

To study the preferred antihypertensive drugs in patients suffering from diabetes mellitus at a tertiary care hospital of Uttarakhand with an emphasis on compelling indications

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Received: 04 July 2016

Accepted: 06 August 2016

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ABSTRACT

Background: People with diabetes are more likely to also have high blood pressure. Hypertension can increase the risk of diabetes complications and is a powerful risk factor for development of a wide variety of cardiovascular, cerebrovascular and renal diseases. The treatment of hypertension in patients with diabetes thus becomes all the more important and may effectively prevent cardiovascular events. This study was thus planned with the aim to study the preferred antihypertensive drugs in patients suffering from diabetes mellitus and to teach UG students about the clinical importance of compelling indications in the treatment of hypertension.

Methods: A total of 100 prescriptions of patients suffering from hypertension and diabetes mellitus were collected from diabetic hypertensive visiting the department of Medicine. Data was analysed in terms of percentage to find out the most and least preferred antihypertensive drugs in diabetes mellitus.

Results: ACE inhibitors (30.95%) and ARBs (30.16%) were the most preferred, diuretics (19.84%), and CCBs (11.9%), and beta blockers (7.14%) were the least preferred antihypertensive drugs in diabetes patients. Three patients were on non-pharmacological treatment and among the remaining 97 prescriptions, monotherapy was the most common mode (70.1%) of therapy for hypertension, and drugs in combination were prescribed to 29.89% patients.

Conclusions: ACE-I and ARBs were the preferred antihypertensive drugs prescribed in diabetic hypertensive. Treatment of hypertension should be individualized depending upon the compelling indications. This should be taught to undergraduate students in a practical way in collaboration with Medicine department.

Keywords: Hypertension, Diabetes mellitus, Antihypertensive drugs, Compelling indications

INTRODUCTION

Diabetes is a chronic disease that affects around 422 million people worldwide.¹ It is a clinical syndrome characterized by chronic hyperglycaemia due to deficiency or diminished effectiveness of insulin which affects carbohydrate, protein and fat metabolism and can produce changes in water and electrolyte balance. Diabetes mellitus (DM) can be divided mainly into type 1 and type 2 based on pathogenesis involved. Type 2 diabetes mellitus (T2DM) is the commonest form constituting 95% of all diabetics.²

Hypertension in diabetes is extremely common, affecting around 20 - 60% of patients with diabetes.³ Also, hypertension is almost twice as common in persons with diabetes as it is in non-diabetics.⁴ In the United States, approximately 30% of patients with type 1 diabetes mellitus (T1DM) and around 50% to 80% of patients with T2DM have associated hypertension.⁵ Another study by Cheung BM done in Hong Kong showed that the prevalence of hypertension in patients with T2DM is approximately 58%.⁶

In diabetes patients with hypertension there is impairment in the normal vasodilator effect of insulin mediated

through nitric oxide, which usually antagonizes the multiple pressure effects of insulin.⁷ This failure of vasodilatation to counter the multiple pressor effects of insulin is thought to directly or indirectly result in a rise in blood pressure.⁸

Hypertension in patients with diabetes plays a vital role in the development and progression of microvascular and macro-vascular changes in diabetes.⁹ Patients with diabetes have a significantly higher risk of cardiovascular diseases, and the presence of hypertension in addition markedly increases the risk of heart attacks and strokes leading to increased morbidity and mortality.^{10,11} Thus, high blood pressure is a powerful risk factor for development of a wide variety of cardiovascular, cerebrovascular and renal diseases.¹²

The treatment of hypertension in patients with diabetes thus becomes all the more important and may effectively reduce the incidence and progression of diabetic complications of retinopathy and nephropathy, cerebrovascular and cardiovascular diseases, and widespread macroangiopathy.¹³ Clinical trials such as the United Kingdom Prospective Diabetes Study (UKPDS) have shown that strict control of blood pressure in comparison with strict glycaemic control provides the greatest favourable impact on progression of chronic kidney disease.¹⁴

As per the seventh report of Joint National Committee (JNC7) on prevention, detection, evaluation and treatment of high blood pressure, hypertension is defined as a blood pressure (BP) above 140/90 mmHg.¹⁵ Various antihypertensive guidelines recommend lower BP (to achieve <130/80 mmHg) due to the higher risk of cardiovascular events in diabetic patients, although the evidence for this is scarce.^{15,16} In contrast, the newer JNC 8 guidelines state that there is no evidence from randomized controlled trials showing that treatment to a systolic pressure of less than 140 mm Hg improves health outcomes in adults with diabetes and hypertension.¹⁷

In the population aged ≥ 18 years with diabetes, JNC8 however recommends initiation of pharmacologic treatment to lower BP at SBP ≥ 140 mm Hg or DBP ≥ 90 mm Hg and treat to a goal SBP <140 mm Hg and goal DBP <90 mm Hg.¹⁷ To reach this blood pressure goal, intensive lifestyle intervention and often combinations of different antihypertensive drugs must be initiated. As per JNC8, the anti-hypertensive drugs started initially in diabetic hypertensive should include a thiazide diuretic, calcium channel blocker (CCB), angiotensin-converting enzyme (ACE) inhibitor, or angiotensin receptor blocker (ARB). If the target BP is not reached within one month after initiating therapy, increase the dose of the initial medication or add a second medication from among thiazide diuretic, CCB, ACE inhibitor, or ARB; do not combine an ACE inhibitor with an ARB. If the target BP is still not achieved, a third drug should be added, and if required, antihypertensive drugs from other classes can

be used (e.g., beta blockers, aldosterone antagonists).¹⁷ In combination treatment, the avoiding cardiovascular events through combination therapy in patients living with systolic hypertension (ACCOMPLISH) trial states that a combination of a renin-angiotensin system blocker and a CCB, especially amlodipine should probably be the first choice.¹⁸

There are some compelling indications in the treatment of hypertension which compel the prescription of certain drugs when these conditions are present along with hypertension. For example, diuretic, beta blockers, ACE inhibitors, ARB and CCB are the drugs which should be prescribed when hypertension is associated with diabetes or coronary artery disease. For the prevention of kidney disease in diabetes, ACE inhibitors or ARBs are the drugs which should be prescribed for hypertension.¹⁵

Literature search did not reveal any such study which could reveal the prescribing pattern of antihypertensive drugs in patients with diabetes in this part of Uttarakhand, India. This study was thus planned to find out the preferred antihypertensive drugs in the treatment of hypertension in patients with diabetes in a tertiary care institute of Uttarakhand. In addition, this study was designed as a teaching tool to MBBS students, to explain them the clinical importance of compelling indications in the treatment of hypertension.

METHODS

The design of this study cross-sectional study was done at Shri Guru Ram Rai Institute of Medical and Health Sciences, Dehradun by department of pharmacology in association with department of medicine from April 2014 to October 2014 as a part of the ICMR-STs project. The study was approved by the Institutional Ethics Committee.

The population of this study was 100 prescriptions were collected from diabetic patients with hypertension attending the out-patient and in-patient department of Medicine. Male or female patients above 18 years of age were included in the study after taking their informed consent. An MBBS second year student was involved in collecting of prescriptions. Pregnant or breast feeding women were excluded from the study.

Data analysis

All anti-hypertensive drugs and their drug classes were recorded. The data were tabulated as mean \pm standard deviation. Results were analysed in terms of percentage using Microsoft excel software.

RESULTS

A total of 100 prescriptions were collected and data was analysed. The demographic and baseline laboratory and clinical characteristics of the patients are given in Table 1.

The mean age of diabetic hypertensive patients was 50.66±7.99 years, with 53% male and 47% female patients. The average duration of diabetes was 8.7±5.6 years and of hypertension was 3.9±2.5 years. Most (61%) of the patients were in the age range of 40-60 years. 10 (10%) patients also had coronary artery disease. All except 3 patients were having type 2 diabetes.

Table 1: Baseline demographic, laboratory and clinical characteristics of the patients.

Baseline characteristics	Value
Age (years)	50.66±7.99
Male/ Female	n = 53 (53%)/n = 47 (47%)
Systolic BP (mmHg)	151.17±29.40
Diastolic BP (mmHg)	86.22±13.06
RBS (mg/dl)	257.82±131.14

All values expressed in mean±SD, except sex; SD, standard deviation.

Antihypertensive drugs

Antihypertensive medications were prescribed to 97 (97%) patients; 3 (3%) patients were advised non-pharmacological interventions. Among the 97 prescriptions with anti-hypertensive drugs, monotherapy was the most common mode (n = 68; 70.1%) of therapy for hypertension, and drugs in combination were prescribed to 29 patients (29.89%).

Table 2: Pattern of use of anti-hypertensive drugs among diabetic hypertensive.

Antihypertensive drugs (monotherapy and combination therapy)	Total number of drugs prescribed (out of total 126 antihypertensive drugs prescribed) to 97 patients (percentage)
Ramipril	39 (30.95%)
Telmisartan	31 (24.6%)
Hydrochlorothiazide	25 (19.84%)
Amlodipine	15 (11.9%)
Olmesartan	7 (5.56%)
Propranolol	5 (3.97%)
Atenolol	4 (3.17%)

A total of 126 antihypertensive drugs were prescribed to 97 patients. The most common antihypertensive drug classes prescribed as monotherapy or in combination were ACE inhibitors (n = 39, 30.95%), followed by ARB (n=38, 30.16%), diuretics (n = 25, 19.84%), CCB (n = 15, 11.9%) and beta blockers (n = 9, 7.14%) (Figure 1). As shown in Table 2, the antihypertensive drug most prescribed was ramipril (n = 39, 30.95%), followed by telmisartan (n = 31, 24.6%), and the least prescribed was atenolol (n = 4, 3.17%).

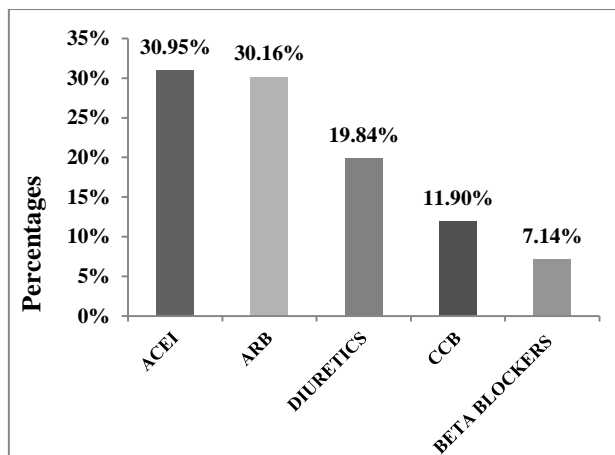


Figure 1: Classes of antihypertensive drugs prescribed to patients with diabetes.

The most common antihypertensive drug classes prescribed as monotherapy (n = 68) were ACE inhibitors (n = 30, 44.12%), followed by ARB (n = 19, 27.94%), CCB (n = 10, 14.70%) and beta blockers (n = 9, 13.24%). The most common antihypertensive drugs prescribed as monotherapy were ramipril (n = 30, 44.12%), followed by telmisartan (n = 16, 23.53%), and the least prescribed was olmesartan (n = 3, 4.41%) (Figure 2).

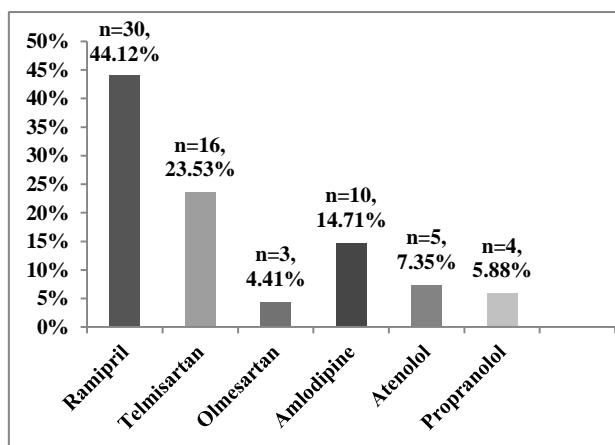


Figure 2: Antihypertensive drugs prescribed as monotherapy in diabetes.

All 29 patients prescribed anti-hypertensive as combination therapy were given two-drugs combination. As shown in Figure 3, the most preferred combination of drug classes for fixed drug combinations (FDCs) were ARB with diuretics (n = 19, 65.52%), followed by ACE inhibitors with diuretic (n = 5, 17.24%), ACE inhibitors with CCB (n = 4, 13.79%), and least prescribed combination was CCB with diuretic (n = 1, 3.45%). The most common anti-hypertensive drug class used for 2-drug combination was diuretic (n = 25, 86.21%), followed by ARB (n = 19, 65.52%), ACE inhibitors (n = 5, 17.24%), and CCBs (n = 5, 17.24%). As shown in figure 3, the most common antihypertensive fixed drug combinations (fdcs) was telmisartan and

hydrochlorothiazide (n = 15, 51.72%), followed by ramipril and hydrochlorothiazide (n = 5, 17.24%), and least common was amlodipine and hydrochlorothiazide that were prescribed to one patient (3.45%).

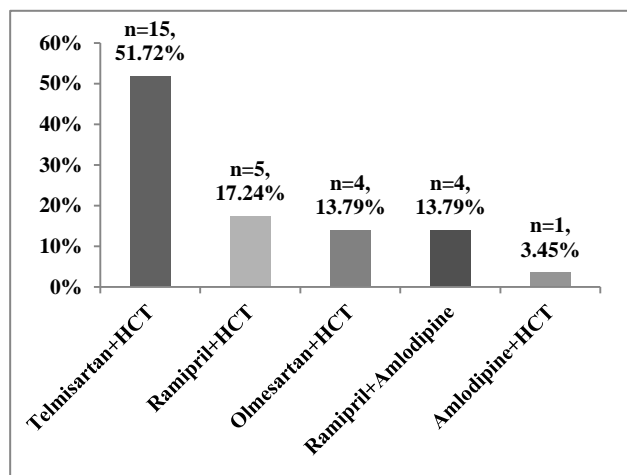


Figure 3: Antihypertensive drugs prescribed as combination therapy in diabetes.

Patients with coronary artery disease along with diabetes and hypertension were prescribed either combination of ACE-I with diuretics or ACE-I with beta blockers. Five patients with cerebrovascular accidents were prescribed ACE-I alone or ACE-I with diuretics.

Antidiabetic drugs

For anti-diabetic therapy, most (79%) of the patients were prescribed combination therapy (79%; 2-drug therapy - 71%, triple drug therapy - 8%) and for monotherapy only insulin (16%) and metformin (5%) were used (Table 3). Metformin either as monotherapy or in combination therapy was prescribed to all patients on oral hypoglycaemic drugs. Of the sixteen patients who were on insulin, three were having T1DM.

Table 3: Anti-diabetic drugs prescribed to diabetic hypertensive.

Anti-diabetic drugs	Number of patients	Percentage
Metformin+Glimepiride	58	58%
Insulin	16	16%
Sitagliptin+Metformin	9	9%
Pioglitazone+Metformin+ Glimepiride	8	8%
Metformin	5	5%
Glibenclamide+Metformin	4	4%

DISCUSSION

The decision to initiate pharmacologic treatment in hypertension recognizes consideration of several factors;

the degree of blood pressure elevation, the presence of target organ damage and the presence of clinical cardiovascular disease or other risk factors.¹⁵ Considering antihypertensive pharmacotherapy in diabetes, beta blockers are not recommended as they decrease the awareness of hypoglycaemia and may cause fatigue. Thiazide-type or loop diuretics in DM can aggravate metabolic alterations, especially hypokalemia and need monitoring. CCBs and ACE inhibitors have equivalent antihypertensive efficacy, although CCBs may cause oedema. ACE inhibitors and ARBs are helpful in patients with diabetes, particularly if micro-albuminuria or renal insufficiency is present, do not impair carbohydrate and lipid homeostasis or peripheral perfusion and can effectively improve heart failure.^{17,19}

In our study, ACE inhibitors and ARBs were the most commonly prescribed antihypertensive drug classes, followed by diuretics, CCBs and beta blockers; as was seen in a number of studies.²⁰⁻²³ For monotherapy, ACE inhibitors (ramipril) and arbs (telmisartan, olmesartan) were the most common antihypertensive used, however in combination therapy thiazide diuretic (hydrochlorothiazide) was the most prescribed, followed by ACE inhibitors and ARBs. The use of ARB and ACE-I among diabetic hypertensive patients is in accordance with the JNC-8 and American diabetes association (ADA) recommendations for the management of hypertension among diabetic hypertensive.²⁴ As per JNC-8, in general nonblack population with diabetes, initial antihypertensive treatment should include a thiazide-type diuretic, CCB, ACE inhibitor, or ARB.¹⁷ They do not recommend beta blockers among the first or second line drugs for diabetic hypertensive, and in our study also beta blockers were the least utilized, especially in combination therapy. Diuretics were not utilized for single drug therapy in our study, although they are among the first line drugs recommended by JNC-8 for diabetic hypertensive.

There are no clear cut guidelines as to the number of anti-hypertensive drugs that should be prescribed to diabetic hypertensive patients, however various studies have shown that many people will require three or more drugs to achieve the recommended target.³ In a number of studies combination therapy was more commonly used, in contrast to our study and the study by McAlister FA, where monotherapy was more common.^{20-22,25,26} This could be probably associated with relatively shorter history of duration of hypertension in our study. Also, the study by Johnson et al shows slightly higher mean age of the population (61.2±11.5 years) and higher number of patients with CAD (34.4%).²¹

In another study in Chennai, ACE inhibitors with thiazide diuretics (34.3%), and ARBs with thiazide diuretic (26.5%) were the most common drugs used for FDC, as was the norm in present study. For monotherapy, ACE inhibitors (52.30%) and ARBs (23.80%) were the more common prescribed class followed by cardioselective

beta-blockers (9.50%), CCBs (9.50%) and diuretics (4.70%); these were quite similar to our study although diuretics were not used for monotherapy in our study.²² The findings in a survey done among diabetic hypertensive in Odisha were quite different from our study and JNC-8 and ADA guidelines, where for monotherapy beta blockers (metoprolol) were the most commonly prescribed; and in combination therapy, CCBs (amlodipine) and beta blockers (atenolol or metoprolol) were given to most patients.²⁵

As many studies demonstrate the benefits of ACE inhibitors on multiple adverse outcomes, including both macro-vascular and microvascular complications in diabetic hypertensive patients, the established practice of choosing an ACE inhibitor or ARB as the first-line agent in most patients with diabetes is reasonable.³ However, hypertension treatment decisions should be individualized based on the age, gender, clinical characteristics of the patient, including comorbidities as well as tolerability and cost.

CONCLUSION

ACE-I and ARBs were the preferred antihypertensive drugs prescribed in patients with diabetes and hypertension. This is in accordance with JNC guidelines, as in patients of hypertension, diabetes becomes a compelling indication to prescribe ACE-I and ARBs. Furthermore, patients with coronary artery disease, cerebrovascular accidents and diabetes are more compelling to prescribe drugs acting on renin angiotensin system.

Funding: No funding sources

Conflict of interest: None declared

Ethical approval: The study was approved by the Institutional Ethics Committee and approved by ICMR under the Short Term Studentship Program

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Cite this article as: Kumar H, Gupta M, Dutta SB, Varma A, Singh A, Beg MA. To study the preferred antihypertensive drugs in patients suffering from diabetes mellitus at a tertiary care hospital of Uttarakhand with an emphasis on compelling indications. *Int J Basic Clin Pharmacol* 2016;5:2032-7.