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RATIONALITY OF FIXED DRUG DOSE COMBINATION – A PROSPECTIVE VIEW IN A TERTIARY CARE HOSPITAL

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ABSTRACT

Cardiovascular morbidity and mortality can be markedly reduced by achieving clinical blood pressure (BP) goals. Fixed dose combination helps to attain the BP goal earlier than would be the case with monotherapy. The main aim of the present study was to assess the prescribing pattern of fixed dose combination (FDC) of antihypertensive drugs. A prospective observational study was conducted in the cardiology department of multispeciality tertiary care hospital for a period of six months. All hypertensive patients prescribed with anti-hypertensive FDCs were randomly selected and their outpatient records were monitored and documented in a specially designed proforma and the data was then suitably analyzed. During the study period, 150 patients met the selection criteria, a total of 26 different anti-hypertensive FDCs were found. Most of the patients on FDCs were in an age group of 60-69 years with an almost equal distribution among both genders. Only 10% of patients presented with hypertension alone. Most of the patients had other concomitant illnesses (heart diseases, followed by dyslipidemia and diabetes mellitus). Most commonly used combination was the RAAS inhibitor (ACEI/ARBS) with diuretic combination (32.6%), followed by RAAS inhibitor with calcium channel blocker (28%). Only one triple drug combination of olmesartan/amlodipine/hydrochlorothiazide was prescribed, which was also most commonly prescribed. The present study emphasizes the need to formulate and implement appropriate prescribing guidelines for FDCs based on local prescribing, and to conduct further studies to analyse and improve the prescribing patterns and promote rational drug use.

KEYWORDS: Antihypertensive-blood pressure-fixed dose combination-hypertension-prescribing pattern.

INTRODUCTION

Hypertension is a heterogenous, hemodynamic disorder, associated with an increase in total peripheral vascular resistance and is an important risk factor for cardiovascular morbidity and mortality. According to Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 8) guideline the goal BP for patients with age ≥ 60 years is <150/90 mmHg and for age < 60 years is <140/90 mmHg.

In an analysis of worldwide data for the global burden of hypertension, 20.6% of Indian men and 20.9% of Indian women were suffering from hypertension in 2005. The rates of hypertension in percentage are projected to go up to 22.9 and 23.6 for Indian men and women, respectively by 2025.[4] Drug selection in an individual is mainly based on his age and co- morbid conditions. Although it is occasionally possible to identify a specific cause for hypertension in some patients, BP elevation is usually multifactorial, making it very difficult, to normalize pressure by only a single pressor mechanism.[14] Addition of a second drug from a different class should be initiated when use of a single drug in adequate doses fails to achieve the BP goal. When BP is more than 20/10 mmHg above goal, consideration should be given for initiating therapy with two drugs, either as separate prescriptions or in fixed-dose combinations.[7]

Fixed dose combinations are pharmaceutical formulations that contain two or more drugs in fixed ratio. Some of the merits offered by FDCs include; reduced pill burden[2], improved compliance[6], reduction of total daily dose and adverse effects[6], reduction of overall cost of therapy[6], and attainment of BP goals more quickly. Combination therapies with agents having complementary mechanism of action may provide advantages of each type of agent and reduce some of the adverse effects of high dose of individual drug.[5] The demerits offered by them are; dose of one ingredient alone cannot be altered[8], different pharmacokinetic properties can pose difficulty in frequency of administration and in case of development of ADR, it is difficult to withdraw the suspected drug alone, increased number of drug-drug interactions.[9]

Hypertension is a chronic disorder and necessitates administration of drug throughout the life. Although it offered many advantages over monotherapy, choice of fixed dose combinations depends upon the risk factors, presence of co-morbidities, and should be tailored according to individual patients to obtain maximum benefit. The current study assesses the prescribing pattern of antihypertensive fixed dose combinations and gives an overview of the same.

MATERIAL AND METHODS

The study was conducted in the Cardiology department of Cosmopolitan hospital, a tertiary care centre after obtaining approval from the institutional ethical committee. The study was designed as a prospective observational study. This was a 6 months study conducted from December 2015 to May 2016.

Sample Size: The sample size was calculated using the formula based on descriptive study. The calculated minimum sample size was 130 patients but the recruitment continued during the study period and a total of 150 cases were included in the study.

Inclusion Criteria: Hypertensive patients who are on fixed dose combination treatment, all outpatients attending the cardiology department, patients with age ≥ 18 years, and patients of both genders. *Exclusion Criteria:* Patients aged below 18 years, patients with incomplete medical records, patients who are not willing to participate in the study, patients who are only on monotherapy for hypertension, patients admitted in wards other than cardiology department, patients who are pregnant, and/ or breastfeeding.

Based on inclusion and exclusion criteria all the antihypertensive prescriptions containing FDCs issued during the period of 6 months were collected and relevant data was documented in a specially designed data collection form i.e., proforma. It consisted of the patients demographics, past medical history, duration of hypertension, present medications including FDCs, details of all antihypertensives prescribed observed.

Statistical analysis: All statistical analysis was performed using the statistical software SPSSv13.0 for windows. Parametric data were expressed as mean ± standard deviation (SD) for continuous variables.

RESULTS

On the basis of the study conducted in the cardiology department of a tertiary care hospital for 6 months the following results were obtained.

Age

On analyzing the case sheets of 150 patients, Figure I was obtained which compared the percentage of FDCs with age of patients. Figure II depicts the number of fixed dose combinations prescribed in a particular age group.

Gender

Among 150 patients, Figure III shows the distribution of patients in accordance with gender.

Duration of hypertension

Figure IV categorizes the patients in percent according to the duration of hypertension.

Co-morbidities

Figure V represents the distribution of sample with respect to the co-morbidities observed.

FDCs prescribed

Figure VI shows the percentage of fixed dose combinations prescribed in hypertensive patients who attended the cardiology department.

Utilization of FDCs in different conditions

Table I shows the number and pattern of prescribing in each co-morbid conditions.

Marketed anti-hypertensive FDCs used in the study

The table II lists the most commonly prescribed brand names of FDCs with the strengths available.

Combinations used

The table III represents the distribution of patients with respect to FDCs.

Past medication history

A total of 150 case sheets were analysed for number of FDCs in past medication history of the patients case sheets and is depicted in Figure VII.

Continuing the past FDCs

Among the total case sheet analysed, Figure VIII shows the number of patients who were still continuing the past FDCs.

Rationality of Prescribing RAAS inhibitor+B Blocker

Figure IX shows the rationality of prescribing the combination of RAAS inhibitor/B blocker in patients with hypertension with or without heart disease.

Table I: Number of FDCs prescribed in hypertension and with co-morbidities.

Groups	RAAS inhibitor + Diuretic	RAAS inhibitor + CCB	CCB + B blocker	Olmesartan + HCTZ + Amlodipine
HTN	9	1	1	4
HTN + DM	1	2	3	3
HTN + Heart disease	4	10	1	-
HTN + DLP	5	3	1	1
HTN + Heart disease + DM	1	5	3	3
HTN + Heart disease + DLP	5	9	2	-

HTN: HYPERTENSION; DM: DIABETES MELLITUS; DLP: DYSLIPIDEMIA

Table II: List of anti-hypertensive FDCs used in this study.

Antihypertensive fixed dose combinations	Brand names	Strengths
Olmesartan + Amlodipine	OLMEZEST AM (Sun Pharma)	20mg/5mg 40mg/5mg
Olmesartan + Amlodipine + HCTZ	TRIOLMEZEST (Sun Pharma)	20mg/12.5mg/5mg 40mg/12.5mg/5mg
Olmesartan + HCTZ	OLMEZEST H (Sun Pharma)	20mg/12.5mg 40mg/12.5mg
Bisoprolol + Amlodipine	CONCOR AM (Merck)	5mg/2.5mg 5mg/5mg
Nebivolol + S-Amlodipine	NEBICARD SM (Torrent pharmaceuticals)	5mg/2.5mg
Amlodipine + Atenolol	AMLODAC AT (Zydus Cadila)	5mg/50mg
Telmisartan + Cilnidipine	ERITEL LN (Eris Life Sciences)	40mg/10mg 80mg/10mg
Telmisartan + HCTZ	TELMIGET H (Lividus)	40mg/12.5mg 80mg/12.5mg
Telmisartan + Amlodipine	TELMIGET AM (Lividus)	40mg/5mg 80mg/5mg
Olmesartan + Metoprolol	OLMEZEST BETA (Sun Pharma)	20mg/25mg
Losartan + Amlodipine	AMLOKIND L (Mankind Pharma)	50mg/5mg
Ramipril + Amlodipine	CARDACE AM (Sanofi India)	2.5mg/5mg 5mg/5mg
Ramipril + Metoprolol	CARDACE METO (Sanofi India)	2.5mg/25mg 5mg/50mg
Telmisartan + Chlorthalidone	ERITEL CH (Eris Life Sciences)	80mg/12.5mg 40mg/12.5mg
Losartan + HCTZ	LOSAR H (Unichem laboratories)	50mg/12.5mg
Atenolol + Indapamide	ATEN D (Zydus)	50mg/2.5mg 50mg/1.5mg
Metoprolol + Amlodipine	PROLOMET AM (Sun Pharma)	50mg/5mg 25mg/5mg
Amlodipine + Perindopril	COVERSYL AM (Serdia Pharmaceuticals)	5mg/4mg 5mg/8mg 10mg/4mg 10mg/8mg
Bisoprolol + HCTZ	CONCOR PLUS (Merck)	5mg/12.5mg
Olmesartan + Chlorthalidone	OLMEZEST CH (Sun Pharma)	20mg/12.5mg 40mg/12.5mg
Nebivolol + HCTZ	NEBICARD H (Torrent pharmaceuticals)	5mg/12.5mg
Atenolol + Lercanidipine	LOTENSYL AT (Sun Pharma)	50mg/10mg
Losartan + Atenolol	LOSAR BETA (Unichem laboratories)	50mg/50mg
Metoprolol + Telmisartan	METOSARTAN (Sun Pharma)	50mg/40mg
S-amlodipine + HCTZ	ASOMEX D (Emcure Pharmaceuticals)	2.5mg/12.5mg
Olmesartan + Indapamide	OLMY D (Zydus Cadila)	20mg/1.5mg

Table III: Drug combinations used.

RAAS inhibitor + Diuretic	RAAS inhibitor + CCB	RAAS inhibitor + B blocker	β blocker + Diuretic	CCB + B blocker	Olmesartan + HCTZ + Amlodipine	CCB + Diuretic
49(32.6%)	42 (28%)	10 (6.6%)	4 (2.6%)	21(14%)	23 (15.3%)	1(0.6%)

RAAS: RENIN ANGIOTENSIN ALDOSTERONE SYSTEM; HCTZ: HYDROCHLOROTHIAZIDE

Illustrations

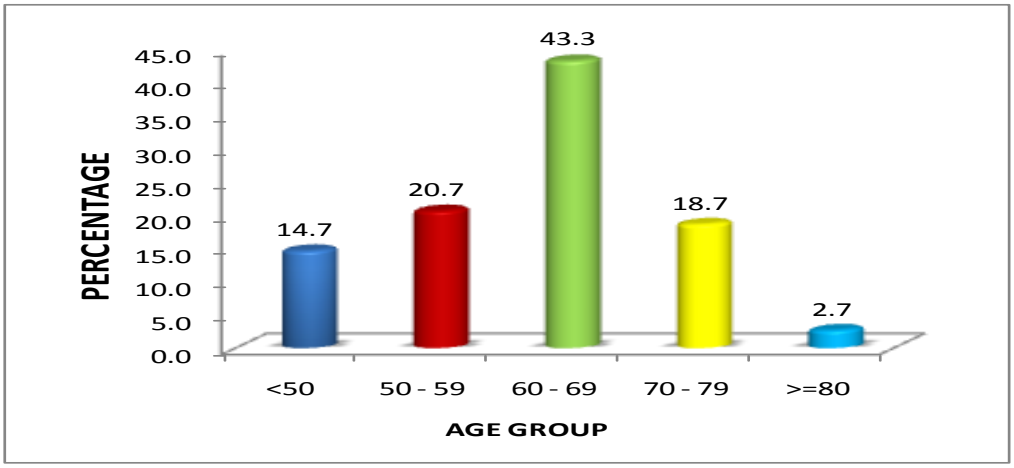

Fig. I: Distribution of age.

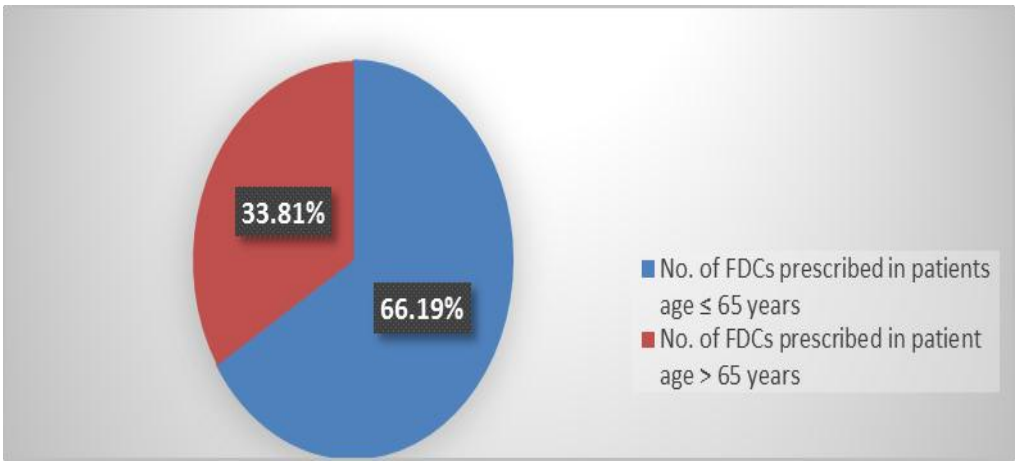

Fig. II: Number of FDCs prescribed in particular age group.

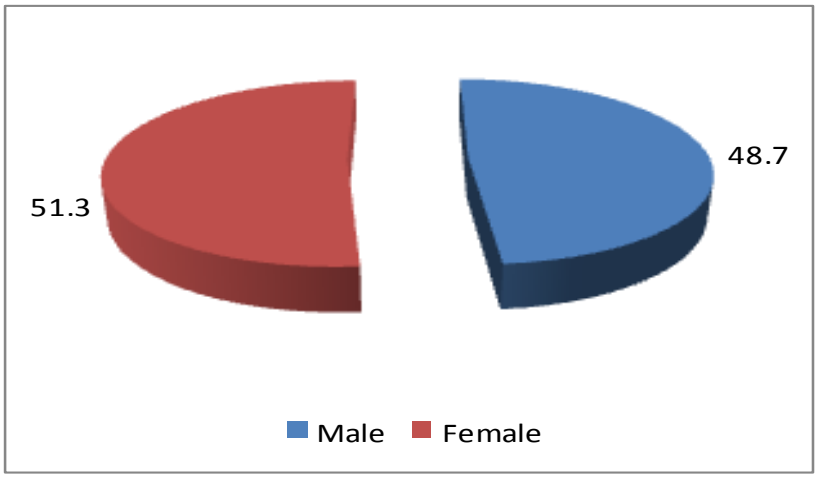

Fig. III: Distribution of gender.

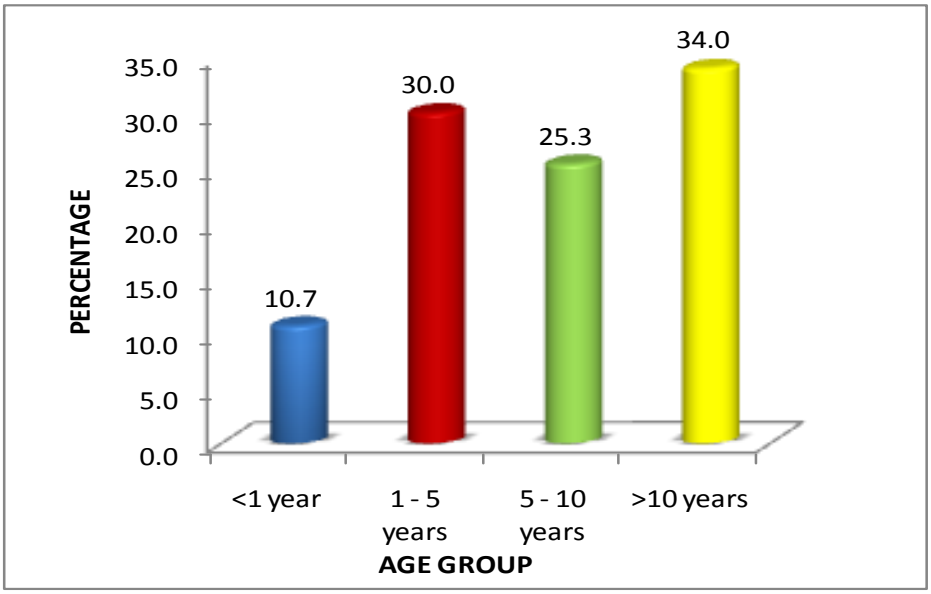

Fig. IV: Distribution of duration of hypertension.

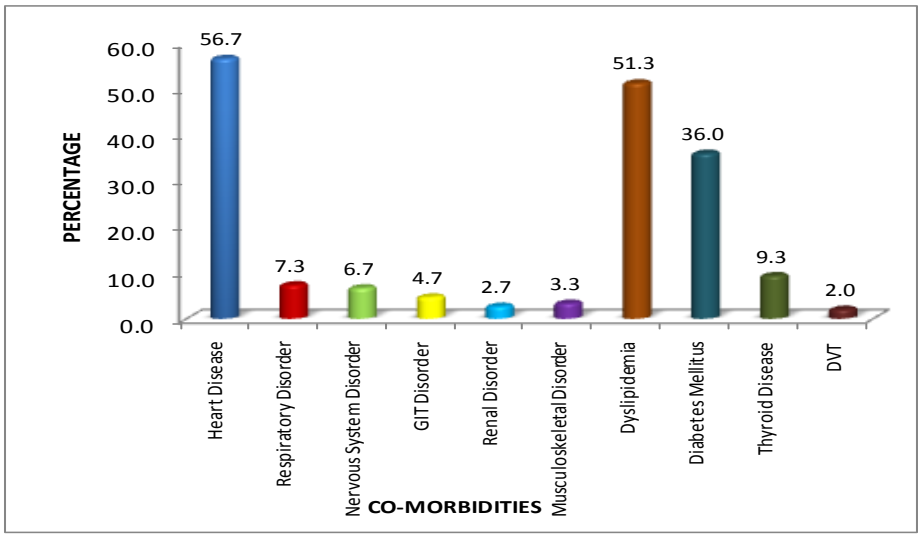

Fig. V: Distribution of co-morbidities.

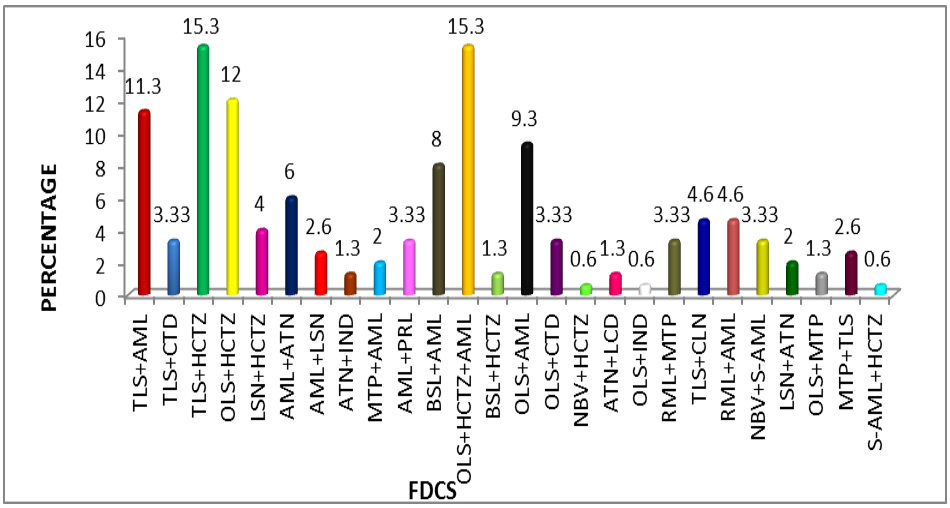

Fig. VI: Distribution of FDCs in patients.

TLS: TELMISARTAN; AML: AMLODIPINE; CTD: CHORTHALIDONE; HCTZ:HYDROCHLOROTHIAZIDE; OLS: OLMESARTAN; LSN: LOSARTAN; AML;AMLODPINE; ATN: ATENOLOL; IND: INDAPAMIDE; MTP: METOPROLOL; PRL: PERINDOPRIL; BSL: BISOPROLOL; NBV: NEBIVOLOL; RML: RAMIPRIL; LCD: LERCANIDIPINE; CLN: CILNIDIPINE; S-AML: S-AMLODIPINE.

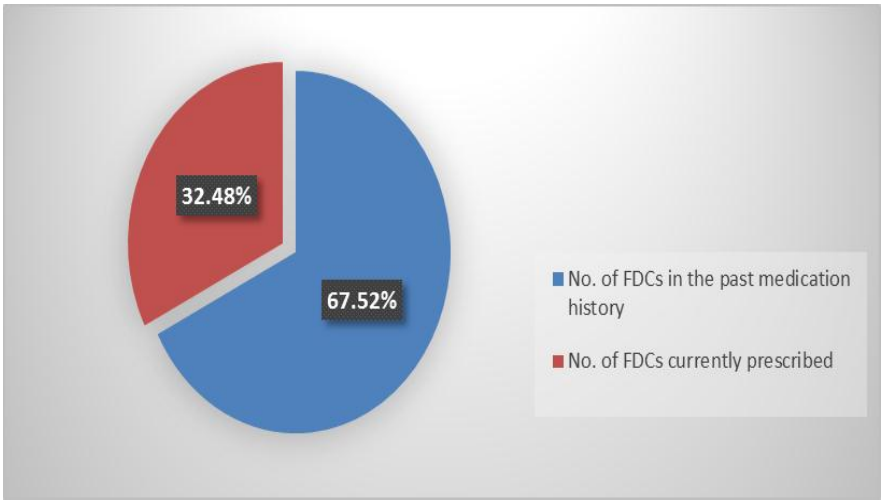

Fig. VII: Number of FDCs found in the past medication history of the patient case sheets.

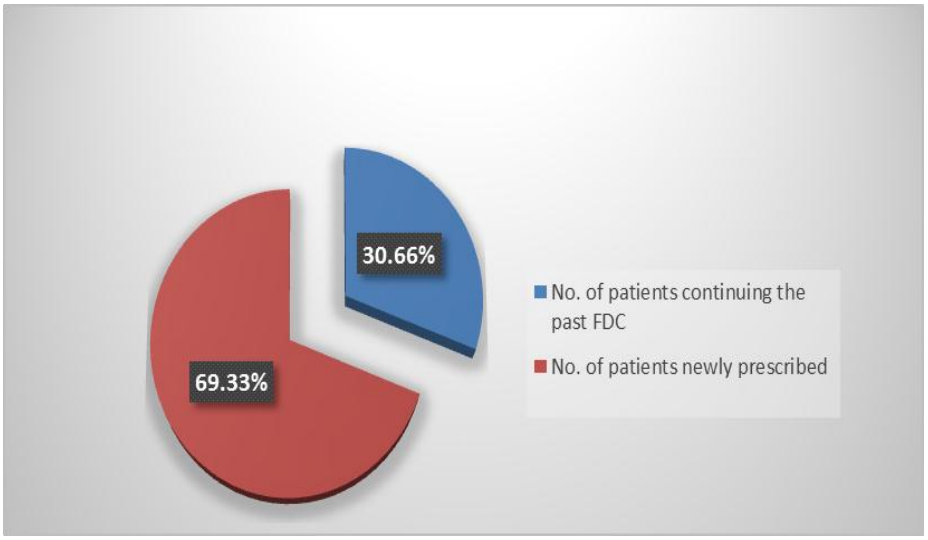

Fig. VIII: Number of patients continuing the past FDCs.

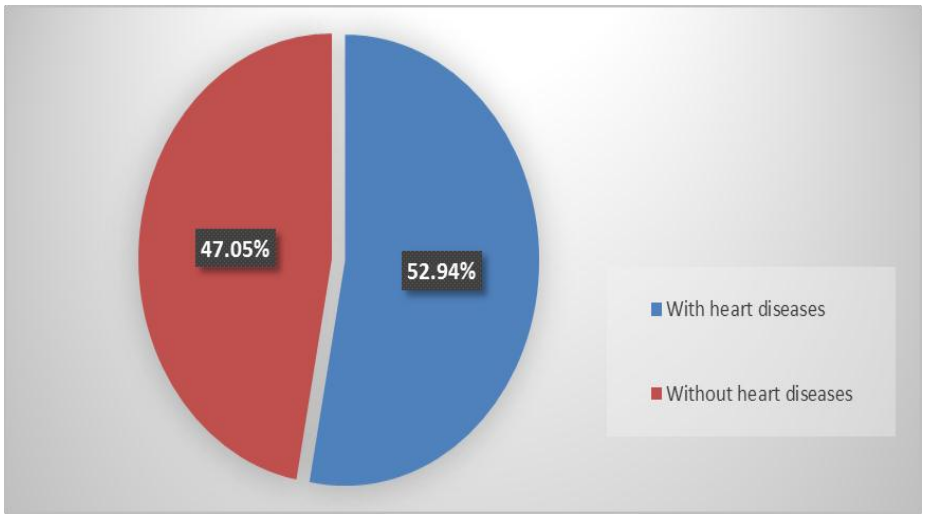

Fig. IX: Graph showing the rationality of prescribing of RAAS inhibitor and beta blocker.

DISCUSSION

The prospective observational study was conducted for a period of six months in the outpatients of the cardiology department who are prescribed with anti-hypertensive FDCs. A total of 150 patients met the inclusion criteria.

Age

Out of 150 patients analysed for taking anti-hypertensive fixed dose combinations in the cardiology department of a tertiary care hospital, most of them were in the age group 60-69 with a mean of 61.5 ± 10.5. This age group is associated with multiple illness and polypharmacy and hence necessitating the need for prescribing FDCs, and when compared with the study of Londhe SP et al on prescribing pattern of FDCs, a similar result was obtained. But comparatively more number of FDCs were prescribed in patients aged ≤ 65 years.

Gender

Among 150 patients, 77(51.3%) were females and 73(48.7%) were males. Almost nearly equal numbers of males and females were observed in our study. The study has similar findings with the study conducted by Pamidi Pradeep et al on prescribing pattern of anti-hypertensive drugs. The risk of hypertension is similar in males and females after menopause.

Duration of hypertension

Comparatively prescriptions of anti-hypertensive FDCs were more commonly observed in patients with longer duration of hypertension than in recently detected hypertensives. Adherence rate decreases with increasing duration of hypertension, but FDCs promote better compliance, persistence with treatment and motivate patients to adhere to lifelong therapy.

Co-morbidities

In our study, among 150 patients, only 10% were with hypertension alone. Most of the patients had other concomitant illnesses. The major concomitant diseases present among these hypertensives were heart diseases, followed by dyslipidemia and diabetes mellitus. Spectrums of heart diseases were observed and it covered coronary artery disease, angina, myocardial infarction, heart block, atrial fibrillation, sinus tachycardia and bradycardia, aneurysms, diastolic and LV dysfunction.

Other system disorders consisted of seizures, bipolar disorders, parkinsonism, stroke, active peptic ulcer disease, GERD, NAFLD, renal failure, osteoarthritis, osteoporosis, bronchial asthma, COPD, thyroid disease and DVT.

Most of the patients had more than one co-morbid conditions, and hypertension with concomitant heart disease and dyslipidemia (13.3%) was the most common.

FDCs prescribed

Twenty-six different anti-hypertensive FDCs were observed in the prescriptions during this 6 months period. Different classes of anti-hypertensives were combined, out of which the most commonly used combination was the RAAS inhibitor (ACEI/ARBS) with diuretic combination. Among the diuretics, hydrochlorothiazide was most commonly combined with other anti-hypertensives.

Most of the FDCs prescribed were dual drug combinations. Only one triple drug combination of olmesartan +amlodipine + hydrochlorothiazide was prescribed, which was also most commonly prescribed. In a similar study by Vijayakumar et al on prescribing pattern of cardiovascular FDCs, reported that amlodipine/atenolol was the most commonly prescribed combination followed by telmisartan/HCTZ. In contrast our study found that the triple drug combination of olmesartan/amlodipine/HCTZ and telmisartan/HCTZ was the most commonly prescribed FDC.

Utilization of FDCs in different conditions

RAAS inhibitor/diuretic FDC was more frequently prescribed in patients with hypertension alone which was followed by the triple drug combination. In cases with diabetes mellitus and hypertension, calcium channel blocker/beta blocker and the triple drug combination was prescribed equally. RAAS inhibitor/ calcium channel blocker was most commonly prescribed in patients with hypertension/heart disease, hypertension/heart disease/diabetes mellitus and hypertension/heartdisease/dyslipidemia. In patients suffering from hypertension and dyslipidemia, RAAS inhibitor/diuretic was most frequently prescribed.

Combinations used

Out of 150 prescriptions, 49(32.6%) were the combination of RAAS inhibitor/Diuretic,42(28%) were of RAAS inhibitor/calcium channel blocker, 21(14%) of Calcium channel blocker /Beta blocker, 18(12%) were the triple drug combination of Olmesartan, Amlodipine, and Hydrochlorothiazide, 10(6.6%) were of RAAS inhibitor/Beta blocker, 4(2.6%) of Beta blocker/Diuretic and only 1(0.6%) were the combination of Calcium channel Blocker/Diuretic.

Among the RAAS inhibitor/Diuretic, the combination of telmisartan and hydrochlororthiazide was most commonly used, followed by olmesartan and hydrochlorothazide, olmesartan + chlorthalidone, losartan + hydrochlorothiazide, telmisartan + chlorthalidone, and olmesartan + indapamide.

Rationality of Prescribing RAAS inhibitor+B Blocker

On analyzing the prescriptions, four combinations of RAAS inhibitor + Beta blocker were observed. The API of the combinations to be used for the treatment of hypertension, should have an additive BP lowering effect by acting on complementary mechanisms involved in the

pathogenesis of hypertension and blocking the counter-regulatory pathways triggered by one another.[45] The rationale of using such a combination for the sole purpose of treating hypertension is a question mark, as this combination will produce only a modest incremental BP lowering effect because of overlap in their mechanism of action (RAAS inhibition). Owing to such a scenario, the ARB + Beta blocker combinations as an anti-hypertensive is not considered rational, however, these agents are commonly combined and are recommended in patients with heart failure and in post MI patients because of their established effects in reducing the mortality in these populations.[45]

Major limitation of the study is it is monocentered, with limited duration and sample size.

CONCLUSION

FDCs have found a tremendous benefit in various chronic disorders, one among is hypertension. Even though FDCs presents with an array of benefits, it's inappropriate and irrational use is a global problem, which need to be corrected. For this, an important parameter is to study the prescribing pattern of FDCs in either a department, hospital or a group of hospitals. The information gathered gives an overview of prescribing patterns of anti-hypertensive FDCs in real life. The study emphasizes the need to formulate and implement appropriate prescribing guidelines on fixed dose combinations based on local prescribing, and to conduct further studies to analyse and improve the prescribing patterns and promote rational drug use.

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