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DIFFERENT PROMINENT CHOICES OF FIXED DRUG COMBINATION THERAPY FOR THE MANAGEMENT OF HYPERTENSION AND OTHER CARDIOVASCULAR DISEASE WITH SEVERAL THERAPEUTIC OUTCOMES

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ABSTRACT

Hypertension is a major preventable danger factor for atherosclerosis and ischemic heart disease. Acquiring the objective blood pressure level by monotherapy can be challenging currently, especially for the patients who are suffering from other diseases meanwhile. It is exhibited that a majority of hypertensive patients need two or more antihypertensive drugs to lower their blood pressure effectively. Subsequently, fixed-dose which can be defined as that several active agents were combined in single pharmaceutical formulations appears to be a novel and underlying power in overcoming the cardiovascular disease. In Clinical practices proved that fixed-dose combinations had many advantages comparing with single drug and separate agents in terms of effects, convenience, compliance, and costs to a certain extent. From the patient's perspective, the fixed-dose combination therapy will be increasingly used in blood pressure control in the future. In this review, we analyze the most latest information available regarding the treatment of hypertension with combination treatment.

KEYWORDS: Antihypertensive drugs, fixed dose combination therapy, cardiovascular disease, Hypertension, Monotherapy, and Therapeutic Outcomes.

INTRODUCTION

Hypertension, it's a typical upset, ought to take the foremost responsibility for the morbidity and mortality caused by sickness within the world each year. High blood pressure is that the preliminary reason for upset (CVD) and deaths globally.[1] As early as 1999, according to WHO/ISH guidelines have suggested the monotherapy from six categories and fixed-dose with the definition of mixing 2 or additional active agents during a single pharmaceutical formulation for the initial treatment of high blood pressure, that's to mention, most patients want combination therapy to manage their disease.[2] Hypertension disease continues to rise worldwide and it is been projected 1 billion people will suffer with the disease by the year of 2025 because of poor control include physician dormancy and poor patient compliance and adherence due generally to complicated drug regimens. Since high blood pressure could be a complex condition, its management would require the administration of multiple medicine with complementary mechanisms of action.[3] Three single-pill triple-combination treatments are accessible and each includes an agent affecting the renin-angiotensin aldosterone pathway (either an immediate renin inhibitor or an angiotensin II receptor blocker) in combination with a calcium channel blocker and diuretic. It is, therefore, vital to mix completely different medicine with complementary mechanisms of action into one pill. Based on basis of recent studies have shown that triple-drug combinations are viable effective, safe and well tolerated by the patients. Three different triple-drug, fixed-dose combinations have recently been approved by the FDA for the treatment of hypertension, including, Valsartan / amlodipine besylate / hydrochlorothiazide.[4] The use of single-pill, triple-combination medication medical aid has been shown to be effective, well-tolerated, and convenient treatment methods which will facilitate patients succeed BP management. The advantages of a combination tablet are improving adherence to medication, and reduce cost. The benefits of a mixture pill are raising adherence to medication, and scale back price. The target of the current study is to

develop a stable triple drug combination of Valsartan, Amlodipine and HCTZ for effective and convenient use for treatment of high blood pressure for patients who needs multiple anti-Hypertensive dosing. The Antihypertensive regimens that include agents with complementary mechanisms of action may bring about more prominent decreases in BP than the single-agent components. For example, the use of a calcium channel blocker, an angiotensin receptor blocker, and a thiazide diuretic represents a logical choice for combination treatment. A calcium channel blocker restrains the transmembrane convergence of calcium ions into vascular smooth muscle and cardiac muscle, an angiotensin receptor blocker hinders angiotensin II–mediated vasoconstriction and renal sodium retention, and a thiazide diuretic reduces intravascular volume and total body sodium.[5]

Advantages of fixed-dose combinations Vs Monotherapy

1. Monotherapy versus combination therapy

Various clinical trials show that most hypertensive patients were unlikely to achieve a normal blood pressure by taking single drug for a quite long term. Hence, doctors tend to give a higher dose at the first time, however, high dose treatment usually only bring a modest antihypertensive impact stepped with some certain side effects supporting the perspective that patients may not obtain more at a higher dose when adrug can't meet their needs at a recommended dose.[6]

2. Combination therapy with separate agents versus Fixed-dose combinations

Combination treatment ascends as an alternative for the patients who fail to lower their blood pressure by monotherapy or who are in co-morbidities conditions. Combination treatment was classified into two kinds: one is different drugs were prescribed separately; the other is drugs in fixed-dose combinations. Undoubtedly, the former brought much difficult for the patients especially the elders who were tired of taking a series of pills every day. Be that as it may, the fixed-dose combination can solve this difficult well by offering a relative simple regimen with fewer pills or once-daily dosing. Although fixed-dose formulations are still in suspicious by physicians in some areas, it should be acknowledged that fixed-dose in combination is a natural trend in the historical backdrop of improving the blood pressure control.[7]

3. Fixed-dose combinations

When monotherapy was replaced by fixed-dose combination pills, one may ask whether fixed-dose formulations can offer enough benefits to overcome traditional monotherapy. Fixed dose Combination pill as a promising decision to hypertensive patients may have some potential superiorities as follows: Firstly, fixed-dose formulations generally can give patients some surprising effects comparing with only taking anyone ingredient of the combinations. Fixed-dose combinations some cases may provide a synergistic impact in a perfect combination except the usual addictive effect. Since drugs in formulations, from various classes exert their impacts based on individual mechanism with different action sites and action time, fixed-dose combinations in hypertension have a potential for a modest and long term action. Clinical trials demonstrated that angiotensin II receptor blockers (ARB) such as valsartan can minimize the peripheral edema caused by a calcium channel blocker such as amlodipine which is in show with the notion that combining two antihypertensive agents from various classes in a formulation in many cases may partly offset the adverse impacts from each other.[8] In addition, all the side effects from drugs in combination can likewise be decreased because of the low dose. In synopsis, for rational fixed-dose combinations, they may control hypertension well without additional side effects. Then, there is a psychological issue must be taken into consideration in treating the chronic disease. Since most hypertension patients are older folks, who have poor memory and can't act easily, the convenience and compliance brought by treatment are particularly important. Combination therapy with fixed-dose generally can exhibit its effects with fewer pills or once-daily dosing formulation, and then improve patients' compliance and psychological state largely. Finally, cost may also be an obstacle in blood pressure control for part patients. Combination treatment with fixed-dose may be less costly than the drugs administered separately, what's more, combination therapy may reduce the recommending cost with less drugs and offer the poor patients a lower overall health care costs. Fig 1showed advantages of fixed-dose combinations versus monotherapy and separate agents.[9]

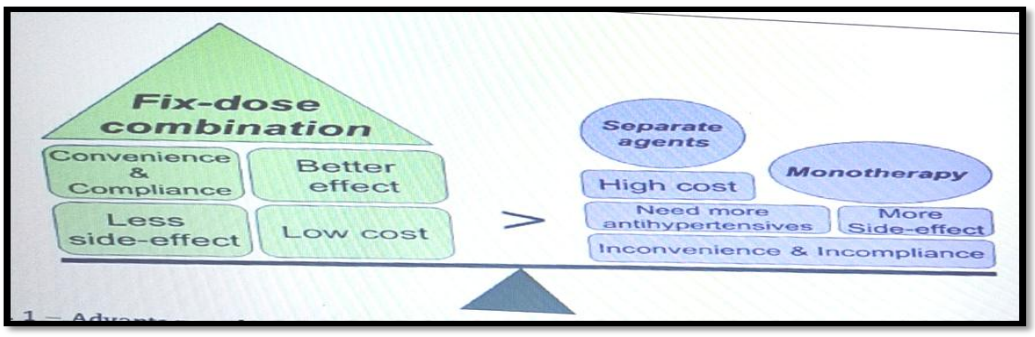

Figure 1: Advantages of Fixed dose combination Vs Monotherapy.

Rationale for combination therapy in Hypertension

The reasoning for combination therapy in hypertension is hence straight forward. First, it's to mix medication performing on totally different physiological systems in an exceedingly state of affairs wherever the phenotypes isn't best-known and wherever a medicine 'attack' on 2 (or more) systems can have a bigger impact on pressure level reduction than blind monotherapy. Second, it's an effort to dam counter restrictive responses that are activated by the perturbation of the pressure level restrictive mechanisms once a physiological system is blocked with single-drug medical care. Third, the hypertensive population includes several with levels of pressure level categorized as moderate or severe (stage two hypertension).There is general consensus that those with systolic blood pressures 160 mmHg and/or diastolic pressures 100 mmHg fall into this classification. They establish 10–15% of hypertensive populations and are at substantially greater risk of a future cardiovascular event. For each 20 mmHg increase in systolic blood pressure, there is an approximate doubling of cardiovascular danger. Clearly the extent of the proportion of the population with hypertension increases with age and this likewise applies to those with stage 2 hypertension. As age advances systolic hypertension predominates and is largely accounted for by loss of snap and increasing rigidity of large arteries. In particular circumstances, insight of the associated risks of additional severe high blood pressure, the recognition that dual (or triple therapy) is invariably required to achieve target blood pressures of ,140/90 mmHg, and that there is a level of urgency in reducing blood pressure to more acceptable levels to combine this danger. The European Guidelines, including their latest update, confirm such a recommendation and also proposes the initiation of combination therapy in those with milder degrees of blood pressure elevation in the presence of multiple danger factors, subclinical organ damage, diabetes, renal, or associated cardiovascular disease.[11] British Hypertension Society Guidelines (largely supported the very fact that there's a scarcity of irregular controlled trial proof to support such practice), it is probable that the results of current trials will give new proof in favour of their early introduction into treatment ways. Definitely, there are concerns that starting therapy with more than one drug could induce significant hypotension and increase coronary risk. In uncomplicated hypertension, lower pressures are well tolerated, for example, as found in the Systolic Hypertension in the Elderly Study, in which diastolic pressures as low as 60 mmHg were achieved in the active treatment group. Current trials comparison initiation of twin medical care vs. ordered monotherapy in cardiovascular disease can aim to clarify the protection of the previous. Fourth, blood pressure variability has been shown to decrease with combination therapy when compared with monotherapy. In spite of the fact that, CCBs and diuretics were most efficacious in reducing visit-to-visit blood pressure variability and also were associated with the most efficacious stroke prevention .In distinction, beta-blocker were shown to extend variability of systolic pressure in a dose-dependent way and also were the least efficacious in stroke prevention. The expansion of a CCB or to a lesser extent of a diuretic to a RAAS inhibitor diminishes variability of systolic pressure, which makes another strong argument for combination therapy.[10]

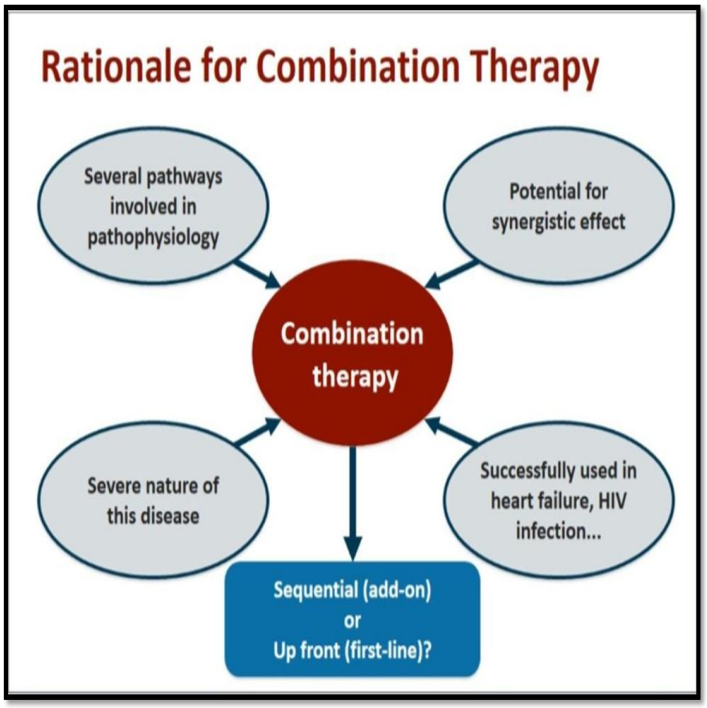

Figure 2: Rationale for combination therapy.

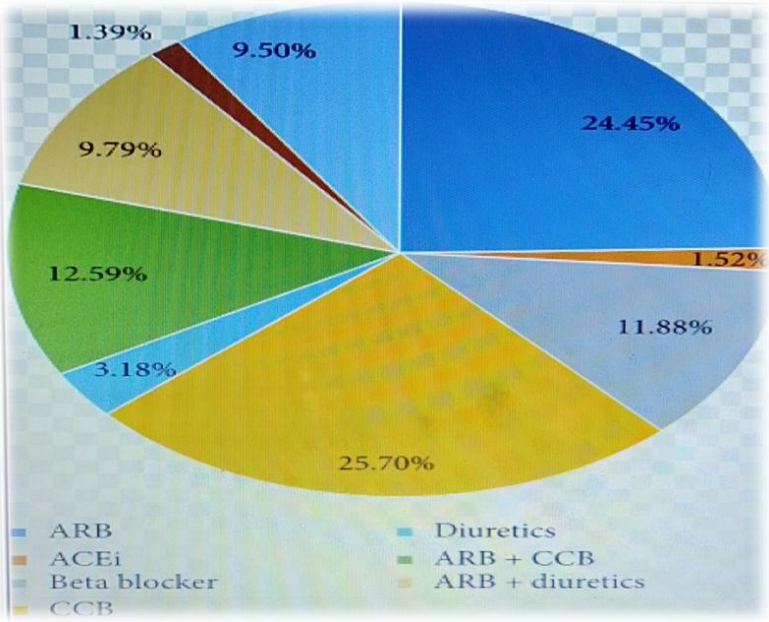

Figure 3: The various Combinations of drugs used in the management of Hypertension.

Preferred combinations

Renin–angiotensin–aldosterone system inhibitors and calcium channel blockers

Additive vital sign of reduction in blood pressure has been documented with the mixture of associate degree ACE-Inhibitor, ARB, or DRI with a CCB. The common dose-dependent adverse result of CCB monotherapy is peripheraloedema. The addition of a RAAS blocker has been shown to mitigate this adverse effect.[12] As stated above, the accomplish trial showed that fixed combination of associate degree ACE-Inhibitor (benazapril) with a CCB (amlodipine) was a lot of useful with relevance morbidity and mortality reduction than the fixed combination of a similar ACE-Inhibitor with hydrochlorthiazide. The combined cardiovascular outcome was comparative in the two groups. Maybe the most logical explanation for these findings is that the disadvantage of the beta-blocker routine observed in hypertension trials in uncomplicated patients was offset by the known advantages of beta blockade in the context of established coronary artery disease.[13] Diuretics, by depleting intravascular volume, activate the RAAS that causes salt and water retention moreover as vasoconstriction. Theexpansion of a RAAS blocker attenuates this counter regulatory response. Chlorthalidone has been shown to be more effective than hydrochlorothiazide in reducing blood pressure and should therefore be the preferred agent to be combined with a RAAS blocker. Unfortunately most RAAS inhibitors are available only in a fixed-dose combination (FDC) with hydrochlorothiazide.[14] RAAS blocker buffer CCB-induced activation of the sympathetic nervous system and thusly the RAAS. Likewise the negative sodium balance brought by CCBs adds to the antihypertensive effect of RAAS blocker. Dose-dependent CCB induced peripheral edema is also decreased within the presence of an RAAS blocker.[15]

Beta-blockers and diuretics

The addition of diuretics has been shown to enhance the medication efficacy of beta-blockers within the patients with low blood pressure. However, each of those drug categories are shown to have similar adverse effects therein they enhance the risk of glucose intolerance, the event of new-onset diabetes, fatigue, and sexual pathology. Outcome studies have shown a morbidity and mortality reduction with diuretics and beta-blockers together with **C**alcium channel blockers and diuretics.[16] However, inside the value preliminary, hydrochlorothiazide was added as a second step in patients randomized to amlodipine and the diuretic/CCB combination was well tolerated, although there was a higher risk of new onset diabetes and hyperkalaemia when put next with the valsartan arm. As the based antihypertensive drugs, thiazide diuretics additionally can be joined with b-blockers. It is known that b-blockers can decreases cardiac output, inhibit the secretion of renin and weaken the function of peripheral sympathetic and thus obtain antihypertensive effects.[17] Attributable to the restraint of the production of renin and angiotensin II brought by b-blockers, combinations of these two agents exhibit a significant reduction in side effects caused by thiazide diuretics such as intravascular volume depletion and total body Na loss. Late preliminary results showed that fixed-dose combination of nebivolol and hydrochlorothiazide was effective in controlling blood-pressure levels without a side effect on glucose and lipid profile during the Study.[18]

Calcium channel blockers and beta-blockers

The combination of a beta-blocker with a dihydropyridine CCB has added blood pressure reduction and, in general, is well tolerated. In contrast, beta-blockers must not be combined with nondihydropyridine calcium blockers, for example,

verapamil or diltiazem. The negative chronotropic effect of both of these drugs may be result in heart block or bradycardia.[19] The combination of a dihydropyridine CCB with either verapamilor diltiazem has been shown in a recent meta-analysis topossessan additive result on blood pressure lowering while not significantlyincreasing adverse events. Dual CCB blockade could also be helpful inpatients with documented angioedema on RAAS inhibitors or in patients with advanced renal failure at risk for hyperkalaemia.[20]

Table: FDA-Approved Combination Products to Treat Hypertension.

GENERICS	BRAND	STARTING DOSE (mg)	MAXIMUM DOSE (mg)
AMLODIPINE-BASED COMBINATIONS			
Aliskiren ;amlodipine	Tekamlo	150;5	300;10
Benazepril ;amlodipine	Lotrel	10;2.5	40;10
Olmesartan ;amlodipine	Azor	20;5	40;10
Telmisartan ; amlodipine	Twynsta	40;5	80;10
Valsartan; amlodipine	Exforge	160;5	320;10
Amlodipine;HCTZ;olmesartan	Tribenzor	5;12.5;20	10;25;40
Amlodipine ;HCTZ;valsartan	Exforge HCT	5;12.5;160	10;25;320
Aliskiren;amlodipine;HCTZ	Amturnide	150;5;12.5	300;10;25

GENERICS	BRAND	STARTING DOSE (mg)	MAXIMUM DOSE (mg)
HCTZ-BASED COMBINATIONS			
Aliskiren;HCTZ	Tektuma HCT	150;12.5	300;25
Amiloride;HCTZ	Moduretic	5;50	10;100
Benazepril;HCTZ	Lotensin HCT	5.6;25	20;25
Candesartan;HCTZ	Atacand HCT	16;12.5	32;25
Captopril;HCTZ	Capozide	25;15	150;50
Enalpril;HCTZ	Vaseretic	5;12.5	20;50
Eprosartan;HCTZ	Teveten HCT	600;12.5	900;25
Fosinopril;HCTZ	Monopril HCT	10;12.5	80;50
Irbesartan;HCTZ	Avalide	150;12.5	300;25
Lisinopril;HCTZ	PrinzideorZestoretic	10;12.5	80;50
Losartan;HCTZ	Hyzaar	50;12.5	100;25
Methyldopa;HCTZ	Aldoril or Aldoril D	250;15	750;50
Metoprolol;HCTZ	Dutoprol (extended release or Lopressor HCT)	100;12.5 100;25	200;25
Moexipril;HCTZ	Uniretic	15;7.5	30;50
Olmesartan;HCTZ	Benicar HCT	20,12.5	40;25
Propranolol;HCTZ	Inderide	40;25	160;50
Quinapril;HCTZ	Accuretic or Quinaretic	10;12.5	40;25
Spironolactone;HCTZ	Aldactazide	25;25	100;100
Telmisartan;HCTZ	Micardia HCT	40;12.5	160;25
Trimterene;HCTZ	Dyazide or Maxzide	37.5;25	75;50
Valsartan;HCTZ	Diovan HCT	160;12.5	320;25
Bisoprolol;HCTZ	Ziac	2.5;6.25	20;12.5

GENERICS	BRAND	STARTING DOSE (mg)	MAXIMUM DOSE (mg)
OTHER COMBINATIONS			
Aliskiren;valsartan	Valturna	150;160	300;320
Atenolol;chlorthalidone	Tenoretic	50;25	100;25
Azilsartan;chlorthalidone	Edarbyclor	40;12.5	40;25
Bendroflumethiazide;nadolol	Corzide	5;40	5;80
Chlorthalidone;clonidine	Closrenor or combipress	15;0.1	300;0.6
Trandolapril;verapamil	Tarka	1;180	8;240

Fixed Dose Combinations approved by FDA

ACEIs/ARBs with Diuretics

RAAS inhibitor and a diuretic combination can offset the diuretic-induced increase in plasma renin activity. The salt loss will add to the antihypertensive impact of RAAS blocker. Furthermore, an ARB will also attenuate the metabolic impacts of thiazide diuretics like hypokalemia and hyperglycemia. A few investigations have shown the antihypertensive adequacy of this mix in low dosages, showing significantly more prominent decreases in BP

and higher reaction rates than both of the medicines alone. The investigation extrapolated saving one death over 5 years for every 79 patients with this ACEI/Diuretic combination.[21] Additionally clinical investigations have shown mix of the ARB, irbesartan with HCTZ to be safe and powerful in patients with moderate to serious hypertension, independent of standard BP level, age, stoutness, race, diabetic status, and the metabolic condition and have an altogether more prominent portion subordinate BP bringing down impact than either specialist alone. Likewise early morning BP was decreased inferring the long duration activity of combination. Thus it seems that the combination of a RAAS blocker and a low dose thiazide is useful if treatment with a CCB cannot control BP in patients with hypertension.[22]

Thiazide diuretics plus ACEI/ARB

Recently, the use of fixed-dose combinations in hypertension is being a latest trend and technique in clinical practice, many more combination products were developed especially the drugs comprising of thiazide diuretics and ACEI/ARB. When elderly patients treated with ACEI alone neglect to accomplish ideal blood pressure, fixed-dose combinations consist of thiazide diuretics and ACEI can often perform a favorable effect demonstrating that thiazide diuretics and ACEI can make up an practically ideal gathering[23]. Diuretics would induce increased sodium loss and intravascular volume depletion when exerting their effects which can lead to an activation of renin-angiotensin aldosterone system (RAAS) thus boosting the antihypertensive effect of ACEI. Study in uncontrolled hypertensive patients with a fixed-dose combination of ramipril/hydrochlorothiazide guaranteed the powerful impacts of combinations mentioned above. Based practically a similar system, the combination of thiazide diuretics and ARB shows an additive antihypertensive effect. ARB additionally can reduce the potassium loss and hyperuricemia caused by thiazide diuretics owing to the interdiction of aldosterone secretion. The combination of candesartan and hydrochlorothiazide was likewise shown to be an excellent alternative in treating hypertension for its outstanding efficacy and tolerability. Fixed-portion mixes of ARB and thiazide diuretics not only exerted a superior efficacy but also maintained the outstanding tolerability profile of the ARB in clinical practice.[24]

ACEIs with CCB

In patients with both diabetes and hypertension, ACEIs provide clinical benefits that appear to be independent of BP decrease .The ANDI study demonstrated that in hypertensive patients with diabetes whose BP was not controlled with 20 mg quinapril alone, inception of combination therapy by adding 5 mg amlodipinebesylate to quinapril 20 mg was more effective in reducing BP than increasing the dose of quinapril to 40mg.[25]

ACEI with ARB

An ACEI/ARB routine hypothetically may give the upside of a more complete blockade of the RAAS.ARB will reduce the ACEI get away from phenomenon, a mechanismby angiotensin II returns to pretreatment levels despite continuous ACEI treatment. Besides, angiotensin II produced by ACEI-independent pathways will get blocked by ARBs.[26] Moreover the ACEI itself hinders bradykinin debasement. Clinical investigations of appropriately dosed ACEI and ARB mixture have shown critical improvement as to target organ harm, explicitly cardiovascular breakdown and proteinuria. The first main significant assessment here was the CALM (Candesartan and Lisinopril Microalbuminuria) trial, which was designed to compare the effect of candesartan 16 mg or lisinopril 20 mg or then again both on BP and urinary albumin-creatinine ratio in 197 type 2 hypertensive microalbuminuric diabetic patients.[27] This mix treatment was altogether more powerful than monotherapy in decreasing BP and brought about a more prominent decline in albuminuria, albeit this was measurably critical just when the combination was contrasted with candesartan monotherapy. In the Combination Treatment of angiotensin II receptor blocker and Angiotensin-Converting Enzyme inhibitorin nondiabeticrenal Disease (COOPERATE) trial, the frequency of a composite renal outcome was diminished by about 60% with mixed treatment comparative with both monotherapies. However, BP was not brought down to an essentially more prominent greater than either treatment alone. The Randomized Evaluation of methodologies for left Ventricular Dysfunction (RESOLVD) pilot study on patients with cardiovascular breakdown, getting candesartan, enalapril, or the mix treatment, showed combined treatment to have a more valuable impact on heart volumes and discharge fraction.[28]

Fixed-dose combinations and outcome benefits

In a recent review of the potential benefits of FDC formulations over their corresponding free drug elements given singly, it had been shown that the FDCs were related to considerably higher Compliance and a non-significant improvement in persistence with treatment.[29] Additionally, in a meta-analysis of nine studies comparing the administration of FDCs with their separate components, the adherence rate was improved by 26% in patients receiving FDCs In trials within which pressure information were according, use of FDCs was related to a non-significant lowering of systolic and diastolic blood pressure (4.1 and 3.1 mmHg, respectively) compared with the corresponding medication administered singly.[30]

Blood pressure control in practice

Worldwide surveys of pressure level management to targets counseled by national and international guidelines have systematically unconcealed that in clinical follow the standard goal of a pressure level ,140/90 mmHg is reached by solely a minority of patients.[31] Whereas

there are many unit explanations for physicians failing to attain target blood pressures, as well as poor compliance or concordance with drug taking by patients, white coat cardiovascular disease, unknown secondary causes of cardiovascular disease, and true resistant cardiovascular disease, within the majority of cases therapeutic inertia on the a part of the physician plays a significant role. There's smart proof that once physicians area unit baby-faced with patients on treatment for cardiovascular disease, however WHO haven't reached goal blood pressures, they're reluctant to extend drug doses or initiate second and third-line combination medical care. Clearly lack of education and failure to appreciate the importance of lowering blood pressure to focuses to prevent cardiovascular outcomes associated with uncontrolled blood pressure are important issues.[32] The historical focus on diastolic pressure as the basis for inception of therapy and as a treatment target is another. In practice, diastolic focuses of, 90 mmHg are far more normally attained than systolic targets of 160 mmHg. Excuses such as the following example—'It's a little bit higher today (cold weather, rush to clinic, stress at work, domestic problems etc) however we will perceive what it resembles in a few weeks/months time' are all too frequent.[33] This major problem can be overcome (as we observe in trials) when physicians or nurses are obliged to follow goal directed treatment calculations dictated by a trial protocol, and when 'excuses' cannot be made to avoid changes in medications when blood pressures are not at target. This has added to upgrades in the levels of blood pressure control in the population and has been accompanied by the increasing use of combination therapies.[34]

CONCLUSION

Fixed dose combinations are recommended as an effective and safe regimen for initiating therapy for the patients with serious complications. Each drug in perfect combination will exert its best adequacy with different side effects. In addition to that, FDC also brought economical benefits for patients with fewer medications compared with several drugs administered separately. In hypertension, the underlying rationale for combination treatment is somewhat different. The choices of combinations depend on risk factor as well as presence of comorbidities like diabetes, renal dysfunction and the adverse effects and tailored according to individual patients. On the basis of clinical practice and market research, FDC formulations are becoming a promising choice for hypertensive patients gradually.

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