AJMHR
Asian Journal of Medical and Health Research
Journal home page: www.ajmhr.com

Evaluation of rationality of fixed dose combination (FDC) of antihypertensive drug in a Multi-specialty tertiary care hospital in south India.

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ABSTRACT

Most of the patients in current scenario are treated with more than one anti-hypertensives and most often with fixed dose combinations. Hence the use and efficacy of fixed dose combination are controversial and is the most debated issue in Indian perspective. The aim of this prospective observational study was to evaluate the rationality of fixed dose anti-hypertensive combinations used in our hospital. The study was conducted in the cardiology department of multispeciality tertiary care hospital in South India. A total of 150 hypertensive patients prescribed with anti-hypertensive FDCs were randomly selected and their outpatient records were monitored and documented in a specially designed proforma for a period of six months. During the study period, 150 patients met the selection criteria, a total of 26 different anti-hypertensive FDCs were found, among them 7 were irrational. Among the 26 different anti-hypertensive fixed dose combinations analyzed, 19 FDCs (73%) were found to be rational and 7 combinations (27%) were found to be irrational for using in hypertension with a mean of 8.6 ± 2.7. During this limited study period with only 26 anti-hypertensive FDCs, we were able to find an irrational FDC, which clearly show an urgent need to conduct further studies on evaluating the rationality of FDCs as a whole. The Indian laws are not properly defined to grant marketing approvals of FDCs by State or Central Drug Controlling Authorities. Hence this study enlightens the role of clinical pharmacist in defining the efficacy, safety, suitability, rationality & withdrawal of FDCs.

Keywords: Hypertension, Fixed dose combination, Rationality, Clinical pharmacist, Drug Controlling Authorities.

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Received 16 July 2016, Accepted 20 September 2016

Please cite this article as: Neethu J., Evaluation of rationality of fixed dose combination (FDC) of antihypertensive drug in a Multi specialty tertiary care hospital in south India.. Asian Journal of Medical and Health Research 2016.

INTRODUCTION

Hypertension is a heterogenous, hemodynamic disorder, associated with an increase in total peripheral vascular resistance caused by constriction of small arterioles. 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. [1]

Based on the outcome of the combination, the efficacy of the antihypertensive drug, and its safety and/or tolerability, fixed dose combinations are subdivided into preferred, acceptable, unacceptable or ineffective combinations. [2,3]

Table 1: Classification of combinations based on preference.

Antihypertensive fixed dose combinations	Brand names	Strengths
Olmesartan + Amlodipine	OLMEZEST AM	20mg/5mg 40mg/5mg
Olmesartan + Amlodipine + HCTZ	TRIOLMEZEST	20mg/12.5mg/5mg 40mg/12.5mg/5mg
Olmesartan + HCTZ	OLMEZEST H	20mg/12.5mg 40mg/12.5mg
Bisoprolol + Amlodipine	CONCOR AM	5mg/2.5mg 5mg/5mg
Nebivolol + S-Amlodipine	NEBICARD SM	5mg/2.5mg
Amlodipine + Atenolol	AMLODAC AT	5mg/50mg
Telmisartan + Cilnidipine	ERITEL LN	40mg/10mg 80mg/10mg
Telmisartan + HCTZ	TELMIGET H	40mg/12.5mg 80mg/12.5mg
Telmisartan + Amlodipine	TELMIGET AM	40mg/5mg 80mg/5mg
Olmesartan + Metoprolol	OLMEZEST BETA	20mg/25mg
Losartan + Amlodipine	AMLOKIND L	50mg/5mg
Ramipril + Amlodipine	CARDACE AM	2.5mg/5mg 5mg/5mg
Ramipril + Metoprolol	CARDACE METO	2.5mg/25mg 5mg/50mg
Telmisartan + Chlorthalidone	ERITEL CH	80mg/12.5mg 40mg/12.5mg
Losartan + HCTZ	LOSAR H	50mg/12.5mg
Atenolol + Indapamide	ATEN D	50mg/2.5mg 50mg/1.5mg
Metoprolol + Amlodipine	PROLOMET AM	50mg/5mg 25mg/5mg
Amlodipine + Perindopril	COVERSYL AM	5mg/4mg 5mg/8mg 10mg/4mg 10mg/8mg
Bisoprolol + HCTZ	CONCOR PLUS	5mg/12.5mg
Olmesartan + Chlorthalidone	OLMEZEST CH	20mg/12.5mg 40mg/12.5mg

Nebivolol + HCTZ	NEBICARD H	5mg/12.5mg
Atenolol + Lercanidipine	LOTENSYL AT	50mg/10mg
Losartan + Atenolol	LOSAR BETA	50mg/50mg
Metoprolol + Telmisartan	METOSARTAN	50mg/40mg
S-amlodipine + HCTZ	ASOMEX D	2.5mg/12.5mg
Olmesartan + Indapamide	OLMY D	20mg/1.5mg

List of anti-hypertensive FDCs used in this study.

Preferred	Acceptable	Less effective
ACE inhibitor/diuretic	β-Blocker/diuretic	ACE inhibitor/ARB
ARB/diuretic	CCB (dihydropyridine)/β-blocker	ACE inhibitor/β-blocker
ACE inhibitor/ CCB	CCB/diuretic	ARB /β-blocker
ARB/CCB	Renin inhibitor/diuretic	CCB (nondihydropyridine)/ β-blocker
	Renin inhibitor/CCB	
	Thiazide diuretics/K+-sparing diuretics	Centrally-acting agent/β-blocker

Combination therapy versus fixed dose combinations:

There are two types of combination therapy:

- Drugs given in fixed dose combination
- Various drugs prescribed separately.

Fixed dose combination (FDC) is defined as combination of two or more active ingredients in a single pharmaceutical formulation in a fixed ratio of doses. Using FDC simplifies regimen with fewer pills which are preferred mainly for elderly patients who are uncompliant to monotherapy.

Some of the merits offered by FDCs include;

- Simpler dosage schedule improves compliance and therefore improves treatment outcomes [5.]
- Reduced in advertent medication errors [5].
- More convenience in prescribing [4].
- 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 [6].
- Blood pressure targets will be attained more quickly [7.]
- Reduced pill burden [4].
- The demerits offered by them are;
- Dosage alteration of one drug is possible without alteration of other drug [5].
- More difficult to pinpoint the offending agent responsible for the adverse reaction [5].
- FDC dosing is inflexible and cannot be regulated to patient's need [4].
- Increased number of drug-drug interactions [8].

Dual fixed dose combination:

Combination therapy is used when adequate BP lowering is not achieved with monotherapy. Blood pressure is a multi-regulated variable and require administration of two or more antihypertensive drugs with different and complementary mechanisms of action. It is to be noted that a single drug can control BP in no more than 1 out of 4 or 5 patients, but two drugs can be successful in 60% of hypertensive individuals.

Treatment with a two-drug antihypertensive combination is especially recommended either in high risk patients to minimize the development / progression of target organ damage / vascular complications or in patients with stage 2 hypertension.

Triple fixed dose combination:

Triple fixed dose combinations are a choice when patients can't obtain target blood pressure with two drugs in combination. Three-in-one fixed dose combination of reserpine, apresoline and hydrochlorothiazide was the first triple fixed dose formulation to be marketed in US [8.] Tribenzor, a triple fixed dose combination consisting of amlodipine, olmesartan medoxomil and hydrochlorothiazide, was approved by FDA in July 2010, and trial certificated that the formulation can provide an effective and safe hypertension controlling obese patients except the normal hypertensive patients [8]. Researchers on the triple therapy exhibited improved adherence and clinical outcomes without increasing cost. Thus triple fixed dose combinations seem to have a market prospect in the near future.

MATERIALS AND METHOD

A prospective observational study was conducted in the Cardiology department of Cosmopolitan hospital, a tertiary care center. In this study, the data of 150 patients were collected randomly for a period of 6 months. Based on inclusion and exclusion criteria 150 prescriptions issued during the period of 6 months were randomly collected and the relevant data was analyzed and tabulated in a specially designed data collection form.

Inclusion criteria:

- ❖ Hypertensive patients who are on fixed dose combination treatment.
- ❖ All outpatients attending the cardiology department.
- ❖ Patients with age ≥ 18 years.
- ❖ 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.

Patient's demographic details, pertinent laboratory and clinical information were collected during the outpatient hours and by reviewing the medical records. A comprehensive seven-point criterion developed by Panda et al was used for the evaluation of rationality of the FDCs which indicate all dimensions of defining a rational FDC. Each FDC was assessed for number of active pharmacological ingredients, approval by regulatory authority, listing in WHO Essential Medicine List (EML) or National List of Essential Medicine (NLEM). The maximum scoring of seven point criteria is 14 with each criterion carrying a score of 2 and score ≥8 is considered rational.

RESULTS AND DISCUSSION

On the basis of the study conducted in the cardiology department of a tertiary care hospital for 6 months the following results were obtained. All FDC containing prescriptions issued in the department were collected. During the study period, about 150 prescriptions containing anti-hypertensive FDCs were obtained, which met the inclusion criteria of our study.

FDCs prescribed:

Twenty-six different anti-hypertensive FDCs were observed in the prescriptions during this 6 months period. The figure:1 shows the percentage of fixed dose combinations prescribed in hypertensive patients who attended the cardiology department. 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.

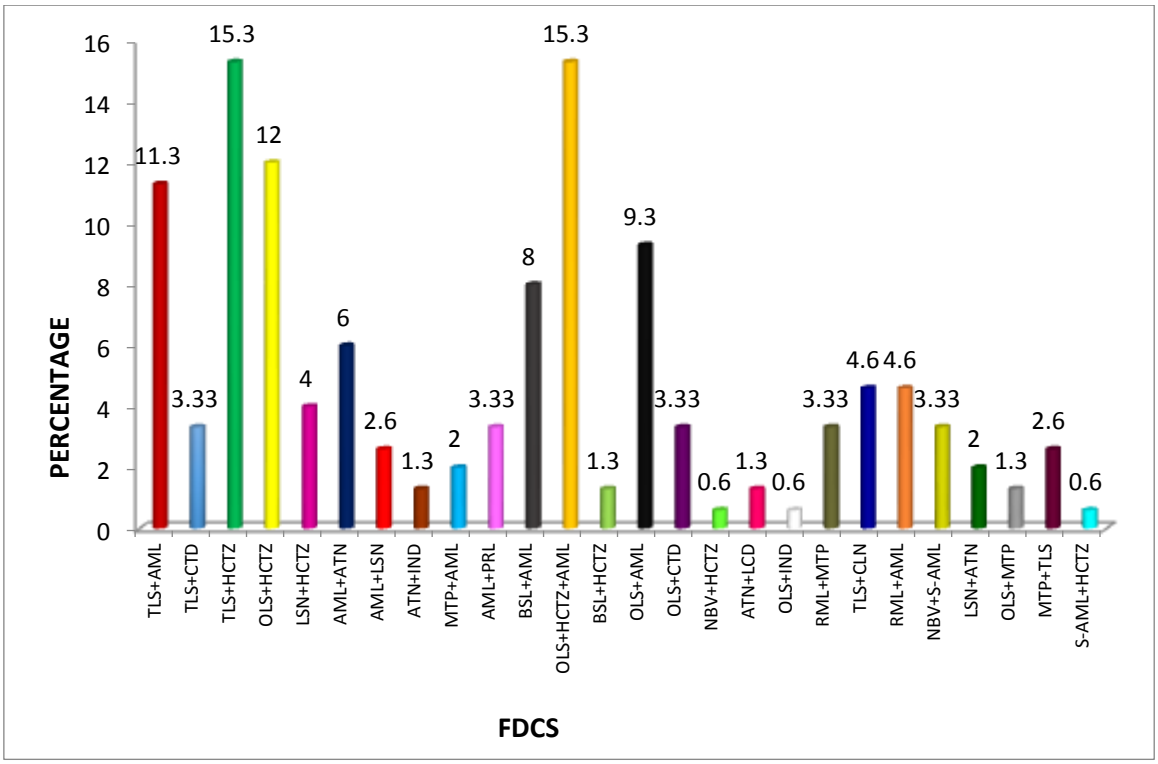

Figure 1: Distribution of FDCs in patients

Marketed anti-hypertensive FDCs used in the study

A total of 26 FDCs where observed in the study, the table:1 shows the list of most commonly prescribed brand names of FDCs with the strengths available.

Rationality of anti-hypertensive FDCs:

The FDCs used in the study was analyzed according to seven point criteria and following percentage of FDCs were categorized as rational and irrational shown in figure: 2. Table 2 shows the scoring of FDC according to seven point criteria.

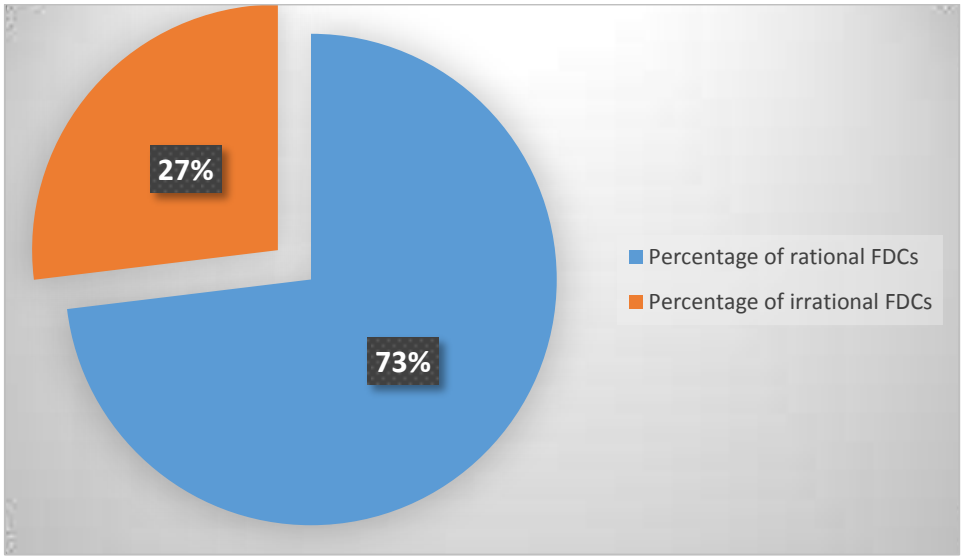

Figure 2: **Distribution of rationality of anti-hypertensive FDCs**

Table 2: Scoring by Seven Point Criteria

Antihypertensive FDC's	Seven Point Criteria							
	1	**2**	**3**	**4**	**5**	**6**	**7**	**Total Score**
Losartan/HCTZ	1	2	2	2	2	2	2	13
Telmisartan/CTD	-2	2	2	2	2	2	2	12
Amlodipine/Atenolol	2	2	2	2	-2	-2	2	10
Amlodipine/Bisoprolol	1	2	2	2	-2	-2	2	9
Amlodipine/Metoprolol	1	2	2	2	-2	-2	2	9
Atenolol/ Indapamide	-1	2	-2	2	-2	-2	2	7
Bisoprolol/ HCTZ	1	2	-2	2	-2	-2	2	7
Telmisartan/ Amlodipine	1	2	2	2	2	2	2	13
Olmesartan/Amlodipine	1	2	2	2	2	2	2	13
Telmisartan/Cilnidipine	-2	2	2	2	2	-2	2	10
Telmisartan/Metoprolol	1	2	-2	2	-2	-2	-2	5
Losartan/Atenolol	1	2	-2	2	-2	-2	-2	5
Amlodipine/Perindopril	1	2	2	2	2	2	2	13
Nebivolol/HCTZ	1	2	-2	2	-2	-2	2	7
Lercanidipine/Atenolol	1	2	-2	2	2	-2	2	9
S-amlodipine/HCTZ	1	2	-2	2	-2	2	2	9
Ramipril/Metoprolol	1	2	-2	2	-2	-2	-2	5
Ramipril/Amlodipine	1	2	2	-2	2	2	2	11
Olmesartan/ Indapamide	-2	2	-2	2	2	2	2	10
Olmesartan/HCTZ/ Amlodipine	1	2	2	2	2	2	2	13
Olmesartan/ Chlorthalidone	-2	2	2	-2	2	2	2	10
Nebivolol/ S-amlodipine	-2	2	-2	2	2	-2	2	8
Olmesartan/Metoprolol	1	2	-2	2	-2	-2	2	7
Losartan/Amlodipine	-1	2	2	-2	2	2	2	11
Olmesartan/HCTZ	1	2	2	-2	2	2	2	11
Telmisartan/HCTZ	1	2	2	-2	2	2	2	11

Rationality of FDCs need to be assessed at the early phase of its development, since it is difficult to establish the bioavailability studies of APIs in an FDC. But the pharmaceutical companies are promoting FDCs without proper bioavailability studies, as a result of which many FDCs are flourishing in the Indian market. This facilitates the need of using comprehensive criteria to assess the rationality.

Among the 26 different anti-hypertensive fixed dose combinations analyzed, 19 FDCs (73%) were found to be rational and 7 combinations (27%) were found to be irrational for using in hypertension with a mean of 8.6 ± 2.7.

The results of the assessment showed that for 80.7% of FDCs, the individual components were present in any one or both the EML of WHO or NLEM of India. However, 19.2% of FDCs, the individual components were absent in both the list. The dose and proportion of each API present in FDCs (100%) matched with the recommended doses.

Among the FDCs, 57.6% of combinations had published evidence on the efficacy and safety over individual drugs administered separately whereas, for 42.3% of FDCs lack data on clinical safety and efficacy, thereby a definite conclusion was not achieved. FDCs of such category were Lercanidipine + Atenolol, S-amlodipine +HCTZ, Atenolol + Indapamide, Nebivolol + S-amlodipine.

Of the 26 FDCs analyzed, 21 FDCs (80.7%) were found to be more cost-effective than their individual components. For a few FDCs, like Ramipril/Amlodipine, Losartan/Amlodipine, Olmesartan/HCTZ, Telmisartan/HCTZ, and Olmesartan/Chlorthalidone the cost of the combinations was more than the added individual component's cost.

For 57.6% FDCs studied, there was published evidence on the reduction of dose of individual drugs or their adverse effects. 53.8% FDCs had no unfavourable pharmacokinetic or pharmacodynamic interactions between APIs, whereas, for 38.4% of FDCs had unfavourable pharmacodynamic interactions. For Nebivolol/S-amlodipine, S-amlodipine/HCTZ, Telmisartan/Cilnidipine and Lercanidipine/Atenolol, the interactions between their respective components were not available in the databases.

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. Such rationale of combination can be seen in most of the FDCs in the present study except the combination of RAAS inhibitor (ACEI/ARBs) with a beta blocker.

=On analyzing the prescriptions, four combinations of RAAS inhibitor + Beta blocker were observed. Even though the combination of RAAS inhibitor + Beta blocker is not an irrational combination for patients with heart diseases, in this study, about 47.05% of hypertensives without heart diseases were prescribed with this combination. 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[31]

Even though beta-blocker and diuretic FDC is classified as an acceptable combination for treating uncomplicated hypertension, its use is currently out of favour because of new- onset diabetes. Also there is an increased risk of fatigue, sexual dysfunction and glucose

intolerance. Reserved for patients with hypertension plus another condition that would benefit from a beta-blocker (e.g., heart failure, post MI, angina etc).[33]

Dihydropyridine calcium channel blockers and beta- blocker FDC is considered to be an acceptable combination for treating uncomplicated hypertension, whereas, non-dihydropyridine calcium channel blockers, such as verapamil and diltiazem should be avoided in combination with beta-blockers due to their additive effects in heart rate and A-V conduction that may result in symptomatic bradycardia and atrioventricular block. Out of the various such combinations, the FDCs lercanidipine/atenolol and nebivolol/s-amlodipine lack published data on its safety and efficacy as well as the interactions between their respective components were not available in the databases.

Even though nebivolol/s-amlodipine is a favourable combination in terms of nebivolol which have an excellent glycemic and lipid profile and the chirally pure s-amlodipine, but there are no favourable and ample studies done on the combination outweighing its benefit to risk. In the same way, more studies on lercanidipine combinations should be done to fully establish its role in effectively reducing BP.

The triple drug combination of olmesartan/amlodipine/hydrochlorothiazide is found to be more efficacious and safe in reducing the high blood pressure in comparison with monotherapy or a combination of two drugs (namely olmesartan+ hydrochlorothiazide) of similar dose. Their efficacy was even extended to patients with chronic co-morbidities who were unable to reach their BP goal. Even though amlodipine is documented to cause pedal edema, the side effect was attenuated by the inclusion of hydrochlorothiazide. Similarly, the side effects of hydrochlorothiazide (namely hypokalemia) were ameliorated by the addition olmesartan, which is known to cause hyperkalemia. Hence this particular triple drug combination is proven as best.

Irrational Combinations found

After analyzing the FDCs according to the criteria, the table:3 show the irrational FDC.

Table 3: **List of irrational combinations.**

1.	Telmisartan +Metoprolol
2.	Losartan + Atenolol
3.	Olmesartan + Metoprolol
4.	Atenolol + Indapamide
5.	Bisoprolol + Hydrochlorothiazide
6.	Nebivolol + Hydrochlorothiazide
7.	Ramipril + Metoprolol

Rationality of Prescribing RAAS inhibitor + B Blocker:

On screening for irrational prescriptions of RAAS inhibitor/β blocker, the following results were obtained which is shown in figure: 3. Even though the combination of RAAS inhibitor

+ Beta blocker is not an irrational combination for patients with heart diseases, in this study, about 47.05% of hypertensives without heart diseases were prescribed with this combination.

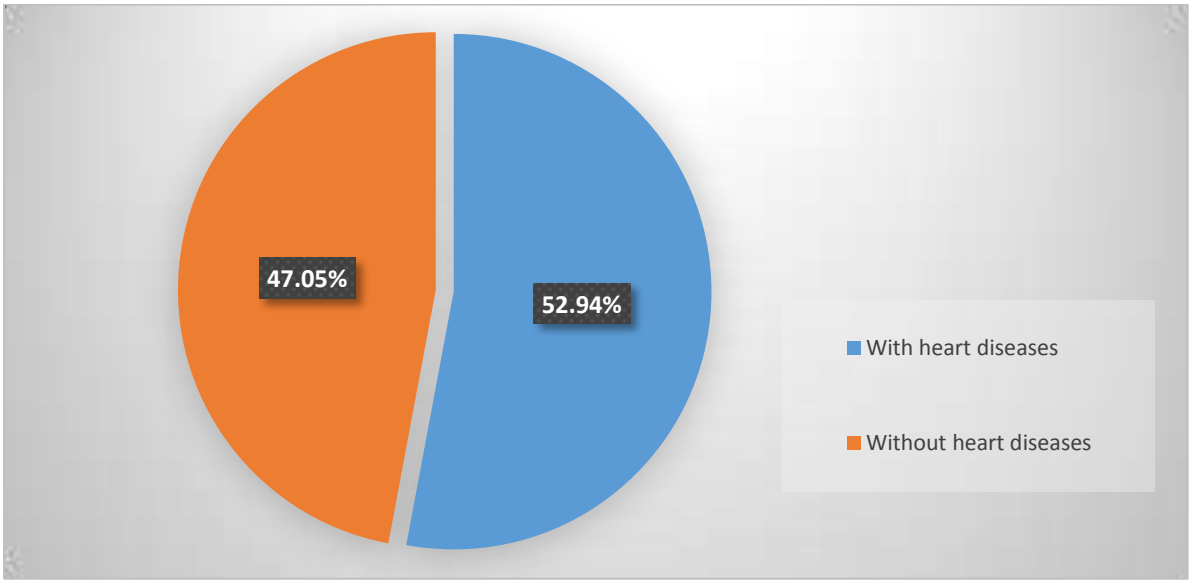

Figure 3: **Graph showing the rationality of prescribing of RAAS inhibitor and beta blocker.**

Rationality scoring:

After analyzing the FDCs with 7 point criteria the following results were obtained mentioned in table:4 and figure: 4. Rationality of the FDCs was evaluated using a comprehensive seven-point criterion developed by Panda et al which indicated all dimensions of defining a rational FDC. The maximum scoring of seven point criteria is 14 with each criterion carrying a score of 2 and score ≥8 is considered rational.

Scores of the present study ranged between 4 and 14. Out of the 7 irrational FDCs, four FDCs scored 7 and three FDCs scored 5.

Table 4: **Rationality score of antihypertensive FDCs.**

Rationality score	Number of FDCs	Percent
<=7	7	26.9
7 – 9	5	19.2
9 – 11	7	26.9
11 – 14	7	26.9

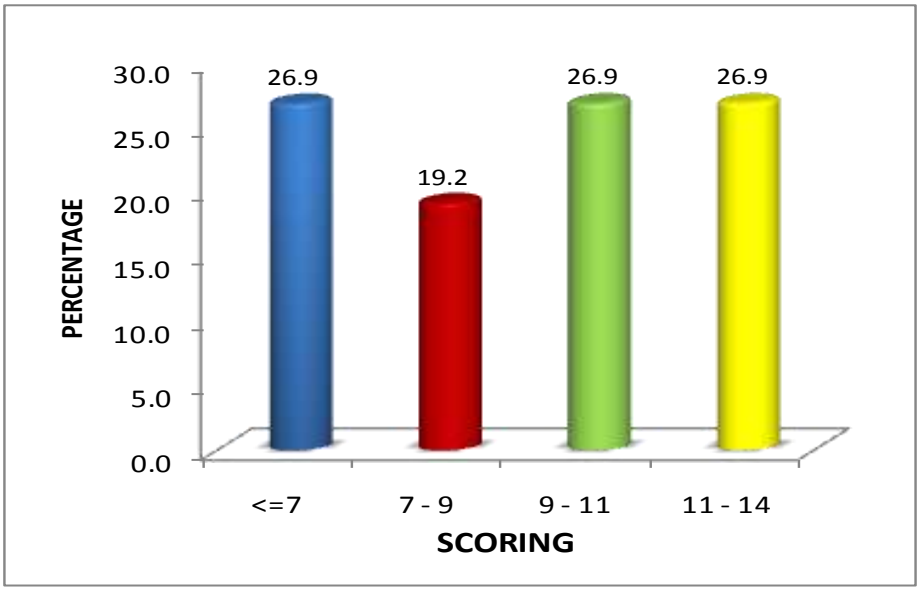

Figure 4: **Graph showing rationality score of anti-hypertensive FDCs**

CONCLUSION

The present study was conducted to evaluate the rationality of fixed dose combinations (FDC) of antihypertensive drugs. FDCs have found a tremendous benefit in various chronic disorders, one among is hypertension. Majority of studies conducted were based on cardiovascular and antibiotic combinations. In such a perspective, our study is the first to focus on anti-hypertensive FDCs alone. Even though FDCs presents with an array of benefits, it's inappropriate and irrational use is a global problem, which need to be corrected. This can only be done by analyzing the rationality of various individual FDCs belonging to different classes. This study has made a systematic point-by-point evaluation of fixed dose combinations for managing hypertension, on the basis of the comprehensive criteria. A large majority of FDCs were found to reasonably comply with the criteria to assess the rationality of FDCs. However, certain FDCs failed to meet the criteria. The major problem faced in assessing rationality was the absence of published evidences on fixed dose combinations. Hence it is very critical to perform such studies as well as to publish the results irrespective of the outcome obtained. As a clinical pharmacist, it is the need of the hour to elevate influence beside the growing list of irrational FDCs and try to reduce the enormity of this problem by providing information regarding their efficacy, safety, suitability, and rationality to all including DCGI to endeavor against irrational FDCs in the Indian market.

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