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Evaluation of the Rationality of Fixed Dose Combinations of Cardiovascular drugs in a Multispecialty Tertiary care hospital in Coimbatore, Tamilnadu, India.

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Abstract:

***Plan**: To assess the Rationality of Fixed dose combinations (FDC) of Cardiovascular drugs in a multidisciplinary hospital in Coimbatore, India*

***Prologue**: Rationality of fixed dose combinations (FDC) containing cardiovascular drugs is one of the controversial and debated problems in today's health care practice. Research in this field has not been flourished and limited data are available regarding rationality of fixed dose combinations. A prospective and descriptive study was conducted in the cardiology and general medicine department of a 550 bedded multi-specialty tertiary care teaching hospital for a period of six months.*

***Methodology**: The rationality was assessed using seven-point criteria. Hundred prescriptions were analyzed during the study period which included 606 cardiovascular drugs. Of these, 21.78% were cardiovascular fixed dose combinations. The most commonly prescribed combinations were aspirin + clopidogrel (38.63%) followed by furosemide + spironolactone (15.9%) and telmisartan + hydrochlorothiazide (12.88%). There were 18 different fixed dose combinations of cardiovascular drugs. Among the combinations, 35.71% were rational with respect to all the seven criteria with a scoring of 14 (100%). Around 11.11% combinations scored 13 while 55.56% scored 8 - 12 and 5.56% scored 7.*

***Outcome**: The results indicated that most of the prescribed cardiovascular FDCs in the multidisciplinary tertiary care hospital selected were rational and found to comply with the seven point criteria scale.*

***Keywords:** Fixed dose combinations (FDC), cardiovascular drugs & prescriptions, seven point scale assessment.*

1. Introduction

Cardiovascular diseases are those diseases that affect heart or blood vessels which include arteries and veins. The major risk factors for a fatal cardiovascular disease are high blood cholesterol, high blood pressure, smoking, diabetes, poor diet and overweight. The common cardiovascular diseases are aneurysm, angina, atherosclerosis, cerebrovascular accident (stroke), cerebrovascular disease, congestive heart failure, coronary artery disease, myocardial infarction (heart attack) and peripheral vascular diseases (1). 80% of deaths due to chronic diseases are in low and middle income countries and half are women. Prevalence of CVD in adults has risen four-fold in 40 years and in rural areas it doubled over the past 30 years (2).

In 2005, 53% of the deaths were due to chronic diseases of which 29% was CVD. By 2020, CVD will be the largest cause of deaths in India.

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WHO estimates that India lost a billion dollars in 2005 and likely to lose 237 billion dollars by 2015 in national income from deaths due to heart disease, stroke and diabetes (3). Cardiovascular diseases are increasing mainly due to diet containing fatty foods, stressful or deskbound physical jobs, obesity, decrease in good cholesterol i.e. HDL, weight gain in the abdominal region, some environmental factors like low birth weight and malnutrition.

Patients predisposed to diabetes are more prone for heart attacks as diabetes and cardiovascular diseases are well correlated (4).Various drugs used to treat cardiovascular diseases include diuretics, angiotensin converting enzyme inhibitor, angiotensin receptor blocker, Calcium channel blocker, beta-blockers, alpha blockers, central sympatholytics, vasodilators, nitrates, potassium channel openers, fibrinolytic agents, ionotropic agents, anticoagulants, antiplatelets, dyslipidaemic agents, antiarrhythmic agents and cardiac glycosides (5). Usage of fixed dose combinations in cardiovascular diseases have many advantages such as reduction in cost, adverse effects and dose, ease of use by patients, improved patient compliance and medication adherence (6).

Examples of some commonly prescribed fixed dose combinations in cardiovascular diseases are amlodipine + atenolol, aspirin + clopidogrel, telmisartan + hydrochlorothiazide, atorvastatin + ezetimibe, amlodipine + losartan, etc. (7). Though there are many advantages with FDCs, the use of irrational FDCs can lead to increased adverse reactions, unnecessary hospitalization and financial burden to the consumers. There are unfortunately no worldwide acceptable criteria to define irrational FDCs and no uniform principles or international standards for their development and regulatory assessment (8). Ramipril + telmisartan, atorvastatin + nicotinic acid and enalapril + losartan are examples of some irrational FDCs used in cardiovascular diseases (9). The extent of use of FDCs in cardiovascular diseases and their rationality are not much reported in India. Hence the aim of the present study was to study the prescribing pattern and to assess the rationality of cardiovascular FDCs.

2. Study Protocol

2.1. *Seven-point scale assessment*

A prospective - descriptive study was conducted in the cardiology and general medicine department of a 550 bedded multi-specialty tertiary care teaching hospital for a period of six months. A comprehensive seven-point criterion developed by Panda et al (6) was used for the evaluation of rationality of the FDCs. These criteria include all the dimensions of defining a rational FDC and appropriate weighting (score) has been attached to each criterion. The total score thus obtained by a FDC will reflect its standing on the scale.

The first point in the seven-point criteria for evaluating the rationality of FDCs is that each active pharmaceutical ingredient (API) of the combination should preferably be in the 'essential medicines list' (EML) of WHO or in the National List of Essential Medicines (NLEM) of India. Secondly, the dose of each API should meet the requirements for a defined population group. The dose and proportion of each API present in FDC should be appropriate for the intended use. Thirdly, the combination should have the advantage of established evidence of efficacy and safety. Further, the overall cost of the combination should preferably be less than the cost of the individual components.

The FDC should facilitate either the reduction of the dose of individual drugs or their adverse effects. The pharmacokinetic (PK) parameters of each API should not be affected. There should be no unfavourable pharmacokinetic interaction between the APIs. In case of the PK parameters being different, the clinical benefits should be taken into consideration. Lastly, the individual drugs should have different mechanism of action. The maximum scoring of the seven point criteria was 14 with each criterion carrying a score of 2.

3. Results and discussion:

Hundred prescriptions containing cardiovascular drugs were analysed during the study period. Age of the patients ranged from 13 to 82 years with a mean 59.31 ± 12.45 years. Their major diagnosis included systemic hypertension (42%), ischemic heart disease (26%) and myocardial infarction (8%). Type 2 diabetes mellitus was the most frequent (21.43%) concomitant disease among these patients. A total of 1189 drugs were prescribed to these patients with a mean of 9.95 ± 3.66 drugs per patient.

The major therapeutic categories of drugs prescribed were anti-platelets (11.52%), diuretics (10.26%), proton pump inhibitors (6.9%), antibiotics (6.9%), anti-diabetics (6.22%) and others (4.04%). The major group of cardiovascular drugs prescribed were anti-platelets (22.61%), statins (11.06%), loop diuretics (8.42%), and β-blockers (8.09%). Among these, 132 (21.78%) prescriptions contributed cardiovascular FDCs (Table I). There were 18 different cardiovascular FDCs prescribed; 38.63% were a combination of clopidogrel + aspirin. Furosemide + spironolactone contributed 15.91% while telmisartan + hydrochlorthiazide contributed 12.88%. Two FDCs with three individual components were also noted during the study period.

Rationality of prescribed FDCs:

The results of evaluation indicated that both the individual components were present in EML of WHO and NLEM of India for 11.1% of FDCs. In case of 66.6% of FDCs, at least one component was present in either EML of WHO or NLEM of India or both. Atorvastatin, fenofibrate, ezetemibe, nebivolol, bisoprolol, ramipril and clopidogrel were absent in both EML of WHO and NLEM of India. The dose and proportion of each API present in FDCs (100%) was found to be appropriate for the individual use. Among the FDCs, 88.8% of the combinations possess the advantage of efficacy and safety over individual drugs administered separately based on established evidences. There was no established evidence in terms of therapeutic efficacy and safety for the two combinations such as metoprolol + amlodipine and nebivolol + s-amlodipine. Most of the FDCs (94.4%) were costs effective when compared with their individual components except nebivolol + s-amlodipine which cost more than the individual components. Figure I illustrates the difference in the cost of individual drugs and their combinations for the commonly prescribed brand names. Fourteen (77.7%) FDCs provide published literature on the reduction of either dose of individual drugs or their adverse effects.

Clopidogrel in combination with aspirin significantly reduces collagen - induced platelet aggregation compared with both monotherapies, suggesting a synergistic platelet inhibitory effect. In addition, the combined treatment resulted in a mild inhibition of aggregation induced by stimulation of platelet thrombin receptor and was more effective in inhibiting platelet activation by thrombin (10). Aspirin which is non-selective COX inhibitor belonging to the category of salicylates act by inhibiting COX and TXA_2 synthase irreversibly by acetylating one of the serine residues while clopidogrel alters surface receptors on platelets and inhibits ADP as well as fibrinogen induced platelet aggregation (5). But a major drawback of this combination is increased risk of bleeding which should be monitored especially in case of stroke patients (11).

Hypokalemia produced by furosemide is controlled by spironolactone. The dose of spironolactone is reduced in the combination when compared to monotherapy. This FDC has also demonstrated high antihypertensive efficacy when compared with high doses of furosemide and spironolactone monotherapy (12). Furosemide acts on the ascending loop of Henley by inhibiting $Na^+/K^+/2Cl^-$ co-transport. Spironolactone belonging to the category of potassium sparing diuretics acts from the interstitial side of the tubular cell, combines with the mineralocorticoid receptor and inhibits the formation of aldosterone induced proteins (AIPs) thus increases Na^+ excretion and decreases K^+ loss (5).The fixed dose combination of furosemide + amiloride produced a synergistic control of blood pressure, reducing morbidity and mortality events (12).

The combination of telmisartan + hydrochlorothiazide has advantage of improved efficacy since numerous previous studies have demonstrated that activation of renin angiotensin-aldosterone system (RAAS) by hydrochlorothiazide enhances the effects of agents acting through blockade of this pathway. When the patient is salt loaded the BP becomes volume dependent and the antihypertensive effect of the agents acting through RAAS is decreased. This effect can be resolved with the addition of diuretic as the BP becomes more renin dependent (13, 14). Telmisartan acts by blocking angiotensin receptor blocker and hydrochlorothiazide act by inhibiting Na^+/Cl^- co-transport system (4).

The current study has identified that the FDC of metoprolol + amlodipine lacks established evidence of efficacy and safety over single compounds administered separately. The combination has shown significant long term decrease in blood pressure. The acute adverse haemodynamic effect of beta-blocker may be reduced when amlodipine is added. Fatigue associated with beta blockers can be reduced when combined with amlodipine. The combination therapy is associated with hypotension and/or bradycardia due to pharmacodynamic interaction and thus cardiac function has to be monitored especially in patients predisposed to heart failure. Amlodipine belonging to the category of dihydropyridine calcium channel blocker, acts by arterial dilation and metoprolol is a cardio selective β_1-blocker and produce its effect by decreasing heart rate (5, 15).

The combination of ramipril and hydrochlorothiazide is found more efficacious and tolerable when compared to ramipril monotherapy. Efficacy is related to the complementary mechanism of action of each API. Hydrochlorothiazide is known to cause hypokalaemia, hyperuricaemia, hyperglycaemia, and hypercholesterolemia. The addition of ramipril attenuates these effects of hydrochlorothiazide (5, 16).

The combination of losartan and hydrochlorothiazide has advantage of improved efficacy since numerous previous studies have demonstrated that activation of renin angiotensin - aldosterone system (RAAS) by hydrochlorothiazide enhances the effects of agents acting through blockade of this pathway. When the patient is salt loaded the BP becomes volume dependent and the antihypertensive effect of the agents acting through RAAS is decreased. This effect can be resolved with the addition of diuretic as the BP becomes more renin dependent. The addition of losartan ameliorates the hypokalaemia associated with the use of hydrochlorothiazide diuretics (6). The combination produces first dose postural hypotension which should be monitored (14).

The study has also documented that the FDC of atenolol and amlodipine does not possess established evidence of efficacy and safety over single compounds administered separately. The combination produces hypotension and bradycardia and thus cardiac function has to be monitored especially in patients predisposed to heart failure. The acute adverse hemodynamic effect of beta-blocker may be reduced when amlodipine is added. Fatigue associated with beta-blockers can also be reduced when combined with amlodipine (15, 17, and 18).When combined with hydrochlorothiazide, the combination of nebivolol shows an additive effect in reducing systolic and diastolic BP compared with monotherapy. The combination produced significant reduction in BP and prevents end organ damage. Nebivolol is a β_1-adrenergic receptor blocker, reducing peripheral vascular resistance by modulating nitric oxide release (19).

An unfavourable interaction with the combination of atorvastatin + clopidogrel is significant decrease in antiplatelet activity by competing through cytochrome pathway metabolism (20). Atorvastatin acts by inhibiting HMGCoA reductase enzyme, last step in cholesterol synthesis by promoting up regulation of LDL receptors while clopidogrel alters surface receptors on platelets and inhibits ADP as well as fibrinogen induced platelet aggregation. Atorvastatin when combined with clopidogrel attenuates the antiplatelet activity of clopidogrel by competing with the cytochrome metabolic pathway (21).

Amlodipine and losartan FDC has sustained high antihypertensive efficacy when compared with high doses of amlodipine and losartan monotherapy alone. The likelihood of development of pedal edema with amlodipine is decreased when combined with losartan (22). Ezetimibe produces a synergistic control of cholesterol level when used along with atorvastatin.When aspirin and atorvastatin is combined, TXA_2 - dependent aspirin resistance is reduced. This mechanism is especially effective in patients with acute myocardial infarction with persistent platelet TXA_2 production (23).

Studies have shown that combination therapy with drugs of complementary mechanism of action like a CCB, an ARB and a diuretic have better BP control with less adverse effects. When amlodipine is combined with losartan, frequency of the side effect such as pedal oedema is lowered (22).Combining ARB and thiazide diuretics show additional benefits like reduction of metabolic adverse effects such as hypokalaemia and hyperuricaemia caused by diuretic stimulation of RAAS (24).

The FDC of bisoprolol and amlodipine has no established evidence of efficacy and safety over single compounds administered separately. The combination produces hypotension and bradycardia and thus cardiac function has to be monitored especially in patients predisposed to heart failure. The acute adverse haemodynamic effect of beta-blocker may be reduced when amlodipine is added. Fatigue associated with beta-blockers can be reduced when combined with amlodipine (15, 17).

In the present study, the most commonly prescribed FDCs were aspirin + clopidogrel (38.63%), followed by furosemide + spironolactone (15.91%), telmisartan + hydrochlorothiazide (12.88%). A similar study by Vijayakumar et al (7) reported that amlodipine + atenolol was the most commonly prescribed combination (12.8%), followed by aspirin + clopidogrel (11.1%), and telmisartan + hydrochlorothiazide (9.8%).Pharmacokinetic or pharmacodynamic interactions were reported in 6 (33.33%) combinations. Table II presents the interacting drugs, type of interaction, their effects, and severity. Individual components in all the FDCs (100%) have different mechanism of action, resulting in either synergistic or additive effects.

The maximum score for the seven point criteria for assessing the rationality of FDCs was 14, with each criterion carrying a score of 2. Scores obtained in the present study ranged between 7 and 14 with an average of 11.61 ± 2.062. One FDC (nebivolol + s-amlodipine) scored 7, three FDCs (aspirin + clopidogrel, metoprolol + amlodipine and clopidogrel + atorvastatin) scored 8 to 10, seven FDCs scored 11 to 12 and seven FDCs scored 13 to 14. The scoring obtained by each FDC in the present study is shown in Table III. Figure II shows the score distribution for the cardiovascular FDCs prescribed in the present study. A score of 7 was obtained by the combination nebivolol + s-amlodipine. This low scoring was due to the absence of nebivolol in both EML of WHO and NLEM of India. In addition, there was no evidence for the efficacy and safety of this combination. It doesn't facilitate any reduction in dose or adverse effects and cost when combined.

4. Conclusion:

The present study has demonstrated that the prescribing pattern of cardiovascular fixed dose combinations in the current study setting is rationale. Most of the FDCs were cost effective. The dose and proportion of each API present in the FDCs were appropriate for the intended use. Further studies are warranted in order to substantiate the efficacy and safety of those combinations which did not comply with all the criteria in the current study.

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Table 1: Prescribing pattern of cardiovascular FDCs (N = 132)

No.	*Cardiovascular FDCs*	*Brand Names*	*Strength (mg)*	*No. of Prescriptions*	*Percentage*
1	Clopidogrel + Aspirin	CLOPITAB - A	75+75	51	38.63%
2	Furosemide + Spironolactone	LASILACTONE	20+50	21	15.91%
3	Telmisartan + Hydrochlorothiazide	TELSARTAN - H	40+12.5	17	12.88%
4	Metoprolol + Amlodipine	METOLAR - AM	25+5	10	7.57%
5	Ramipril + Hydrochlorothiazide	HOPACE - H	2.5+12.5	6	4.54%
6	Losartan + Hydrochlorothiazide	LOSAR - H	50+12.5	5	3.78%
7	Amlodipine + Atenolol	AMLONG - A	5+50	4	3.03%
8	Clopidogrel + Atorvastatin	CLOPITORVA	75+10	3	2.27%
9	Nebivolol + Hydrochlorothiazide	NEBISTAR - H	5+12.5	2	1.51%
10	Amlodipine + Losartan	AMLOZAAR	5+50	2	1.51%
11	Atorvastatin + Fenofibrate	FIBATOR	10+145	2	1.51%
12	Atorvastatin + Ezetimibe	TONACT - EZ	10+10	2	1.51%
13	Amiloride + Furosemide	AMIFRU	5+40	2	1.51%
14	Atorvastatin + Fenofibrate + Ezetimibe	FIBATOR - EZ	10+160 +10	1	0.75%
15	Aspirin + Atorvastatin	ECOSPIRIN - AV	75+10	1	0.75%
16	Losartan + Amlodipine + Hydrochlorothiazide	AMLOZAAR - H	50+5+12.5	1	0.75%
17	Bisoprolol + Amlodipine	ZABESTA - AM	25+5	1	0.75%
18	Nebivolol + s-Amlodipine	NEBISTAR - SA	5+2.5	1	0.75%

Table 2: Interactions between APIs of FDCs

No.	*Drugs*	*Effect*	*Severity*	*Type*	*Favourable/ Unfavourable*
1	Clopidogrel + Aspirin	Increased risk of bleeding	Minor	Pharmacodynamic	Unfavourable
2	Amlodipine + Atenolol	Hypotension and/or bradycardia	Moderate	Pharmacodynamic	Unfavourable
3	Amlodipine + Metoprolol	Hypotension and/or bradycardia	Moderate	Pharmacodynamic	Unfavourable
4	Ramipril + Hydrochlorothiazide	Postural hypotension (first dose)	Moderate	Pharmacodynamic	Unfavourable
5	Bisoprolol + Amlodipine	Hypotension and/or bradycardia	Moderate	Pharmacodynamic	Unfavourable
6	Clopidogrel + Atorvastatin	Attenuation of antiplatelet activity	Minor	Pharmacokinetic	Unfavourable

Table 3: Scoring by criteria

Sl.No.	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*	*11*	*12*	*13*	*14*	*15*	*16*	*17*	*18*
FDC	TLS+HTZ	NBV+HTZ	AML+ATN	AML+LST	ASP+CPL	FRM+SPL	ATV+EZM	ATV+FNF	ATV+FNF+EZM	LST+HTZ	ASP+ATV	AML+FRM	MTP+AML	RML+HTZ	LST+AML+HTZ	CPL+ATV	BPL+AML	NBV+S-AML
Total score	13	13	12	14	9	14	12	12	12	14	11	14	10	11	14	8	11	7

TLS - Temisartan; HTZ - Hydrochlorothiazide; NBV - Nebivolol; AML - Amlodipine; ATN - Atenolol; LST - Losartan; ASP - Aspirin; CPL - Clopidogrel; FRM - Furosemide; SPL - Spironolactone; ATV - Atorvastatin; EZM - Ezetimibe; FNF - Fenofibrate; MTP - Metoprolol; RML – Ramipril

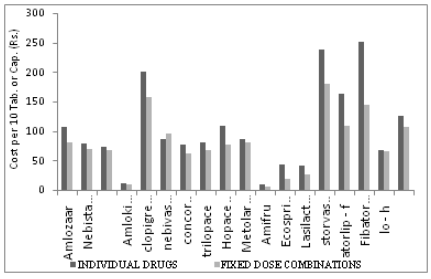

Fig.1. Difference in costs of Individual drugs and their FDCs

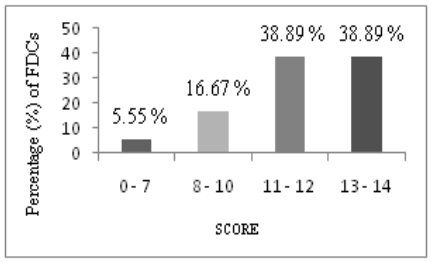

Fig.2. Score distribution of the cardiovascular FDCs

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