ORIGINAL ARTICLE

Quality of Hypertension Management in Type 2 Diabetes in India: A Multisite Prescription Audit

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Abstract

Background and Objective: Renin-angiotensin system (RAS) blockers (angiotensin converting enzyme inhibitors ACEI, angiotensin receptor blockers, ARB) are preferred drugs to control hypertension among diabetic patients. To determine frequency of RAS blocker use in hypertensive patients with type 2 diabetes, we performed a multisite study in India.

Methods: We evaluated physician prescriptions in consecutive patients with type 2 diabetes at 9 sites in India. Details of socio-demographic characteristics, clinical findings and prescription medicines were obtained. Descriptive statistics are reported.

Results: Hypertension treatment details were available in 8056 of 8699 diabetic patients (4829 men, 3227 women). No hypertension was in 3300 (40.9%), hypertension in 3625 (45.0%), and hypertension with vascular disease in 1131 (14.0%). In diabetics with no hypertension, hypertension, and hypertension with vascular disease, respectively, prescriptions of antihypertensive drugs was: RAS blockers in 19.4, 48.2 and 58.1%, beta-blockers in 4.8, 31.6 and 38.8%, calcium channel blockers in 0.4, 27.4 and 14.3% and diuretics in 0.6, 36.4 and 17.1%. ACEIs were prescribed more frequently than ARB's in hypertensive diabetics (60.7 vs 39.2%) as well as in diabetics with vascular disease (58.6 vs 41.4%). In diabetics with hypertension (n=3625) prescription of one, two or three antihypertensive drugs was 49.8%, 33.7% and 3.5% while statins were prescribed in 54.1%.

Conclusion: Use of RAS blockers (ACEI or ARB) in uncomplicated as well as complicated hypertensive patients with type 2 diabetes is sub-optimal. Most of the patients are on one drug and prescription of ≥3 drugs are rare. Statins are prescribed in only a half.

Introduction

Hypertension management in patients with type 2 diabetes is crucial to prevent vascular complications. There is strong clinical trial and meta-analytical evidence that systolic blood pressure (BP) >140 mmHg is harmful and guidelines suggest prompt initiation and titration of therapy to achieve and maintain systolic BP <140 mm Hg in most patients with diabetes.[1] A meta-analysis reported that each 10 mmHg reduction of systolic BP was associated with significantly lower risk of mortality, cardiovascular events, coronary heart disease, stroke, albuminuria and retinopathy in patients with diabetes.[2] Strong evidence also exists from randomized clinical trials that diastolic BP <90 mmHg is associated with decreased adverse vascular complications.[2] Control of systolic and diastolic BP to these levels in all patients with diabetes has been recommended by US, European, British and many other guidelines. [1,3-5] All these guidelines also advise that apart from lifestyle management, first line treatment for BP control among diabetes patients should be renin-angiotensin system (RAS) blockers, either angiotensin converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs). [1,3-5] Other drugs for BP control in diabetics are diuretics, calcium channel blockers (CCBs) and beta-blockers.[6,7] On the other hand, some recent reviews have observed no difference in outcomes using any of the available classes of anti-hypertensive drugs and suggest use of any of these compounds.[8,9] It has also been reported that most patients with diabetes need more than one drug for appropriate BP control. Guidelines also recommend use of statins in all diabetics, especially hypertensive diabetics for lowering cardiovascular risk.[1]

Diabetes in epidemic in India and is an important cause of morbidity and mortality.[10] Global Burden of Diseases Study has reported that in India diabetes led to 3.37% of all deaths in the year 2015, up from 1.23% in 1990.[11] In terms of metabolic risk factors, it is the second most important cause for loss of disability adjusted life years in India after high blood pressure.[12] Better BP control can prevent 20-30% of cardiovascular mortality in patients with diabetes.[1] The Oxford University based Blood Pressure Lowering Trialists' Collaboration has reported that BP control in diabetes can lead to reduced mortality at every level of BP.[13] This group also reported that use of RAS blockers (ACEIs or ARBs, but not both) is associated with 20% lower mortality compared to other drugs such as beta blockers and CCBs.[14]

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Table 1: Demographic and clinical characteristics of the study cohort

Variable	Numbers with data Total, men/ women	Total (N= 8699)	Men (N= 5292)	Women (N=3407)	X2 test p value (male/female differences)
Age-groups					
<40	8699, 5292/3407	1016(11.7)	625 (11.8)	391(11.5)	0.635
40-49		2288(26.3)	1385(26.2)	903(26.5)	0.731
50-59		2815(32.3)	1728(32.6)	1087(31.9)	0.466
60+		2580(29.7)	1554(29.3)	1026(30.1)	0.558
Smoking/tobacco use	7695, 4678/3017	1633(21.2)	1201(25.6)	432(14.3)	<0.001
Regular physical activity	7029, 4372/2657	3150(44.8)	2122(48.5)	1028(38.7)	<0.001
Obesity, BMI ≥25 kg/m2	8699, 5292/3407	3070(35.3)	1773(33.5)	1293(37.9)	<0.001
Hypertension	8673, 5275/3398	4464(51.5)	2583(48.9)	1881(55.3)	<0.001
Cholesterol≥200 mg/dL	3979, 2469/1510	1390(34.9)	824(33.4)	566(37.5)	0.008
LDL cholesterol ≥100 mg/dL	3979, 2469/1510	1989(50.0)	1193(48.3)	796(52.7)	0.007
Triglycerides ≥150 mg/dL	3979, 2469/1510	1403(35.2)	866(35.0)	537(35.5)	0.754
HDL<40/50 mg/dL	3979, 2469/1510	1945(48.9)	1025(41.5)	920(60.9)	0.001
Macrovascular complications					
Coronary heart disease	7131, 4391/2740	1099(15.4)	720(16.4)	379(13.8)	0.003
Others (stroke, PAD)		372(5.2)	232(8.5)	140(5.1)	0.743
Microvascular diseases					
Retinopathy	4851, 2992/1859	298(6.1)	183(6.1)	115(6.1)	0.994
Others		670(13.9)	424(14.2)	246(13.2)	0.357
Chronic renal disease (serum creatinine ≥2.0 mg/dL)	6381, 3915/2466	356(5.6)	267(6.8)	89(3.6)	<0.001

Numbers in parentheses are percent; BMI body mass index; LDL low density lipoprotein; HDL high density lipoprotein; PAD peripheral arterial disease;

Hypertension management in India is characterized by low awareness, treatment and very poor control.[15,16] In India Heart Watch-1 study we reported than among population-based urban subjects with diabetes, hypertension awareness was in 79.9%, treatment in 48.7% and control to BP <140/90 mmHg was in 40.7%.[17] This is much more than general population based studies in India.[18] In India Heart Watch-2 study we obtained treatment patterns in patients with type-2 diabetes at various sites in the country and reported a low use of statins in these patients.[19] In the present prescription-audit report we report prevalence of hypertension in clinic-based patients with type-2 diabetes, types of anti-hypertensive medications in these patients and use of combination therapies.

Methods

We performed a multisite (n=9) registry based study in eight cities across India to determine prescription pattern of antihypertensive drugs in patients with type-2 diabetes.[19] Institutional ethics committee at the central coordinating centre at Jaipur (India), approved the study. Requirement of informed consent from each patient was waivered by the ethics committee because anonymized data were used for analyses. Details of methodology has been reported.[19] We obtained data on successive patients attending the out-patients department as respective centres until the target of 500 patients was reached at each site. A larger sample size was available at the primary site where the proforma was piloted.

Demographic and clinical details were obtained similar to the previous India Heart Watch study.[17] An abbreviated version useful for a disease registry was used in the present study.[19] Socio-demographic factors were education, occupation and socioeconomic status and lifestyle factors included details of smoking and tobacco use, physical activity patterns and diet. Details of concomitant risk factors- overweight or obesity (body mass index, BMI ≥25 kg/m^2), hypertension, hypercholesterolemia, hypertriglyceridemia and low HDL cholesterol as well as duration of diabetes were also obtained. Presence of microvascular diseases were ascertained from medical records with focus on diabetic retinopathy, chronic renal disease (serum creatinine ≥2.0 mg/dl) and overt diabetic foot disease. We did not obtain details of presence of microalbuminuria, proteinuria, albumin-creatinine ratio or ankle-brachial index due to lack of uniform data at all sites. Presence of macrovascular disease was obtained from the patients and included history of overt coronary heart disease, history of stroke or symptomatic peripheral arterial disease with claudication as reported earlier.[19]

Patients were categorized based on absence or presence of hypertension into 3 groups: Group 1 had no hypertension; Group 2 had hypertension without cardiovascular complications and Group 3 had diabetes with evidence of micro-or macro- cardiovascular disease with or without hypertension. Prescriptions were audited for various medications including anti-diabetic, anti-hypertensive and lipid lowering medications. We obtained details of type of antihypertensive medicines. These medicines were classified into drug classes including RAS blockers (ACEIs or ARBs), CCBs, beta-blockers, diuretics and others (mineralocorticoid receptor blockers (spironolactone, epleronone, etc.), alpha blockers (prazosin, etc.), centrally acting drugs (clonidine, moxinodine, etc.) and others. Use of other drugs was low and hence details are not reported.

Statistical analyses: All the data were computerized and quality checks were performed to reduce duplicate and redundant data. Statistical analyses were performed using SPSS for Windows (SPSS, version 13.0). Descriptive statistics are presented with unadjusted data and proportions. Intergroup comparisons were performed using chi-square test. P values <0.05 were considered significant.

Results

We obtained detailed prescriptions in in 8699 patients with type 2 diabetes (men 5292, women 3407) as reported earlier.[19] Details of hypertension status and anti-hypertensive therapies were available in 8056 patients (men 4829, women 3227). Recruitment at different sites has been reported[19] and was Jaipur (3 sites, 42.7%), Nagpur (17.7%), Madurai (11.2%), Dibrugarh (9.2%), Lucknow (9.1%), Udaipur (6.3%) and Jodhpur (3.9%). Demographic and clinical details of the study participants have been reported.[19] 12% study participants were less than 40 years of age. Most of the patients had diabetes for more than 2 years and a third for

Table 2: Demographic and clinical characteristics of diabetic patients without hypertension, with hypertension and hypertension with cardiovascular disease

Variables	Without hypertension			Hypertension			Hypertension and CVD		
	Men (N=2075)	Women (N=1225)	Total (N=3300)	Men (N=2050)	Women (N=1575)	Total (N=3625)	Men (N=704)	Women (N=427)	Total (N=1131)
Age-groups									
<40	318(15.3)	164(13.4)	482(14.6)	210(10.2)	159(10.1)	369(10.2)	16(2.3)	14(3.3)	30(2.7)
40-49	628(30.3)	408(33.3)	1036(31.4)	481(23.5)	381(24.2)	862(23.8)	104(14.8)	54(12.6)	158(14.0)
50-59	645(31.1)	378(30.9)	1023(31.0)	763(37.2)	526(33.4)	1289(35.6)	213(30.3)	132(30.9)	345(30.5)
60+	484(23.3)	275(22.4)	759(23.0)	596(29.1)	509(32.3)	1105(30.5)	371(52.7)	227(53.2)	598(52.9)
Diabetes duration									
<2yr	209(10.1)	149(12.1)	358(10.8)	188(9.1)	133(8.4)	321(8.8)	58(11.5)	45(14.2)	103(12.5)
2-5yr	570(27.4)	339(27.6)	909(27.5)	570(27.8)	442(28.0)	952(26.2)	135(26.8)	81(25.6)	216(26.3)
>5yr	372(17.9)	211(17.2)	583(17.7)	369(18.0)	323(20.5)	692(19.1)	311(61.7)	191(60.3)	502(61.1)
Smoking/tobacco use	520(25.1)	185(15.1)	705(21.3)	458(22.3)	194(12.3)	652(18.0)	95(13.5)	16(3.7)	111(9.8)
Physical active	834(40.2)	383(31.2)	1217(36.9)	736(35.9)	416(26.4)	1152(31.7)	269(38.2)	116(27.1)	385(34.0)
Obesity, BMI ≥25 kg/m2	751(36.2)	502(41.0)	1253(37.9)	699(34.1)	626(39.7)	1325(36.5)	154(21.9)	116(27.2)	270(23.9)
Cholesterol≥200 mg/dL	399(19.2)	264(21.5)	663(20.1)	248(12.1)	199(12.6)	447(12.3)	67(9.5)	40(9.4)	107(9.5)
LDL cholesterol ≥100 mg/dL	656(31.6)	424(34.6)	1080(32.7)	356(17.3)	284(18.0)	640(17.6)	102(14.5)	53(12.4)	155(13.7)
Triglycerides ≥150 mg/dL	371(17.9)	198(16.1)	569(17.2)	360(17.5)	269(17.1)	629(17.3)	72(10.2)	41(9.6)	113(10.0)
HDL<40/50 mg/dL	504(24.3)	435(35.5)	939(28.4)	332(16.2)	352(22.3)	684(18.8)	103(14.6)	85(19.9)	188(16.6)

Table 3: Antihypertensive and other medications in various groups of diabetics

Variables	Without hypertension			Hypertension			Hypertension and CVD		
	Men (N=2075)	Women (N=1225)	Total (N=3300)	Men (N=2050)	Women (N=1575)	Total (N=3625)	Men (N=704)	Women (N=427)	Total (N=1131)
Anti-hypertensive drugs									
RAS blockers	410(19.8)	231(18.9)	641(19.4)	980(47.8)	767(48.7)	1747(48.2)	405(57.5)	202(59.0)	657(58.1)
ACEI	283(69.0)	127(55.0)	410(63.9)	629(64.1)	432(56.3)	1061(60.7)	247(61.0)	138(54.7)	385(58.6)
ARB	127(30.9)	104(45.0)	231(36.0)	351(35.8)	335(43.7)	686(39.2)	158(39.0)	114(45.3)	272(41.4)
Beta blockers	84(5.2)	38(4.1)	122(4.8)	674(32.9)	470(29.8)	1144(31.6)	275(39.0)	164(38.4)	439(38.8)
Calcium channel blockers	04(0.2)	03(0.5)	07(0.4)	541(26.4)	453(28.8)	994(27.4)	89(12.6)	73(10.4)	162(14.3)
Diuretics	05(0.2)	05(0.8)	10(0.6)	746(36.4)	573(36.4)	1319(36.4)	116(16.4)	78(18.3)	194(17.1)
Other drugs									
Anti-diabetes drugs									
Insulin	242(11.7)	115(9.3)	357(10.8)	160(7.8)	134(8.5)	294(8.1)	63(8.9)	34(7.9)	97(8.5)
OAD	1029(49.5)	600(49.0)	1629(49.3)	1092(53.2)	772(49.0)	1864(51.4)	212(30.1)	73(17.0)	285(25.2)
Anti-platelets	400(19.3)	210(17.1)	610(18.5)	352(17.1)	223(14.1)	575(15.8)	438(62.2)	255(59.7)	693(61.3)
Lipid lowering									
Statins	1195(57.6)	662(54.0)	1857(56.3)	1177(57.4)	786(49.9)	1963(54.1)	443(62.9)	261(61.1)	704(62.0)
Fibrates	55(2.6)	25(2.0)	80(2.4)	91(4.4)	60(3.8)	151(4.1)	38(5.4)	33(7.7)	71(6.2)

longer than 5 years. Risk factor details were available in most patients (Table 1) and showed that smoking and/or tobacco use was one-fifth while moderate to high physical activity in less than half. Hypertension was in 51.5%, total cholesterol ≥200 mg/dl in 34.9%, LDL cholesterol ≥100 mg/dl in 50.0%, triglycerides ≥150 mg/dl in 35.2% and low HDL cholesterol in 48.9%. Macrovascular complications such as coronary heart disease was in 15.4% and others (stroke, large vessel peripheral arterial disease in 5.2% while macrovascular complications such as retinopathy, diabetic foot or advanced chronic renal disease (creatinine ≥2.0 mg/dl) was in 6.1%, 13.9% and 6.8% respectively.

Clinical characteristics in those without hypertension (n=3300, 40.9%), with hypertension (n=3625, 45.0%) and with cardiovascular disease with/without hypertension (n=1131, 14.0%) are shown in Table 2. Patients with hypertension with or without cardiovascular disease were significantly older and had greater diabetes duration. Prevalence of various risk factors was lower in group with hypertension and cardiovascular disease (Table 2).

Prescription of various classes of anti-hypertensive drugs in the total cohort was: RAS blockers (ACEIs or ARBs) in 3045 (37.8%), beta-blockers in 1705 (21.2%), calcium channel blockers 1163 (14.4%), and diuretics in 1523 (18.9%). Details of prescriptions of various classes of anti-hypertensive drugs in diabetics without hypertension, with hypertension and with macrovascular or microvascular cardiovascular disease are shown in Table 3. Among hypertensive diabetics, the commonest anti-hypertensive drug prescribed were RAS blockers followed by diuretics, calcium channel blockers and beta-blockers. Among diabetics with cardiovascular disease, the commonest antihypertensive drugs were also RAS blockers followed by beta blockers, calcium channel blockers and diuretics. RAS blockers were prescribed in 19.4% non-hypertensive diabetics, 48.2% hypertensive diabetics and 58.1% diabetics with cardiovascular disease (Figure 1). ACE inhibitors were prescribed more frequently as compared to ARB's in all the three groups. Ratio of ACEI:ARB in various groups was 64:36 in non-hypertensive diabetics, 56:44 in hypertensive diabetics, 59:41

in diabetics with cardiovascular disease (Table 3). Beta-blockers were prescribed in almost similar proportions in hypertensive diabetics without or with cardiovascular disease while CCB's and diuretics were prescribed more in simple hypertensives without cardiovascular disease (Table 3). Prescription of insulin was low in all the three groups. Anti-platelet drugs were prescribed mostly in diabetics with cardiovascular disease (61.3%). Statin prescriptions were significantly greater in those with cardiovascular disease (62.0%) as compared to diabetics without hypertension (56.3%) and with hypertension (54.1%) ($p<0.05$).

Mono-therapy with an antihypertensive drug was the most frequent type of prescription in all the three groups and was in 18.1% in diabetics without hypertension, 49.8% in hypertensive diabetics and 42.5% in diabetics with cardiovascular disease. Two-drug anti-hypertensive therapy was in 33.7% hypertensive diabetics and 28.1% diabetics with hypertension and cardiovascular disease while three drugs or more were used in very small proportions (Figure 2). In the diabetic hypertensive group, combination of RAS blocker with a diuretic was the most commonly prescribed in 575 (47.0%) CCB-beta blocker combination in 556 (45.5%) and RAS blocker-CCBs combination in 393 (32.1%). We also assessed prevalence of controlled hypertension (defined as systolic BP >140 mmHg and diastolic BP >90 mmHg) in diabetic patients with hypertension. Controlled BP was in 387 (31.7%) diabetic hypertensives. When BP control was defined by systolic BP less than 140 mmHg it was in 425 (34.8%) patients.

Discussion

This multisite prescription audit among diabetes patients in India shows that renin-angiotensin system blocking drugs, ACE inhibitors or ARBs, are the most frequently prescribed anti-hypertensive drugs in these patients. The prescription of this class of drugs is much lower than optimal compared to various international clinical practice guidelines (Table 3). Mono-therapy is the most common and BP control is observed in only a third of diabetic patients with hypertension.

Blood pressure control in diabetics can be achieved by combination of health-promoting lifestyles (regular physical activity, healthy diet, smoking cessation) and drug therapies. Most of the current guidelines advise that RAS blockers should be the first line treatment of hypertension in these patients (Table 3). On the other hand, some meta-analysis suggest that any class of drugs is appropriate as long as BP is under control.[8] Our study shows that there is a low use of RAS blockers (ACEIs or ARBs) in patients with uncomplicated hypertension in diabetics in India. Although the prescriptions of RAS blockers was greater in diabetic hypertensives with cardiovascular disease, it is still suboptimal (Table 4). We have not assessed the reasons for low use of RAS blockers. This is a study limitation and could be due to multiple reasons that influence prescribing by physician collectively called physician mindlines.[20] Only a very few studies of this type are available in world literature. The Swedish National Diabetes Registry reported that about 76% of patients with diabetes and hypertension were on ACE inhibitors or ARBs.[21] The US NHANES studies have also reported similar data although the use was lower than Swedish registry.[22] A number of clinical trials have reported substantially greater prescriptions of RAS blockers in diabetic patients,[23] but these studies are not comparable to our study. Patients enrolled in clinical trials are typically more compliant and do not reflect the real-world

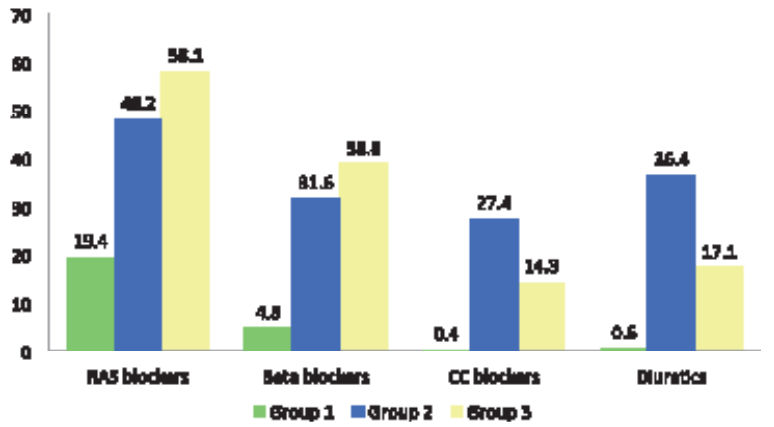

Fig. 1: Prescriptions of various anti-hypertensive drug classes in diabetics without hypertension (Group 1), diabetics with hypertension (Group 2), and diabetics with cardiovascular disease and with/without hypertension (Group 3)

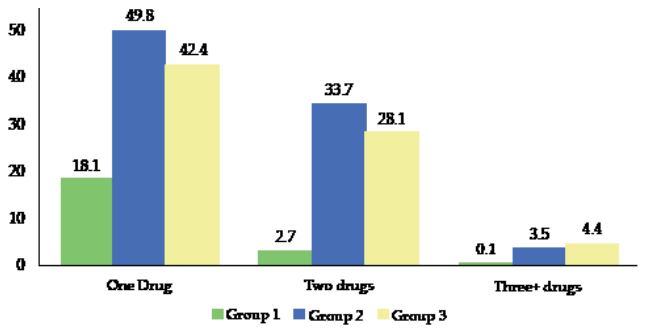

Fig. 2: Prescriptions of one drug, two drugs or three drugs in diabetics without hypertension (Group 1), with hypertension (Group 2), and with cardiovascular disease (Group 3)

Table 4: Quality gaps in management of hypertension in diabetes in the present study compared to international guidelines

	ADA 2016	EASD 2016	JNC-8 2014	ESC/ESH 2013	British NICE 2011	Present study
RAS blockers in hypertension with diabetes	>90%	>90%	>90%	>90%	>90%	48.2
Statins in high risk diabetes	>90%	>90%	>90%	>90%	>90%	54.1
Aspirin in uncomplicated diabetes	None	None	None	None	None	15.8

ADA American Diabetes Association Guidelines, EASD European Association of Study of Diabetes Guidelines, JNC Joint National Committee Guidelines, ESC/ESH European Society of Cardiology/European Society of hypertension Guidelines, NICE National Institute of Clinical Excellence Guidelines.

practice.[24] Only a few studies in India have reported prescription patterns in patients with hypertension[25,26] but we could not find any recent study that has focused on anti-hypertensive drugs in diabetics, hence our data are not locally comparable. A study among elderly diabetics with hypertension in China has reported much greater use RAS blockers.[27] In this study, the most commonly prescribed drugs were RAS blockers (77%), followed by CCBs (65%) and β-blockers (45%). Combinations of two drugs was the most common way in antihypertensive medication (41%) and three drugs or more was in 29%. In contrast to our study, combinations of CCB and ARB were the more common in the Chinese study.

The ACCORD study has reported that level of BP control in patients with diabetes should be 130-140 mm Hg systolic and 85-90 mmHg diastolic and lower levels are associated with greater cardiovascular events.[28] A tighter control has been suggested in the past by various international guidelines[5,7] but following the publication of ACCORD study most have revised the targets for BP control in patients with diabetes.[1,3] In the ACCORD study the most common anti-hypertensive drugs were RAS blockers followed by thiazide-like diuretics and CCBs.[28] However, more than 80% of patients were on RAS blockers, much more than the present study.

Our study has a number of limitations. We have evaluated prescription patterns of qualified endocrinologists, diabetologists and physicians at secondary and tertiary care.[19] To really assess the prescriptions of various anti-hypertensive drugs in diabetes there is a need for audit of larger number of physicians in primary and secondary care. Hypertension is very common in primary care and there are large variations in practice patterns.[29] Secondly, we did not inquire reasons for low use of RAS blockers as well as poor diabetes control in these patients. The study was targeted at practices where reliable data are quickly available and a larger study involving many more physicians is planned to overcome this study limitation Thirdly, level of control of BP can only be assessed by a prospective registry and we used data obtained in a cross sectional study. The current clinic BP may not be the ideal one and a study has reported that home BP or ambulatory BP are more reliable that office BP in predicting outcomes.[30] Poor control of BP could be due to non-adherence to anti-hypertensive medication. This is an important problem not only in low- and middle-income countries where it has been reported in more than half of patients (63%).[31] Non-adherence to antihypertensive medication is also observed in Western European countries and the US.[32] Other imitations are small and non-uniform number of patients at each site, lack of standardized treatment, unavailability of drug dose and absence of outcomes data. These data can be obtained only in a larger and well-funded study and ours is a pragmatic study (registry) with limited budget. Our study shows that there is a need to disseminate healthcare related information to practicing physicians so that optimal drug/s are prescribed and targets are achieved in diabetic patients. This is all the more important at primary care and secondary care levels where it is likely that in patients with diabetes the prescriptions of RAS blockers are lower and BP control is poorer that the present study.[33]

In conclusion this is one of the first large multi-city study that has evaluated anti-hypertensive drug prescriptions, use of combination therapy and level of BP control in patients with diabetes. The results show a sub-optimal prescriptions of RAS blockers (ACE inhibitors or ARBs). Single drug use is high and there is a poor control of hypertension. Policies focused on physician education and continuous prescription audits are needed to better control hypertension not only in diabetics but in all patients with hypertension.

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