Original paper

Antihypertensive Drugs patterns in Diabetes Mellitus and Their Impact on Glycemic Control.

Amir Omran^*

^College of Medicine/ University of Kerbala / Karbala/ Iraq

Abstract

Background: Hypertension management is paramount important in diabetic patients for cardiovascular events reduction. The utilization patterns of antihypertensive agents in diabetic patients must be consistent with recommended guidelines practice to produce a positive metabolic effect on glycemic control with proper control blood pressure and good compliance.

Objectives: The study aims to evaluate utilization prescribing pattern of five groups of antihypertensive agents among Type2 diabetic hypertensive patients and to explore the adherence to prescribing existing guidelines and their impacts on glycemic control.

Design: retrospective descriptive ,cross sectional study

Patients and Methods: A total of 230 Hypertensive Type2 diabetes patients on diet , Metformin and sulphonylureas drugs were enrolled in the study in diabetic clinic at Imam Al-Hussien medical city . The study was done between Jan 2009 And Jan 2014. The attendants' patients used five groups of the Anti-Hypertensive agents in single or in combinations patterns Angiotensin Converting enzymes inhibitor(ACEI), Angiotensin Receptor Blocker(ARB), Calcium Channels Antagonist(CCA), Beta Blocker(BB), Diuretics(Thiazide)). The study followed five groups of antihypertensive drugs for three months to evaluate prescribing patterns accordance to the evidence base guidelines and compare their impact on glycemic control. The study include gender, Age, age distribution, Glycemic control. The study excluded endocrine, liver, and renal diseases, and patients using steroids.

Results: The majority of the patients on Antihypertensive drugs 191 patients (83%) were receiving monotherapy including ACEI 77 (33.5%) patient, ARB 46(20%)patient, BB 60(26.1%) patint, CCB 6 patients (2.6%),Thiazide 2 (0.9%) patients, while two or three drugs combined patterns formed 39 (16.95%) patient.

The proper and adequate glycemic control of both genders are 25.2% . The proper glycemic control of males 40.9% and in females16,7%($P<0.05$) , There were no significant differences of the impact on glycemic control compared between five groups, ACE or ARB compared with single BB (Atenolol, Metaprolol) or CCB, Diuretics, as monotherapy or polytherapy combination patterns.

Conclusion; The utilization patterns of Antihypertensive agents (ACEI,ARBS,BBS) were more commonly prescribed followed by CCB, Thiazide Diuretics ,irrespective of mono or polytherapy. The majority of the patients were on monotherapy pattern.

There was no significant difference among the five groups of Antihypertensive drugs regarding the impact on glycemic control.

*For Correspondence: E-Mail amiromran1953 @Yahoo Com

Introduction

Hypertension (HT) is more common in Diabetics than non-diabetics patients . An aggressive approach to the diagnosis and treatment of   Hypertension in patients with diabetes is required in order to substantially reduce the incidence of both macro vascular and micro vascular complications [1]. The antihypertensive (AHT) agents used in diabetic patients should not only aim to control hypertension (HT) but also at preventing and delaying the development of complications[2]. The majority of hypertensive diabetic patients will require two or more drugs to achieve proper blood pressure (BP) control [3,4,5], because some studies showed that even adherence to existing evidence base guidelines, high proportion of uncontrolled B.P found[6]. It was found that combining AHT drugs from two different classes lowered BP five times more than doubling the dose of single agent[7], in addition to synergistic BP lowering combination therapy allows for lower dosage requirements of each individual agent. This, in turn leads to decreased side effects, thereby improving compliance [8].

Conventionally prescribing practice of antihypertensive (AHT) drugs according to recommended guidelines in   Diabetes having positive metabolic effect were ACEI-(captopril, Enalapril, Ramipril) and ARB-(Valsartan, Losartan, Candasartan) to achieve proper glycemic control comparing with negative metabolic drugs , Beta blockers-(Atenolol, Metaprolol) and diuretics (Thiazide) leading to improper glycemic control while calcium antagonist have neutral effect [5,9,10,11]. New onset diabetes induced by diuretics or B.Bs were not considered as diabetes   because Post prandial glycaemia does not usually exceed 200mg/dl and patient shows no evidence of any vascular complications[12].

ACEI and an ARB improve tissue blood flow and insulin release and enhancing insulin receptors producing proper diabetic control, while negative metabolic drugs worsen glycemic control   by increasing insulin resistance and decrease   insulin secretion by diminish blood flow to Beta cells of   the pancreas and hypokalemia respectively[10]. Hypertensive patients who are receiving BB had 28% high risk of subsequent Diabetes, also each 0.5mg/L decrease in serum K during first year of treatment was associated with 45% high adjusted Diabetes risk [13]. The negative metabolic effects of BB and diuretics depends on the duration (>4 WKs) and the doses (atenolol 50-100 and thiazide 20-50 mg) to achieve effective anti HT control, but this adverse effect must be weighed against proven benefit of BB or diuretics in reducing risk of cardiovascular events [14] . Most of the studies showed that small doses of (BBs, Diuretics) have no significant effects on glycemic control [15], while combination of low dose diuretics with ACEI, ARB or CCB may prevent the metabolic deleterious effects of thiazide diuretics[16]. Anyway   the   use   of medications that can worsen glycemic control are unnecessarily because other treatment options exists[17].

Patients & methods

The study was retrospective, descriptive, cross sectional, conducted among patients attending Diabetic clinic in Imam Al-Hussien medical city in Kerbala governorate in period between (1-1-2009) and (1-1-2014), the study involved T2DM at age of 40Y and older.

Total patients attending Diabetic clinic were 750 patients whom were under my care− only, (total patients were attending Diabetic clinic were 4000 patients) written consent was taken from each patient. Every patient had individuals case sheet.

The study discovered 230 hypertensive patient out of 750 on five groups of anti-Hypertensive drugs encompassed of ACEI, ARB, Calcium channel blocker and Beta blocker, Diuretics (Thiazide).

Total of 230 patients were included in the study, who used single anti-hypertensive drug (ACEI or ARB or BB, CCB, diuretics) or polytherapy were considered a combination of two or three drugs from different classes at any dose and frequency were enrolled in the study. The study compared between the impact of monotherapies or polytherapy patterns on glycemic control(both positive and negative metabolic effects). The following drugs were used in the present study, ACEI (captopril 50-150 mg or enalprile 5−20mg, Lisinoprile 5−40mg) or ARBS (valsartan80 − 160mg, candesartan 8-16 mg or losartan 50-100 mg), B.Bs(Atenolol 50− 100mg, Metaprolol 50− 100mg), CCBs (Amilodipine5−10mg), Thiazide (12.5− 50mg). All these patients had good compliance to their medications (Anti Diabetic and Anti-hypertensive drugs) .

All T2DM patients received metformin (500− 850mg×2) and sulphonylureas group (Glimepiride 2-6mg or Glibenclamide5 −15mg), 36pt (15.7%) added insulin to their oral therapy ofT2 DM to achieve proper glycemic control .The study followed the patients for three months.

Diagnosis of HT in T2DM was$\geq$ 130/80 in sitting position using two office visits over one month period according to guidelines of hypertension in diabetes(according to JNC7 report) [18,19].

Diagnosis of DM were done by symptoms of diabetes plus fasting blood sugar (8-12hr) for 2 visits of $\geq$ 126mg/dl or 2 hours postprandial$\geq$ 200mgldl plus HbA1c $\geq$6.5%.(20,21).(Fasting was defined as no caloric intake for at least eight hr).

The study included also gender and age, age distribution, the impact of AHT drugs on glycemic control.

Diet regimen paper used by all groups of attending patients in diabetic clinic.

The study registered HbA1c at the first time of attending Diabetic clinic and after three months, while FBS and 2hours postprandial blood sugar were measured every day.

Exclusion criteria

1. Smoking
2. Any patient with poor compliant to the treatment.
3. Patient utilized corticosteroid and Phenytoin, Niacin, Olanzapine, Clozapine.
4. Endocrine diseases acromegaly, Cushing syndrome, Renal, Liver diseases, Thyrotoxicosis, Phaeochromo-cytoma
5. Gestational DM
6. Type 1 DM

Results

The mean age of the patients was 54.93 year ± 9.88 year and the comparable figures for males were 53.05 year ± 10.06 year and females 58.36 year ± 8.58 year. The histogram of patients' age distribution is shown in Figure 1. No significant difference were found in the age distribution between males and females (p>0.05). There were no significant difference between age distribution and glycemic control (p>0.05)(tab1)

A total of 230 HT T2 diabetic patient were included in the study The majority of the patients were considered improper glycemic control (172 patients, 74.8%) while 25.2 % have adequate glycemic control. However a significantly higher proportion of males have proper Glycemic control 40.9 % than females were 16.78 % (P< 0.05) (tab2). Males formed the majority of the sampled patients (149 male

patient (63.3%) and 81 female (36.7%) patient (P<0.05). (tab2)

Most of the patients, 191 (83%)patient utilize drugs by monotherapy pattern include ACEIS 77(33.5%), ARBS 46 (20%)patient, BBs 60 (26.1%) patient, CCB 6 (2.6%) patients, Thiazide 2 (0.9%) patients (tab3). The utilization monotherapy of ACEI, ARBs occupied the majority of AHT drugs (53.5%), The least monotherapy utilization are CCB and Thiazide 2,6%,0.9% respectively, while polytherapy formed 39pt(16.9%) divided into two drugs combination 34patient(14.7%) and three drugs combinations formed 5 patients (2.2%) tab3. The utilization two drugs polytherapy of ACEIS or ARBs with thiazide were 1 patient (0.4%), seven patients (3%) respectively. The most common two drugs polytherapy utilization are ACEI+CCA and ARBS+Thiazide (2.6%,3%) respectively.(tab3). In our present study there were no significant difference on impact of glycemic control (p>0.05) between single positive metabolic effect drug in guidelines (ACE or ARB) or their combination s compared with single or combination patterns of

traditional negative metabolic effect drug (BB, Thiazide) and CCB (tab 4,5,6).

Discussion

The study shows that 30.6 % of attending T2DM patients to the diabetic clinic are hypertensive compatible to other studies in Iraq [22] and differ from others studies(India 47.5% , KSA 54.9%) [6, 23].

The mean age of both gender was 54.93 year Compatible to the other studies as in king Saudi Arabia(KSA)[24]. The peak of age distribution for D.M patients(46−55y were 37% and56− 65y were 37.8%) which compatible with most studies[25]. The study shows no significant association between age and glycemic control (Tab1). Males formed the majority of the patients (males63.3%, females36.7%)which similar to other studies [24,26].

The study discovers gloomy Picture related to poor glycemic control (73.8%) in patients using five groups of antihypertensive drugs which indicate poor health diabetic care program and social Health education. This result compatible with Kindy (Baghdad) and Basra Diabetic centers .[22]
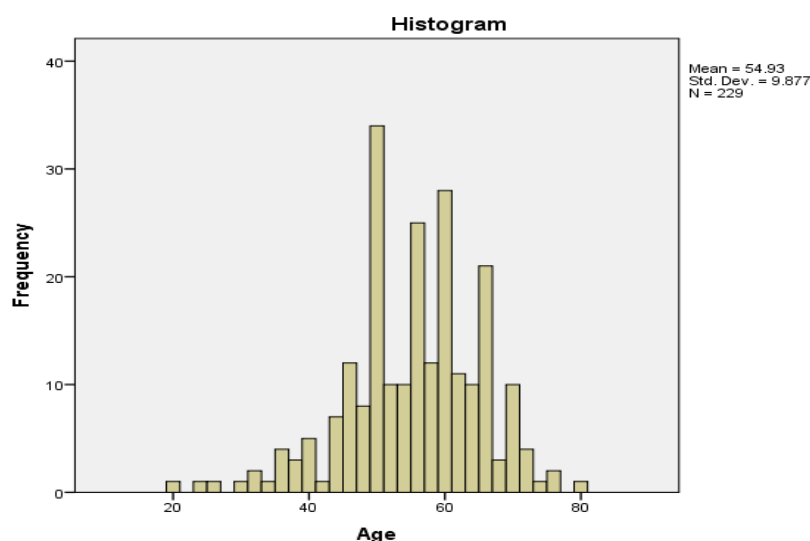
Figure 1. The age distribution of diabetic patient in Diabetic clinic at Imamm Al Hussain Medical city in Kerbala .

Table 1. The age distribution by Glycemic control among diabetic patient in Diabetic clinic at Imamm Al Hussain Medical city in Kerbala (n=230)

Age category	Diabetes mellitus control		Total
	Controlled Diabetes	Uncontrolled Diabetes	
25-45 year	10 (29.4%)	24 (70.6%)	34 (100.0%)
46-55 year	19 (22.4%)	66 (77.6%)	85 (100.0%)
56-65 year	21 (24.1%)	66 (75.9%)	87 (100.0%)
>65 year	8 (38.1%)	13 (61.9%)	21 (100.0%)
Total	58 (25.6%)	169 (74.4%)	227 (100.0%)

X^2 =2.55, p=0.466

Table 2. The gender distribution of Glycemic control among patient in Diabetic clinic at Imamm Al Hussain Medical city in Kerbala .

	Diabetes		Total
	Controlled	Uncontrolled	
Males	33 (40.7%)	48 (59.3%)	81 (100.0%)
Females	25 (16.8%)	124 (83.2%)	149 (100.0%)
Total	58 (25.2%)	172 (74.8%)	230 (100.0%)

X^2=15.98 ;p<0.05

Table 3. Antihypertensive regime distribution among diabetic patients Al Hussain Teaching hospital in Kerbala medical city (n=230)

Regime	Antihypertensive drug type	Frequency	Percent
Mono-therapy	ACE	77	33.5
	ARB	46	20
	CCA	6	2.6
	BB	60	26.1
	Thiazide	2	0.9
	Total	191	83.0
Di-therapy	ACE+CCA	6	2.6
	ACE+BB	7	3
	ACE+Thiazide	1	0.4
	ARB+CCA	2	0.9
	ARB+BB	5	2.2
	ARB+Thizide	7	3
	CCA+BB	4	1.7
	BB+Thiazide	2	0.9
	Total	34	14.8
Tri-therapy	ACE+CCA+BB	1	0.4
	ARB+CCA+BB	2	0.9
	ARB+BB+Thiazide	2	0.9
	Total	5	2.2
Grand Total		230	100

Table 4. The distribution of antihypertensive drug use with impact on glycemic control among diabetic patient in Diabetic clinic at Imamm Al Hussain Medical city in Kerbala (n=230)

Regime	Antihypertensive drug type	Controlled Frequency	Percentage	Uncontrolled	Total Freq.	Percentage
Mono-therapy	ACE	20	26.0	57	74.0	77
	ARB	11	23.9	35	76.1	46
	CCA	1	16.7	5	83.3	6
	BB	13	21.7	47	78.3	60
	Thiazide	2	100.0	0	0.0	2
	Total	47	24.6	144.0	75.4	191.0
-Di-therapy	ACE+CCA	3	50.0	3	50.0	6
	ACE+BB	1	14.3	6	85.7	7
	ACE+Thiazide	0	0.0	1	100.0	1
	ARB+CCA	1	50.0	1	50.0	2
	ARB+BB	1	20.0	4	80.0	5
	ARB+Thizide	0	0.0	2	100.0	2
	CCA+BB	2	50.0	2	50.0	4
	BB+Thiazide	0	0.0	2	100.0	2
	Total	8	35.1	14.8	64.9	22.8
Tri-therapy	ACE+CCA+BB	1	100.0	0	0.0	1
	ARB+CCA+BB	0	0.0	2	100.0	2
	ARB+BB+Thiazide	0	0.0	2	100.0	2
	Total	1	31.3	2.2	68.8	3.2
Total		85	49.4	100	58.1	172

Table 5. The distribution of Glycemic control by type of antihypertensive drug (single and improper combinations)

	Controlled Diabetes	Uncontrolled Diabetes	Total
Proper Single and Combinations	31 (25.2%)	92 (74.8%)	123 (100.0%)
Improper Single Antihypertensive	27 (25.2%)	80 (74.8%)	107 (100.0%)
Total	58 (25.2%)	172 (74.8%)	230 (100.0%)

chisq=0.00,p=.996

Table 6. The distribution of diabetes control by type of antihypertensive drug combinations (Proper and improper combinations)

	Controlled Diabetes	Uncontrolled Diabetes	Total
Proper Combinations	31 (25.2%)	92 (74.8%)	123 (100.0%)
Improper Antihypertensive	27 (25.2%)	80 (74.8%)	107 (100.0%)
Total	58 (25.2%)	172 (74.8%)	230 (100.0%)

chisq=0.167 P=.683

The study shows high prevalence of adequate glycemic control in males than females 63-7% and 37.3% respectively (p< 0.05)compatible with other study [27], this may be explained as the myths and misconceptions about diabetes and its management were more common in females .These misconceptions and inadequate knowledge had a significant influence on diabetic control [28]. It is imperative for physicians to understand myths and misconceptions in a particular

community about diabetes to improve patients care.

The present study shows the majority of prescribing of antihypertensive drugs utilization were monotherapy (83%) (ACEIs, ARBs, Beta-blockers, CCB, Thiazide diuretics), in comparison with polytherapy combinations enrolled all five groups utilization were (16.95%) (tab 3) while most of other studies have opposite results as polytherapy formed more than 50%(29), while other studies had similar results[30] that may explain high prevalence of uncontrolled B.P in Kerbala prevalence (not measured) because the prescribing pattern reflected the physicians attitude toward the disease and their therapeutic knowledge[7,8].

In the present study ACEs, ARBs, BBs were more commonly prescribed drugs, followed by CCAs and Thiazide irrespective of mono or polytherapy (tab3) that were inconsistent with evidence guidelines and different from other studies in which diuretics formed 41% of AHTdrugs [29]. The study show high prevalence of ACEs and ARBs utilization (53.5%) ,BBs formed (26%) which were in accordance with Joint National committee (JNC7) guidelines in reducing incidence of CVD, stroke and Reno protection that considered as area of improvement in AHT therapy for diabetic patients [31]. while in new guidelines criteria (JNC8) in which BBs were shifted to 2nd or 3rd line AHT treatment [32]. In our study the combined ARB+CCB formed (0.9%) which is not consistent with evidence based practice guidelines as they are potentially antiproteinuric effect in patients with type 2 diabetic nephropathy, even when their renal function is reduced [33].

The present study shows low prevalence utilization of CCB (2.6%) and Thiazide (0.9%) that were not consistent with evidence of guidelines in comparison with other most studies' (in KAS, CCB 43%,

ACEIS 36.2%, ARBS 34.9%, Diuretics 34.2%,BBS 16.2%) [34]. This mean that the core results of our study generally not compatible with recommended accordance to JNC7 andJNC8 guidelines. This result of low prevalence of thiazide utilization which consistent with evidence based traditional recommended guidelines antihypertensive drugs in diabetes avoiding diuretics (thiazide) as they cause hypokalemia which lead to insulin resistance and decrease insulin secretion [10], while in JNC7 guidelines ACEIs plus diuretics are widely used to achieve blood pressure control in 80 % of the patients comparison with other studies [35].

ONEAST study results confirm that ARB+Diuretic combinations reduce BP further than monotherapies in HT diabetic patients with safety profile [33]. The study shows limited utilization of CCB in comparison with high prevalence used in other studies as it traditionally considered neutral drug on glycemic control [10,11,12]. The wide used of BBs (26%) related to their low cost and old famous drug. This result was not consistent with new JNC8 recommended guidelines because BBs worsen glycemic control and abolished symptoms of Hypoglycemia and causing insulin resistance with weight gain [32,36] .

The important finding in this study was proving that no significant difference seen in glycemic control   among two groups of Anti-hypertensive drugs(ACEI , ARB) compared with Beta blockers, CCBs, thiazide type diuretics   or their combinations especially When the later were used in lower doses which match with most of the studies [14,37,38].

Conclusion

 In the present study, the monotherapy represent the majority of prescribing patterns of antihypertensive agents .The single drug used in large proportion of diabetic hypertensive patients were ACEI, ARB, BB followed by CCBs and diuretics

irrespective to mono or polytherapy which is generally not consistent with recommended evidence based practice guidelines. Areas of improvement include increasing ACEIs, ARBs used. The study proved that there were no significant difference among ACEIs, ARBs comparing with BBs, thiazide diuretics, CCBs in mono or polytherapy patterns regarding to the impact of proper glycemic control.

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