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ORIGINAL ARTICLE

A COMPARATIVE STUDY OF ACE-INHIBITORS WITH OTHER ANTI-HYPERTENSIVE DRUGS IN HYPERTENSIVE DIABETIC PATIENTS IN A TERTIARY CARE HOSPITAL

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ABSTRACT: The incidence of hypertension and diabetes mellitus is rising on an alarming rate in the developing countries; these two disorders frequently occur together in a patient. Hypertension is the most important modifiable risk factor for coronary heart disease, stroke, CHF, end stage renal disease and peripheral vascular disease. Drugs like ACE inhibitors used in the treatment of hypertension are known to have beneficial effects in reducing complications associated with diabetes mellitus. In this study an attempt is made to see the rationality among the prescriptions and also to compare the efficacy, safety and tolerability of ACE-inhibitors with other anti-hypertensive drugs among diabetic hypertensive patient and to see the rationality among the prescriptions. **METHODS AND MATERIALS:** This 15 month prospective study was conducted on 100 diabetic-hypertensive patients attending Basaveshwar Teaching and General Hospital, Gulbarga. **CONCLUSION:** We summarize the overall effectiveness of all our anti-hypertensive drugs based on the results obtained from this data. The fall in both average SBP and average DBP reflects the effectiveness of the treatment employed by the physicians in the hospital. We also observed a general decline in the blood sugar values. The results of this study indicate that by re-establishing the dominance of ACE inhibitors in the treatment of diabetic-hypertensive.

KEYWORDS: Drug Prescribing Pattern, Drug Utilization Study, ACE Inhibitors, Anti-hypertensive, Defined daily dose.

INTRODUCTION: The incidence of hypertension and diabetes mellitus is rising on an alarming rate in the developing countries; these two disorders frequently occur together in a patient.

Approximately 285 million people worldwide in 20-79 year age group had diabetes mellitus in 2010 and by 2030, 438 million people of the adult population is expected to have diabetes. International diabetic federation also estimates that as many as 183 million people are unaware that they have diabetes.[1]

Hypertension is the most important modifiable risk factor for coronary heart disease, stroke, CHF, end stage renal disease and peripheral vascular disease. Drugs like ACE inhibitors used in the treatment of hypertension are known to have beneficial effects in reducing complications associated with diabetes mellitus.

Drug utilization (DU) studies are powerful tools to ascertain the role of drugs in the society. They provide a sound socio medical and health economic basis for health care decision making. Drug utilization research is an essential part of pharmacoepidemiology as it describes the extent, nature of drug exposure.[2] The World Health Organization (WHO) in 1997 defined drug utilization as the marketing, distribution, prescription and use of drugs in a society, with special emphasis on the resulting medical, social and economic consequences.[3]

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Defined Daily Dose (DDD) is the estimated average maintenance dose per day of a drug when used in its major indication.[4]

Pharmacoepidemiology is defined as the study of the use of and effects of drugs in large numbers of people.[5]DU studies also reveal quality of drug prescribing by important predetermined criteria including DDD.[6]

Despite extensive research, trials, public awareness and advances in the prevention and treatment of hypertension and diabetes mellitus, morbidity and mortality especially due to the ophthalmic and renal complications are high. In this study an attempt is made to see the rationality among the prescriptions and also to compare the efficacy, safety and tolerability of ACE-inhibitors with other anti-hypertensive drugs among diabetic hypertensive patient and to see the rationality among the prescriptions.

MATERIALS AND METHODS: This prospective study was conducted on 100 diabetic-hypertensive patients attending Basaveshwar Teaching and General Hospital, Gulbarga. The duration of the study was 15 months from December 2012 to March 2014.

Patients' case sheets were scrutinized for demographic data, provisional diagnosis, comorbid conditions, presumed site and nature of infection, duration of stay in the hospital and results of laboratory investigations. All the relevant data were entered and documented in case record forms (CRF).

LABORATORY INVESTIGATIONS:

- Blood glucose level.
- Lipid profile.
- Microalbuminuria.

Following (WHO core indicator) drug used indicators were determined:

1. Prescribing indicator.
2. Patient care indicator.
3. Facility indicator.
4. Complimentary indicator.

Inclusion Criteria: Patients aged between 18 to 90 years of either gender admitted in the Hospital for treatment of diabetes with hypertension and related disorders.

Exclusion Criteria:

- Patients aged below 18years, and above 90 years.
- Pregnant women.

Statistical Analysis: The data collected were statistically analyzed. Wherever necessary, the results were depicted in the form of percentages with tables and graphs using Microsoft Word and Excel version 7. For statistical significance, the statistical software SPSS version 17.5 was used.

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RESULTS:

Gender	Number	Percentage (%)
Male	63	63%
Female	37	37%
Total	**100**	**100%**

Table 1: Demographic data

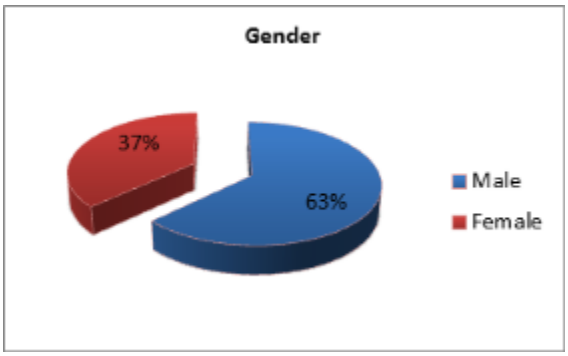

Figure 1

Age Groups (in years)	No. of Patients	Percentage (%)
18-30	1	1%
31-40	5	5%
41-50	15	15%
51-60	34	34%
61-70	26	26%
71-80	12	12%
81-90	7	7%

Table 2: Age wise

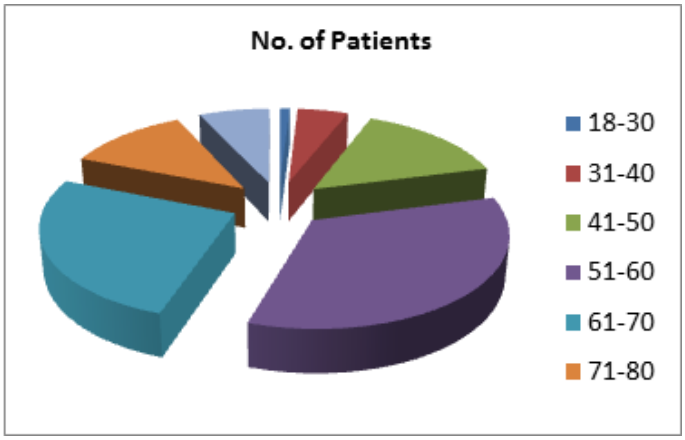

Figure 2

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Diagnosis	Number	Percentage (%)
Newly Diagnosed	9	9%
Previously Diagnosed	91	91%
Total	**100**	**100%**

Table 3: Distribution of patients according to status of diagnosis

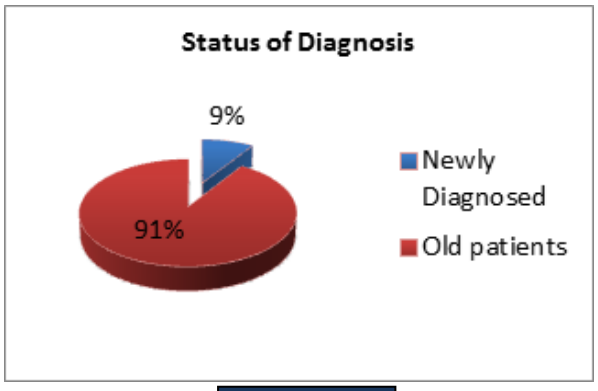

Figure 3

Days	Duration of Stay	Percentage (%)
0-5	71	71%
6-10	22	22%
> 10	7	7%

Table 4: Distribution of patients according to duration of stay in the hospital

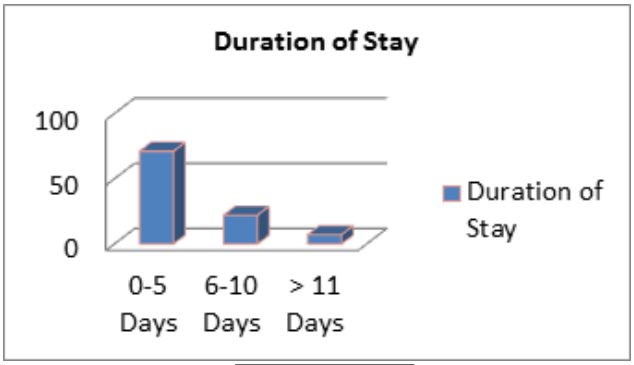

Figure 4

No. of Drugs	No. of Patients	Percentage (%)
0-5	46	46%
6-10	52	52%
>11	2	2%

Table 5: Distribution of patients according to average number of drugs administered

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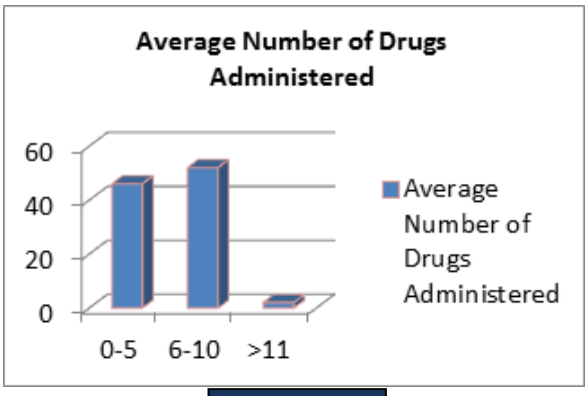

Figure 5

Mode of Administration of Drugs	No. of Patients	Percentage (%)
Intravenous	197	32%
Oral	362	59.5%
Subcutaneous	40	6.5%
Nebulization	8	1.3%
Nasal Drops	1	0.16%
Total	**608**	**100%**

Table 6: Distribution of patients according to the various routes of administration of drugs

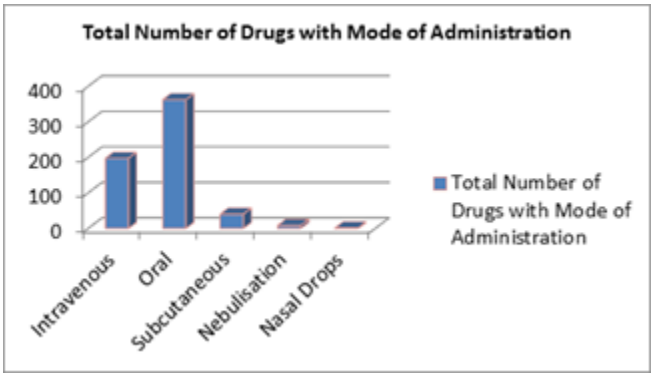

Figure 6

Blood Pressure	Average
SBP Admission	156
SBP Discharge	131
DBP Admission	90
DBP Discharge	78

Table 7: Distribution of patients according to Blood Pressure readings (SBP and DBP) at admission and discharge

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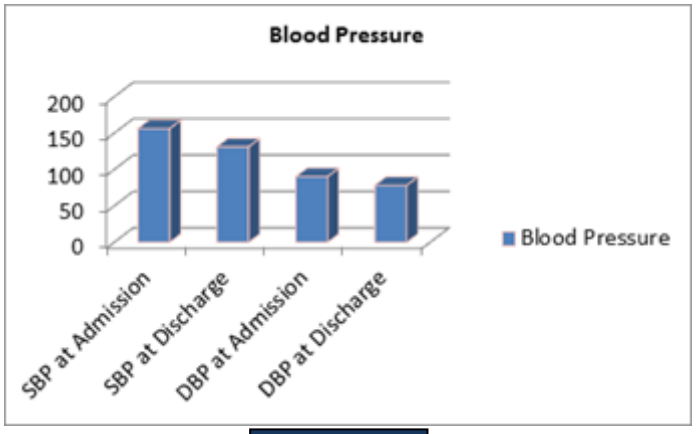

Figure 7

Blood Sugar on Admission	No. of Patients	Percentage (%)
<100	6	6%
101-150	20	20%
151-200	22	22%
>200	52	52%

Table 8: Distribution of patients according to Blood Sugar on Admission

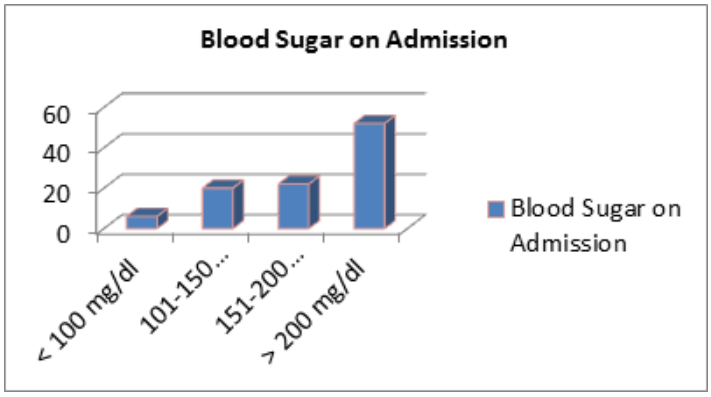

Figure 8

Blood Sugar on Discharge	No. of Patients	Percentage (%)
<100	12	12%
101-150	46	46%
151-200	28	28%
>200	10	10%

Table 9: Distribution of patients according to Blood Sugar on Discharge

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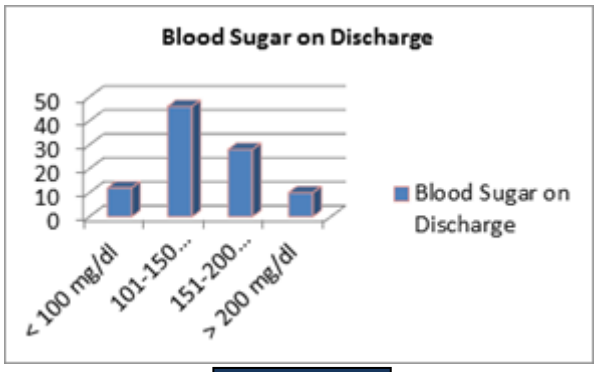

Figure 9

Albuminuria	No. of Patients	Percentage (%)
Positive	32	32%
Negative	68	68%

Table 10: Distribution of patients according to status of Albuminuria

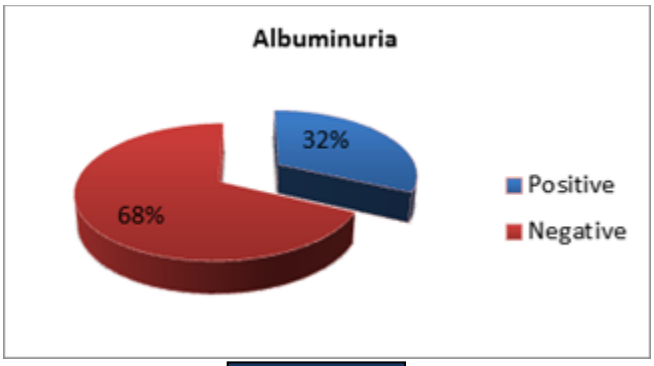

Figure 10

Drugs Used	+++ to +	+++ to ++	++ to +	Trace to Nil	No Change
ACE alone	8	-	-	6	-
ARB alone	-	-	-	4	-
ARB + ACE	1	-	-	-	-
CCB + ACE	-	-	4	2	-
CCB + ARB	-	4	-	-	-
Beta Blocker + ACE	-	2	-	-	-
CCB alone	-	-	-	-	1

Table 11: Distribution of patients according to change in urine albumin levels after therapy with various anti-hypertensive agents

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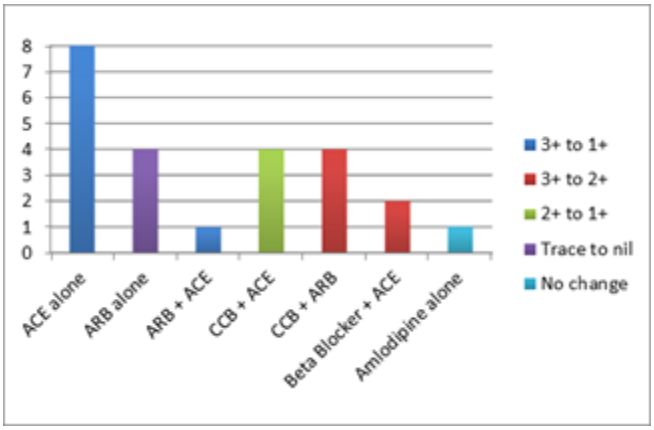

Figure 11

Drug Groups	Number of Patients	Percentage (%)
ACEIs	19	19%
ARBs	7	7%
β Blockers	7	7%
CCBs	7	7%
ACEIs + ARBs	3	3%
ACEIs + β Blockers	5	5%
ACEIs + CCBs	9	9%
ACEIs + Diuretics	7	7%
ACEIs + αβ Blockers	3	3%
ARBs + β Blockers	1	1%
ARBs + CCBs	5	5%
ARBs + Diuretics	7	7%
β Blockers + CCBs	4	4%
β Blockers + Diuretics	1	1%
CCBs + Diuretics	2	2%
CCBs + αβ Blockers	1	1%
Diuretics + αβ Blockers	2	2%
ACEIs + ARBs + Diuretics	2	2%
ACEIs + CCBs + Diuretics	4	4%
ARBs + β Blockers + Diuretics	1	1%
ARBs + CCBs + Diuretics	1	1%
ACEIs + Diuretics + CCBs + αβ Blockers	1	1%
ARBs + β Blockers + CCBs + Diuretics	1	1%
Total	**100**	**100%**

Table 12: Distribution of patients according to the drugs administered

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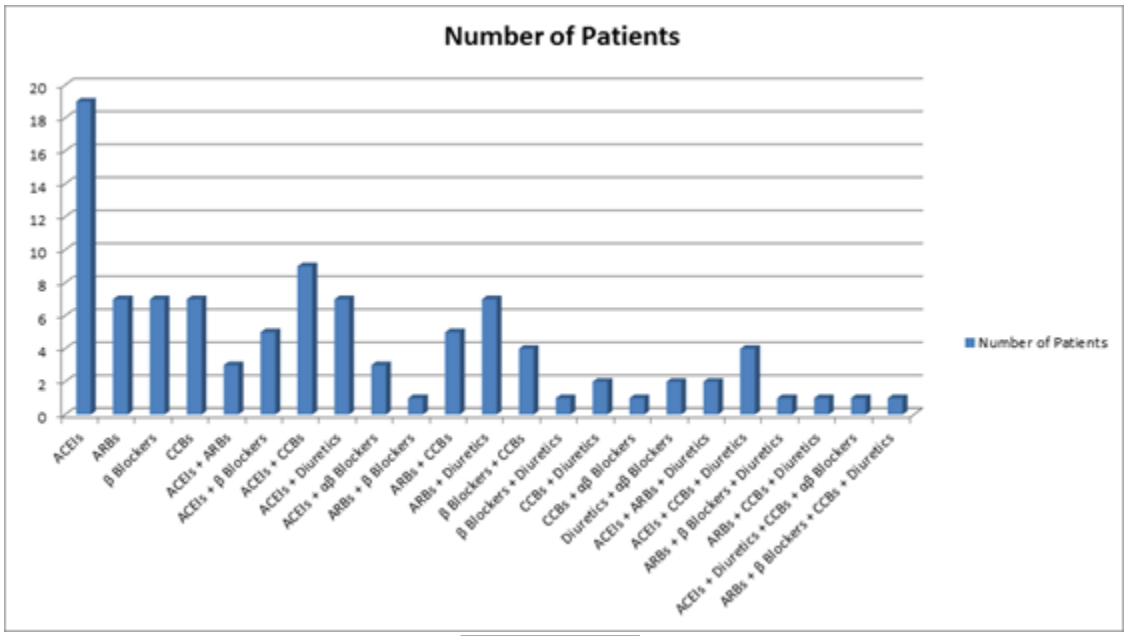

Figure 12

Drugs	SBP Admission	SBP Discharge	DBP Admission	DBP Discharge
ACEIs	150.7	122.6	87.3	77.6
ARBs	155.4	131.4	92.5	79.1
β Blockers	142	130	84	79.7
CCBs	175.4	144.2	97.4	75.7
ACEIs + ARBs	169.3	130	103.3	76
ACEIs + β Blockers	151.6	122.5	88.4	72.5
ACEIs + CCBs	135.3	124	81.5	73.7
ACEIs + Diuretics	155.4	122.6	92.8	78.3
ACEIs + αβ Blockers	161.3	136	98.6	83.3
ARBs + β Blockers	220	180	130	100
ARBs + CCBs	170	144	90	87.2
ARBs + Diuretics	148.2	132	80.8	72.8
β Blockers + CCBs	125	120	77.5	72.5
β Blockers + Diuretics	190	106	110	80
CCBs + Diuretics	165	130	100	70
CCBs + αβ Blockers	110	90	70	70
Diuretics + αβ Blockers	165	133	100	82
ACEIs + ARBs + Diuretics	125	120	75	83
ACEIs + CCBs + Diuretics	224	144	111	82.5
ARBs + β Blockers + Diuretics	200	160	100	80
ARBs + CCBs + Diuretics	180	140	100	80
ACEIs + Diuretics + CCBs + αβ Blockers	170	136	90	80
ARBs + β Blockers + CCBs + Diuretics	150	110	90	70

Table 13: Distribution of patients according to action of Various Drug Classes on SBP and DBP on Admission and Discharge

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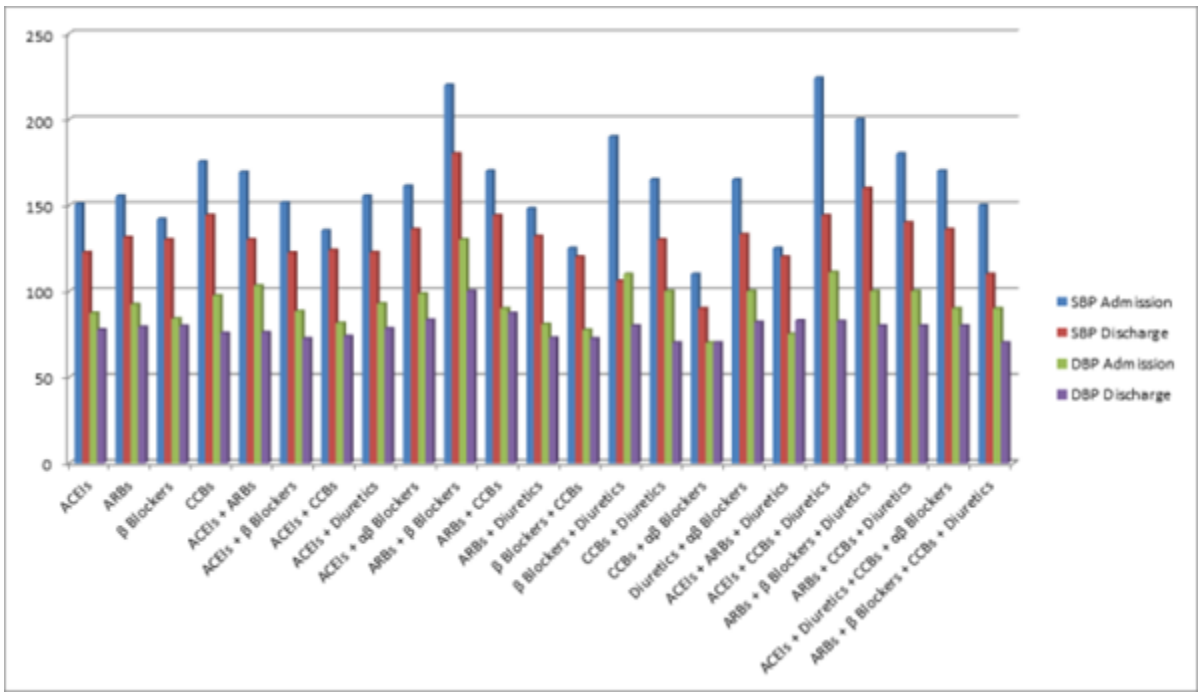

Figure 13

Outcome of Treatment	Number of Patients	Percentage (%)
Improved	86	86%
Worsened	5	5%
LAMA	5	5%
Death	4	4%

Table 14: Distribution of patients according to outcome of treatment

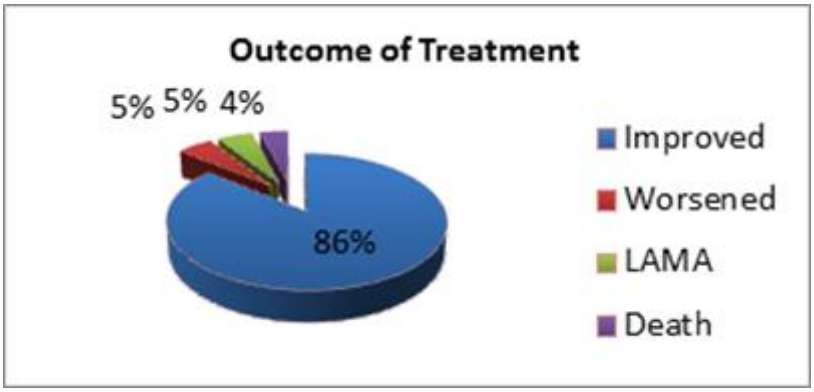

Figure 14

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Drugs	Number of Drugs Available	Percentage (%)
Total Drugs Prescribed	608	100%
Drugs Available In-Hospital Pharmacy	589	96.8%

Table 15: Table depicting the number of drugs prescribed versus the number of drugs available in the In-Hospital Pharmacy

Figure 15

Name of Drug	ATC-Code	WHO-DDD (mg)	Obtained DDD (mg)
Enalapril	C09AA02	10	15
Ramipril	C09AA05	2.5	2.6
Perindopril	C09AA04	4	4
Losartan	C09CA01	50	40
Telmisartan	C09CA07	40	26.6
Furosemide	C03CA01	40	72
Atenolol	C07AB03	75	26
Amlodipine	C08CA01	5	14
Pantoprazole	A02BC02	40	80
Ondansetron	A04AA01	16	13
Glibenclamide	A10BB01	10	10

Table 16: Comparison of DDD obtained from our study with the WHO-DDD

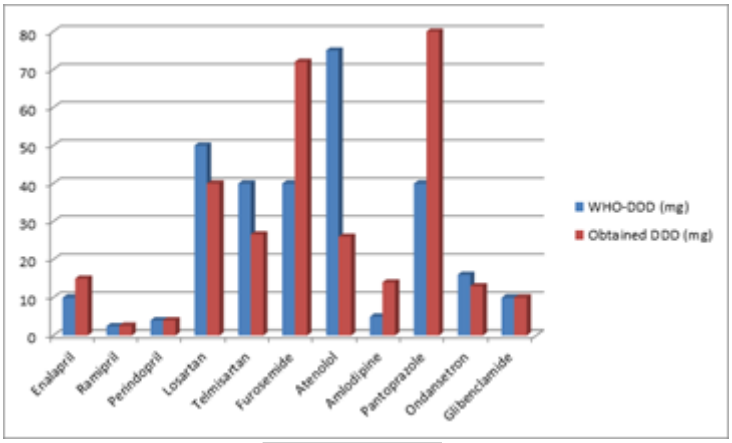

Figure 16

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Prescribing Indicators	Data
Average Drugs Prescribed	6.04
Not mentioned in the Prescription Percentage:	
• Superscription	Nil
• Age	Nil
• Diagnosis	Nil
• Generic Drugs	23%
Prescription of (%):	
• Anti-hypertensive	100%
• Anti-microbials	12%
• Anti-ulcer	74%
• Injections	32%
• On Essential Drug List	94%
Duration of anti-microbial treatment (days)	5

Table 17: Prescribing Indicators

Patient Care Indicators	Data
Average Consultation Time (in minutes)	7.8
Average Dispensing Time (in seconds)	14.1
Drug Dispensed	96%
Adequate Knowledge	64%

Table 18: Patient Care Indicators

Facility Indicator	Data
Availability of Essential Drug List	Yes
Key Drugs Available	92%

Table 19: Facility Indicator

Complimentary Indicators	Data
Without drugs with meal plan	0%
Average Drug Cost (Rs.) Prescription	327.52
Drug Cost on Injection	315.48

Table 20: Complimentary Indicators

DISCUSSION: Diabetes along with hypertension is a very common ailment afflicting millions of people worldwide. The socio-economic stress caused by the morbidity and mortality associated with it is mind boggling. Our study aims to provide a clearer picture regarding the same so as to achieve a better understanding of the disease process, the pharmacotherapeutics and the economic implications involved.

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ACE inhibitors block the generation of angiotensin-II, a potent inducer of intrarenal vasoconstriction. Furthermore, ACE inhibitors increase levels of vasodilator prostaglandins PGI_2 and PGE_2 through inhibition of kinase-II, an enzyme identical to ACE.[7]

According to our study, a majority of hypertensive-diabetics encountered by us were males (63%) (Table-1). This reflects the overall higher prevalence of this disease process in the male gender, which in turn can be linked to other factors more common in males such as cigarette smoking, alcohol consumption, strenuous lifestyle etc.[8]

In our study we found an overwhelming majority of the patients to be in the age group of 51-60 years (34%) and 61-70 years (26%) (table-2). This is in concordance with various other studies which implicate this disease process to be linked to late middle age and the elderly age group. Various factors contribute to the development of hypertension and diabetes mellitus in this susceptible age group which have been quoted in many a studies.[9, 10]

Table-3 of our study clearly depicts that a majority of the patients were previously diagnosed (91%) and newly diagnosed cases formed are just 9% of the total population under study. This reflects the better awareness among people and the better tools of diagnosis available to physicians even in relatively remote areas. Early identification and treatment of hypertensive-diabetics can vastly reduce the morbidity and mortality associated with the disease process.

In our study, while reviewing the total number of days spent in the hospital per patient, we found that 71% of these patients were discharged between 0-5 days (table-4). This shows the better healthcare facilities available to treat the patients when compared with the previous generations and also the changed physician outlook for the necessity of early ambulation.[11]

According to table-5 of our study, 46% were prescribed 0-5 drugs on an average per day and 52% were prescribed 6-10 drugs on an average per day. This reflects the growing trend of current medical practitioners regarding the practice of polypharmacy. This practice needs to be reduced because it can cause economic burden on patients as well as it increases the risk of adverse drug reactions and drug interactions.[12, 13, 14]

Table-7 of our study gives us information on the SBP and DBP at admission and discharge. Therefore, we can conclude that overall effectiveness of our anti-hypertensive drugs based on the result obtained from this data. The average SBP on admission was recorded to be 156mmHg, which on treatment with the various anti-hypertensive drugs reduced to average SBP discharge value of 131mmHg. Similarly average DBP on admission was recorded to be 90mmHg which fell to 78mmHg on discharge. The fall in both average SBP and average DBP reflects that the effectiveness of the treatment employed by the physicians in the hospital. Therefore we conclude from the above data that the pharmacotherapy of hypertension was effective.

Table 8 suggests that a majority of the patients (52%) had blood sugar on admission >200mg/dl, while concurrent data from table 9 reflects that a majority of patients at the time of discharge (46%) now had a blood sugar value in the range 101-150mg/dl. However, we cannot attribute this significant change due to ACE inhibitors or other anti-hypertensive alone as the patients were on concurrent anti-diabetic medication such as insulin or oral hypoglycemic agents.

Tables 10 and 11 give us an idea about the number of cases of albuminuria encountered and the treatment options which were supplied to them. According to table-10, 32% were albuminuria positive, the rest being negative. Table-11 reflects that 43% of the patients who were albuminuria positive were treated with ACE inhibitors alone. Out of these 14%, 8% who were administered ACE

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inhibitor alone exhibited a dramatic fall in albuminuria levels from +++ to +. This is in concordance with various studies by Preston et al, [15] Bojestig et al, [16] Marre et al[17] and Bakris et al.[18]

According to our study, from table-12 we infer that an overwhelming majority of the patients were prescribed ACE inhibitors alone (19%), amongst the drug combinations prescribed ACE inhibitors and CCBs combination was frequently prescribed (9%). This reiterates the view from many studies which state the role of ACE inhibitors as first choice drugs in the treatment of diabetic-hypertensives.[19, 20, 21] Many studies also point out the favorable outcome of BP by treatment with a combination of ACE inhibitor and CCB as supported by the results of our study.[22, 23]

Controversial drug combinations include the use of ACE inhibitors and ARB simultaneously. At present there is conflicting evidence regarding the advisability of combining an ARB with an ACEI in heart failure patients. The Candesartan in Heart Failure Assessment of Reduction in Mortality (CHARM-additive) and the Valsartan on Heart Failure (ValHeFt) studies indicate that this combination decreases morbidity and mortality. In contrast, the VALIANT and ONTARGET (Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint) findings show no added benefits with combination therapy, which was associated with more adverse effects.

Table 13 reveals to us the drugs and their combinations causing a maximal fall in the values of average SBP and average DBP from admission to discharge. The maximum fall in average SBP was noted on administration of a combination Beta blocker + Diuretic (% fall of 45%) and with ACE inhibitor + CCB + Diuretic (% fall of 36%). The maximum reduction in average DBP values was seen with CCB + Diuretic (% fall of 30%), Beta blocker + Diuretic (% fall of 28%) and with ARB + Beta blocker (% fall of 24%). From this we conclude that the most effective drug combination for the overall decrease of BP (i.e. both SBP and DBP) was a combination of Beta blocker + Diuretic which exhibited a SBP fall of 45% and DBP fall of 28%. This is in concordance with the studies conducted by Zacest et al, [24] Bangalore et al, [25] and Sica.[26]

Table 13 also shows us the percentage fall in SBP and DBP by ACE inhibitors alone which was recorded to be 19% and 12% respectively. However, this comparatively meager fall in BP does not fully reflect the role of ACE inhibitors in the pharmacotherapy of diabetic-hypertensive.

Table 16 from our study compares the Obtained DDD with the WHO-DDD. Although most of the drugs are prescribed as per WHO-DDD, some drugs showed significant deviation from the WHO-DDD. Drugs such as Furosemide (72mg), Amlodipine (14mg) and Pantoprazole (80mg) exhibited an Obtained DDD which is almost twice the WHO-DDD. This represents an indiscriminate use of these drugs in our hospital. However, drugs such as Atenolol (26mg) showed a DDD which was half of the WHO-DDD. This shows the inadequate knowledge of the prescribers regarding the dosage schedule of such drugs.

The main purpose of the DDD system was to provide a tool for presenting drug utilization studies, which would allow the measurement of drug consumption across the therapeutic group.

SUMMARY AND CONCLUSION: We summarize the overall effectiveness of all our anti-hypertensive drugs based on the results obtained from this data. The average SBP on admission was recorded to be 156mmHg, which on treatment with the various anti-hypertensive drugs reduced to average SBP discharge value of 131mmHg. Similarly average DBP on admission was recorded to be 90mmHg which fell to 78mmHg on discharge. The fall in both average SBP and average DBP reflects the effectiveness of the treatment employed by the physicians in the hospital.

The blood sugar on admission was recorded to be >200mg/dl in a majority of patients (52%); however at the time of discharge (46%) a blood sugar value in the range 101-150mg/dl. So we observe a general decline in the blood sugar values. But the majority of patients were on various drugs which included subcutaneous insulin and oral hypoglycemic agents; we cannot attribute this fall in blood sugar to ACE inhibitors or any other anti-hypertensive drug as such.

We encountered 32% albuminuria positive patients during the course of our study, in which a majority were prescribed ACE inhibitors and who displayed highly satisfactory results. Despite this fact, our study showed that it was a simple, inexpensive, rational, understandable and easy to use system. It provides the information on drug usage in patients and could be applied as a basis for prescription guidelines. It may be concluded that the drugs used in our study are in adherence with standard treatment guidelines.

The results of this study indicate that by re-establishing the dominance of ACE inhibitors in the treatment of diabetic-hypertensive. Also, a separate study can be conducted on the anti-diabetic action of ACE inhibitor in the absence of blood sugar lowering agents.

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