulin	27	19
3	Glimepiride	2	1
4	Sitagliptin	1	1
5	Glibenclamide	1	1
6	Empagliflozin	1	1

Table 8 and Figure 6 show that a total of 49 patients received two antidiabetic medications. Out of the responses, 33 individuals (44.5%) were using a combination of metformin and glibenclamide, followed by metformin and sitagliptin. However, only a small number of patients were using metformin and a mixture of insulin as a dual therapy. Additionally, due to complications, 30% of the patients used insulin as a monotherapy.

Table 8 Pattern of use of antidiabetic drug combinations (n=49, 44.5%).

Drug combination	No of prescriptions	% Of total prescriptions
2 Drug combination	n=49	44.5%
Metformin + Glibenclamide	33	21
Metformin + Sitagliptin	10	6
Metformin + Glimepiride	3	2
Metformin + Mixture insulin	3	2

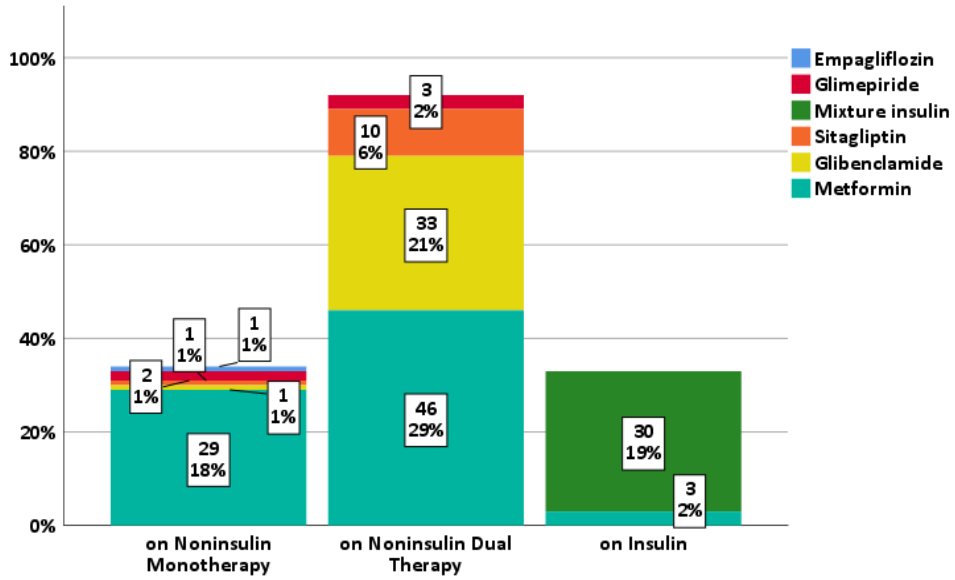

Figure 6 Pattern of use of antidiabetic drug combinations

4. DISCUSSION

The demographic data of our patients revealed a higher proportion of males (66% vs. 34%) than females. This finding can be attributed to the fact that the hospital where the data was gathered primarily offered health insurance coverage for males. Moreover, research has shown that regardless of nationality and ethnicity, the occurrence of hypertension is more common in males compared to females

(Sandberg and Ji, 2012). Furthermore, the age group of 55–65 exhibited the highest prevalence of hypertension among both males and females, accounting for a total percentage of 53%. Lionakis et al., (2012) reported results that align with this observation. The study found that the Renin-Angiotensin-Aldosterone System (RAAS), specifically ACEI or ARBs, was the most common type of medication prescribed, making up 48% of all prescriptions.

Whether administered as monotherapy or in combination, beta blockers followed at 41%, CCB at 5.4%, and thiazide diuretics at 5.4%. The study frequently employed ACE-I and ARBs, aligning with the JNC-8 guidelines. These guidelines recommend using ACEI or ARBs as the initial treatment option for patients with both hypertension and diabetes mellitus due to their renal protective properties. This recommendation is further supported by the United Kingdom Prospective Study Group (UK Prospective Diabetes Study Group, 1998). Furthermore, Lisinopril was the most commonly prescribed drug among ACE-I medications, accounting for 93% of prescriptions, whereas ramipril had a prescription rate of 7%. Multiple studies have demonstrated that ramipril has a greater impact on safeguarding the heart and kidneys in people with diabetes compared to other antihypertensive medications (Lancet, 2000).

Our study may have observed an increase in lisinopril prescriptions due to the medication's unaffected absorption during meals. Furthermore, since all patients receive the same generic medication, effective promotion of lisinopril plays a crucial role in its utilization. In addition, our study revealed that the proportion of men who utilized ACE-I was greater than that of women. The research by McAlister et al., (2006), which demonstrated that women are more susceptible to dry cough than men due to the teratogenic risk associated with ACE-I, aligns with this finding. Clinical trials further support this observation. ARBs are considered a viable substitute for ACE-I, particularly in patients who experience dry cough following ACE-I administration. The study revealed that 90% of patients utilized losartan, making it the most commonly used ARB. Losartan provides renal protection to patients with type 2 diabetes and nephropathy, serving as a valid rationale.

In addition, Losartan showed a decrease in the likelihood of developing primary end-stage renal disease, which aligns with the findings of (Brenner et al., 2001). The present investigation found a high utilization of bata blockers at 41%. Despite their ability to alter blood glucose levels, doctors do not recommend b-blockers as the primary treatment option for hypertensive diabetic patients. Nevertheless, the risk of being overweight is advantageous. We prescribe B-blockers to patients who experience cardiovascular issues, and it is noteworthy that all of our patients exhibited such complications. This recommendation has received endorsement from the JNC 8 panel. When selecting a beta blocker for a hypertensive diabetic patient, it is advisable to opt for a selective beta1 receptor blocker rather than a nonselective beta blocker. This preference is based on the aim of mitigating the adverse consequences associated with the inhibition of the beta-2 receptor.

Still, a new study shows that people would rather use the nonselective vasodilator carvedilol than other beta-blockers because it doesn't have the side effects that other beta-blockers do (Leonetti and Egan, 2012). The present study observed a higher utilization rate of the selective beta-1 blocker bisoprolol compared to carvedilol, with rates of 86% and 14%, respectively. We can attribute this disparity to the effective marketing strategies for generic medicine, which ensured uniform prescriptions for all patients. Additionally, the inexpensive cost of bisoprolol played a significant part in its increased usage. The employment of CCB was limited to the dihydropyridine group due to its higher selectivity towards peripheral blood vessels compared to cardiovascular applications. The sole medication prescribed was amlodipine. Furthermore, amlodipine has a prolonged half-life, making it advantageous because it is administered once a day, thereby improving patient adherence.

The deleterious effects of thiazide diuretics on glucose metabolism, including insulin resistance, reduced glucose tolerance, increased incidence of overt diabetes, and deterioration of diabetic management, need attention. Additionally, studies have shown that thiazide diuretics reduce the effectiveness of hypoglycemic medications like sulfonylureas. Therefore, numerous studies suggest that administering thiazide diuretics to manage hypokalemia could potentially prevent the onset of diabetes. Our study limited the use of diuretics to hydrochlorothiazide because of its vasodilatory properties and its traditional mechanism of action, which involves the reabsorption of sodium from the distal tubule. Furthermore, they exhibit greater efficacy in lowering blood pressure and are more cost-effective in comparison to other cohorts. The research by ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group, (2003) recommends that individuals diagnosed with hypertension prioritize the inclusion of thiazide-type diuretics in their medication regimen.

In the current investigation, the utilization of combination therapy exhibited a higher efficacy rate compared to monotherapy (87.3% vs. 12.7%). This finding aligns with the outcomes reported by (Dhanaraj et al., 2012; Alavudeen et al., 2015). Furthermore, numerous studies have indicated that polytherapy is more advantageous than monotherapy due to the utilization of lower doses of each

medicine, thereby reducing the occurrence of adverse effects associated with either drug individually. Furthermore, effective management of blood pressure leads to improved results. In the context of comparing the achievement of target blood pressure between single medication therapy and combination therapy, it is generally observed that combination therapy tends to yield the most favorable outcomes in terms of tolerability. A meta-analysis conducted by Wild et al., (2004) revealed that combining therapy from two distinct classes led to a significant 5-fold decrease in blood pressure.

Moreover, individuals who have co-morbidities such as type 2 diabetes mellitus (T2DM) and hypertension (HTN) can derive advantages from the combined impact of various antihypertensive medications. This synergistic effect not only reduces blood pressure but also offers targeted protection for cardiovascular and renal health (Reboldi et al., 2009). The JNC8 recommendation suggests that diabetic patients should combine ACEI/ARBs with either a CCB or diuretic. However, in cases where a patient presents with specific indications such as heart failure, atrial fibrillation, or coronary artery disease, beta blockers are required. According to Reboldi et al., (2009) the study conducted by has provided evidence about the selection of ACE inhibitor combinations in hypertensive patients diagnosed with type 2 diabetes. The findings indicate that using a combination of the renin-angiotensin-aldosterone system (RAAS) and calcium channel blockers (CCBs) has resulted in a decrease in blood pressure, CCB-associated edema, and protein urea levels.

The present study observed a prevalence rate of 3.6% for the combination of CCB and ACE-I. Nevertheless, the findings of this investigation diverge from those reported by (Alavudeen et al., 2015). In contrast, the JNC 8 guideline regarded the RAAS group as the primary treatment option for people with diabetes and hypertension, prescribing it as the sole group for monotherapy. The UK Prospective Diabetes Study Group substantiated the significance of the renin-angiotensin-aldosterone system (RAAS) in safeguarding renal function among individuals with diabetes in (UK Prospective Diabetes Study Group, 1998). However, 12.7% of patients used RAAS as a standalone treatment. Comorbidities, particularly cardiovascular problems (CV), predominantly affected our patients, leading to this relatively low percentage. The most commonly prescribed antidiabetic medication in the current study was metformin, either alone or in combination, which aligns with the guidelines of the American Diabetes Association (ADA).

Furthermore, studies have demonstrated that metformin lowers TG and LDL levels while boosting HDL levels (Yandrapalli et al., 2020). The present study found a 30% insulin monotherapy utilization rate. This finding can be attributed to the presence of comorbidities among our patients, which pose challenges in effectively managing blood glucose levels alone through the use of oral hypoglycemic medications. Sirajudeen et al., (2014) conducted a recent study that revealed that the administration of insulin as a standalone treatment resulted in a decrease in HbA1c levels, fasting plasma glucose levels, and postprandial glucose levels. Additionally, the patient experienced effective management of their blood pressure and a notable reduction in their serum cholesterol levels.

5.CONCLUSION

The study's findings show that most patients use polytherapy to manage their blood pressure, while the use of monotherapy is significantly limited. Furthermore, the predominant polytherapy regimen administered to our patients consisted of the RSSA system and beta blockers, mostly due to the presence of cardiovascular problems, specifically IHD. According to the JNC8 guidelines, the optimal combination therapy is the use of RSSA in conjunction with either a CCB or thiazide diuretic. Additionally, it is indicated that the utilization of beta blockers may be warranted in those diagnosed with type 2 diabetes mellitus. Our study aligns with the JNC VIII recommendation. The effective promotion of select generic medicine names on the market incentivizes clinicians to prescribe specific antihypertensive treatments over others.

Consequently, lisinopril was prescribed more frequently under its brand name compared to other ACE-I medications and bisoprolol from beta blockers. Additionally, we observed that females received ARB more frequently. After consulting many doctors, they reported experiencing a dry cough, which aligns with previous research indicating that females are more susceptible to a dry cough than males. We concluded that our study's collective administration of antihypertensive medications was appropriate, but there is potential for more precise customization of drug selection based on demographic information, economic situation, and concurrent medical issues for individual patients. Ultimately, Yemen needs extensive research to improve the accuracy of medicinal prescriptions for patients.

Acknowledgments
Our gratitude goes out to every one of the study participants.

Author Contributions
The data analysis, drafting or revising of the paper, final approval of the publication version, and accountability for all areas of the work were all contributed by all authors.

Informed consent
Not applicable

Conflicts of interests
The authors declare that there are no conflicts of interests.

Funding
The study has not received any external funding.

Data and materials availability
All data associated with this study are present in the paper.

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