Journal of Pharmacoeconomics and Pharmaceutical Management

Journal homepage: http://jppm.tums.ac.ir

Impact of Fixed Dose Combination Treatment on Adherence, Blood Pressure Control, Clinical Outcomes and Cost of Treatment:

Systematic Review of Randomized Controlled Clinical Trials and Cohort Studies

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Citation Davari. M, Kebriaeezadeh. A, Sorato. M. M, Soleymani. F. Impact of Fixed Dose Combination Treatment on Adherence, Blood Pressure Control, Clinical Outcomes and Cost of Treatment, Journal of Pharmacoeconomics and Pharmaceutical Management. 2022; 8(3): 1-14

Running Title Impact of Fixed Dose Combination Treatment on Adherence, Blood Pressure Control, Clinical Outcomes and Cost of Treatment

Article Type Review Article

Article info:
Received: 25.04.2021
Revised: 01.09.2022
Accepted: 13.12.2021

Publisher
Tehran University of Medical Sciences

ABSTRACT

Background: Initial combination therapy, preferentially fixed-dose combination (FDC) therapy is recommended by most of the clinical guidelines for the management of hypertension in adults. However, there is inadequate evidence on the impact of FDC on Blood pressure control, clinical outcomes, and cost of treatment. Therefore, this review was conducted to synthesize evidence impact of FDC treatment strategies on adherence, blood pressure control, clinical outcomes, and cost of treatment.

Methods: We systematically searched articles written in the English language from January 2000 to January 2020 from the following databases: PubMed/Medline, Embase, and Google scholar.

Results: Controlled trials were conducted among 17,465 adult hypertensive patients and retrospective cohort studies were conducted among 1,587,737 adult hypertensive patients. FDC strategy Improved treatment adherence and reduced adverse effects. However, the effect of FDC on blood pressure control, clinical outcomes, overall mortality, major adverse cardiac event-free survival, and overall cost of treatment were variable ranging from small changes to insignificant differences.

Conclusion: Fixed-dose combination therapy improved treatment adherence and reduced side effects. However, the role of FDC on

treatment outcomes like blood pressure reduction, CVD risk factor reduction, reduction in hospitalization rate, and the overall mortality rate was inconclusive. More strong multi-center trials involving patients with good adherence are required to see the actual effect of FDCs on the treatment outcomes of hypertension patients. In addition, ensuring medicine availability and conducting economic evaluations from different perspectives are required to recommend FDC as a first-line treatment option for the treatment of hypertension in adults.

Keywords: Fixed Dose Combination, Hypertension, Blood Pressure Control, Clinical Outcomes, Adherence, Systematic Review.

Introduction

Hypertension is the major contributor to cardiovascular disease-related deaths (1). Lifestyle intervention and antihypertensive drug therapy are the mainstays for blood pressure control and associated risk reduction. Most hypertensive patients require a combination of two or more drugs for the management of their blood pressure. Initial combination therapy preferentially Fixed dose combinations are recommended by most clinical guidelines for the management of hypertension (2-7). However, poor adherence to treatment, misdiagnosis of resistance, physician inertia, and drug interactions are determinants of poor blood pressure control (8-11).

Fixed-dose combination treatments offer several potential benefits, including simplification of the treatment regimen, improving efficacy, reducing clinical or therapeutic inertia in the control of hypertension improving adherence, and minimizing the adverse effects of each agent. An example is the combination of a thiazide diuretic with an angiotensin-converting enzyme inhibitor (ACEI) (12-17).

Disadvantages include initial doses that are often below those that would be started with monotherapy, making it potentially more difficult to achieve the desired dose, the risk of causing orthostatic hypotension in older patients, increased cost, the difficulty for race and gender difference consideration, and limited availability (18).

Several FDC trials were conducted so far in different groups of hypertensive patients. For example, a trial involving hypertensive patients with diabetes (19), adult hypertensive patients (20), high-risk hypertensive patients (21), and hypertensive patients with risk factors (22).

Currently recommended drug classes FDC are renin angiotensin aldosterone system (RAAS) + calcium channel blockers (CCBs). While, RAAS + thiazides/thiazide like diuretics are acceptable (23). Non-preferred FDCs include: CCBs + thiazides/thiazide diuretics, CCB-diuretic, diuretic-diuretic, diuretic-vasodilator, CCB-beta-blocker, and diuretic-beta-blocker combinations, as well as others (1).

Studies suggested that FDC may contribute to global CVD-related morbidity and mortality secondary to improved adherence, synergistic blood pressure reduction, reduced side effects, and blood pressure control (24, 25). However, the quality of evidence and strength of recommendations provided so far are weak and strong evidence is required to recommend FDC as initial antihypertensive therapy for adults with hypertension (14).

Evaluating FDCs in wider populations with well-designed methods involving all types of patients is recommended (24). Similarly, a guideline of the European society of cardiology stated a lack of adequate evidence on the impact of FDC on Blood pressure control and clinical outcomes (7). Therefore, this systematic review was conducted to evaluate the effect of FDC on patient adherence, blood pressure control, clinical outcomes, and cost of treatment among adult hypertensive patients by using Clinical trials and cohort studies conducted from January 2000- January 31, 2020.

Materials and Method

Data sources and search strategy: We have searched articles written in the English language from January 2000 to January 2020 from the following databases: PubMed, Embase, and Google scholar with the systematic search query (see supplementary file). PICO for the systematic review: Population: Adult patients above 18 years with hypertension. Intervention: Fixed dose combination Antihypertensive therapy. Comparison: Standard antihypertensive treatment or loose/ single-pill combination of drugs. Outcome: Treatment adherence, BP control, Clinical outcomes, and Cost of treatment. Study types: Randomized Controlled Clinical Trials and Cohort studies comparing fixed-dose combination with standard antihypertensive therapy or loose-drug

combination therapies. Inclusion and exclusion criteria: Randomized Controlled Clinical Trials and cohort studies comparing fixed dose combination with standard antihypertensive therapy or loose drug combination therapies among adults with hypertension are included. However, studies conducted before January 2000, guidelines, review articles, short communications, and conference proceedings, and articles that don't meet quality evaluation criteria are excluded. Study selection: From the total of 437 articles identified by the literature search 38 potentially relevant articles were selected, after applying the inclusion-exclusion criteria listed above only 15 articles were found to be relevant. To have strong evidence we applied a quality check for selected 15 articles and 11 were found to meet our quality check and considered for review (26) (Figure 1).

Two investigators (MM, MD) independently reviewed each study's abstract against pre-specified inclusion and exclusion criteria. In case of disagreement on the quality of the article two authors discussed In front of the table in presence of the third and fourth authors (AA, FS). We included good-quality RCTs that compared FDC with standard antihypertensive therapy or loose drug combination therapies. Data Extraction and Quality Assessment: Two investigators abstracted study design information, baseline population characteristics, intervention details, BP control, clinical outcomes, and cost data from all included studies into evidence tables. A second investigator checked these data for accuracy. Two investigators independently rated each study's quality as "good," or "poor" by using predefined quality criteria. The quality of Selected RCTs was evaluated by all members of the research team by using the prequalified CONSORT and Delphi Tools (27-29) (table 1) and the quality of cohort studies was evaluated based on quality appraisal criteria of Cohort studies (30) (table 2). We excluded poor-quality RCTs and Cohort studies. In general, good-quality studies did not meet at most one pre-specified criterion. A poor-quality study did not meet at least two criteria and had a fatal limitation. Disagreements among us are managed through discussion in the presence of other authors. Risk of bias assessment: We evaluated the risk of bias by using the Cochrane Risk of Bias Tool for Randomized Controlled Trials. Which contains six major biases that can occur in Randomized clinical Trials including; Selection bias, Reporting bias, other bias, Performance bias, Detection bias, and Attrition bias. Thresholds for Converting the Cochrane Risk of Bias Tool to AHRQ Standards (Good, Fair, and Poor) are as follows. Good quality: All criteria met (i.e. low for each domain). Fair quality: One criterion not met (i.e. high risk of bias for one domain) or two criteria unclear, and the assessment that this was unlikely to have biased the outcome, and there is no known important limitation that could invalidate the results. Poor quality: if one criterion is not met (i.e. high risk of bias for one domain) or two criteria are unclear, and the assessment that this was likely to have biased the outcome, and there are important limitations that could invalidate the results. Or two or more criteria listed as high or unclear risk of bias (31) (Table 3). We evaluated the risk of bias by using the risk of a bias assessment tool for cohort studies (32). The tool contains eight questions with four ratings for each question. Definitely yes (low risk), probably yes, probably no, and no (high risk). All authors evaluated the risk of bias independently and rated the risk bias as high, intermediate, or Low. High risk if the study has concerns for at least questions, intermediate if the study has concerned to one question, and low risk if the study has no risk of bias concern for all six questions. Based on the questions addressing possibility bias questions Pharmacoeconomic studies included in this review have a low risk of bias (Table 4).

Data analysis

We qualitatively described and summarized the evidence. We first described the results of randomized clinical trials comparing fixed-dose combination therapy with free-drug combination or usual hypertension care. We stratified the results by blood pressure reduction, reduction in cardiovascular endpoints, number of antihypertensive medications used, and safety and side effects of the respective RCTs. Secondly, we qualitatively described the Retrospective cohort studies comparing fixed-dose combination therapy with free-drug combination or usual hypertension care. We stratified the results by blood pressure reduction, reduction in cardiovascular endpoints, number of antihypertensive medications used, and safety and side effects of the respective retrospective studies. Finally, we synthesized the results of included studies by examining outcomes, statistical measurements, and the respective recommendations.

Results

We screened 437 abstracts identified from search databases, reviewed 38 full-text of relevant articles, and included 11 articles in the final review. Concerning the type of studies included, five articles were randomized

controlled trials (RCTs) (Table 5) and 6 articles were retrospective cohort studies (Table 6).

A randomized controlled trial among 207 hypertensive patients > 20 years of age in Japan compared the FDC of Losartan and HCT with the respective free combination of revealed that there is no significant difference in blood pressure reduction 131/75 mmHg vs 130/75 mmHg (p=0.096), adherence to antihypertensive drug therapy 98% (p =0.89), serious adverse effect (p=0.99) and mild adverse effect (p=0.31) (33). Randomized and controlled trials were conducted in 20 countries among 11,140 adults with hypertension and diabetes. The trial compared the FDC of perindopril and Indapamide with placebo-matched control and showed that the intervention group has better BP control with mean SBP reduction of 5.6 mmHg (P< 0.0001) and mean DBP 2.2 mmHg (P<0.0001). Similarly, the intervention group has a lower relative risk of micro and macrovascular complications 15.5% Vs 16.8% (HR= 0•91, 0•83–1•00, P=0•04). All-cause mortality and mortality from CVD were also lower in the intervention group 7.3% Vs 8.5% (HR= 0.82, P=0.025) and 3.8% Vs 4.6% (HR= 0.86, P=0•03) respectively (19).

A randomized and controlled trial conducted in New Zealand among 513 hypertensive adults with high risk for CVD compared FDC of ASA+ Simvastatin+ Lisinopril + Amlodipine or hydrochlorothiazide with the respective free combination. The study showed better adherence with FDC at 81% Vs 46% (RR= 1.75, 1.52-2.03, P=0.001). The mean difference in SBP reduction was 4.5 Vs 2.3 mmHg (P=0.21) and the Mean difference in DBP reduction was 2.1 Vs 0.9 (P=0.22). There was no difference in the number of patients with serious adverse events 99 Vs 93 (p= 0.56) among the intervention and control groups (34). A similar RCT conducted in India and Europe among 2004 hypertensive adults with high risk for CVD compared FDC of ASA+ Simvastatin+ Lisinopril + Amlodipine or hydrochlorothiazide with respective free combination showed better adherence with FDC 86% Vs 65% (RR= 1.33, 1.26-1.41, P=0.01). Mean SBP reduction was 2.6 mmHg, and the Mean change in LDL-C from baseline was -4.2mg/dL. There was no difference in the number of patients with serious adverse events 5% Vs 3.5% (p= 0.09) among the intervention and control groups (35). Another RCT conducted in Sir Lanka among 7,000 adults ≥ 18 years with mild and moderate hypertension compared FDC of Telmisartan, Amlodipine, and Chlorthalidone with usual care revealed that better BP target achievement at 6 months 69.5% Vs 55.3% (RR=1.23, P= 0.001) and Self-reported adherence at 6 months was 95% Vs 94.6% (RR= 1.00, P= 0.82) and drug discontinuation due to ADE was 6.6 Vs 6.8 (RR= 0.97, P= 0.92) (36).

A retrospective cohort study among 12, 628 adult hypertensive patients from an Insurance database in the USA compared FDC of valsartan and Amlodipine with a free combination of showed ARB and CCB showed a better adherence rate (OR= 1.38, P= 0.000). Fixed dose combination reduced total medical and pharmacy costs by $3969 vs $7724 (SD%= 9396 Vs & 21092, P= 0.000) (37). A retrospective study conducted in Germany among 81, 958 adult hypertensive patients compared the FDC of Repampril/Amlodipine with its loose combination and Candesartan/Amlodipine with its loose combination. The study revealed lower prescription of co-medications 2.7 ± 2.0 Vs 2.9 ± 2.2 (OR= 0.78, P <0.001) in ramipril/Amlodipine Vs their loose combination. The adherence rate was 65.7% Vs 48.6% (HR=0.65, P< 0.001) and the cost of treatment per person per year was €230.20 Vs €134.16 (P < 0.001). Similarly in Condesartan/Amlodipine FDC Vs their free combination prescription of co-medications 2.9 ± 2.03 Vs 4.0 ± 2.3 (OR= 0.55, P< 0.001). The adherence rate was 55.5% vs 43.1% (HR=0.82, P< 0.001) (10). A retrospective cohort study conducted among 5,680 adult hypertensive patients in Taiwan compared FDC of ARB + CCB with free combination showed excellent adherence in the intervention group 64.97% Vs 56.88% (P< 0.001). Lower risk of major cardiovascular events (MACE) (HR=0.72, P=0.22). Risk of a new diagnosis of CKD (HR=0.87, P=0.348) and Hospitalization for heart failure (HR= 0.71, P=0.041) (38).

A cohort study conducted among 16,505 adult hypertensive patients in Taiwan compared FDC of Amlodipine and Valsartan with a free combination of ARB + CCB showed better adherence with FDC 80.35% Vs 72.57% (p<0.001). The rate of Hospitalization for heart failure was 2.12% Vs 3.26% (p=0.001) and malignant dysrhythmia was 0.18% Vs 0.42% (P=0.021). The degree of MACE-free survival was higher in the FDC group (HR= 0.83, P= 0.003) (39). Another cohort study conducted among 17,465 hypertensive patients aged ≥ 18 years in the USA compared the FDC of ARB+CCB+HCT with a dual or triple pill. The study showed better adherence with FDC 55.31% vs 40.44% (OR=0.45, P< 0.001) when comparing two drugs and 55.31% Vs 32. 31% (OR= 0.26, P< 0.0001) when compared with

three drugs (40). Another Retrospective cohort study was conducted among 1, 587, 737 adult hypertensive patients in USA Compared FDC with Free combination therapy and showed that better adherence rate among FDC groups. Lower hospitalization rate 0.4% vs 0.9% (IRR= 0.77, P < 0.0001). Lower hypertension-related prescription cost $901 Vs 1434 (P< 0.0001)(41).

Discussion

We systematically reviewed Five RCTs involving 20,864 patients conducted in Japan (33), Australia (19), New Zealand (34), India and Europe (35), and Sir Lanka (36). Populations included in the study were adults, adults with high risk for cardiovascular diseases, and≥ 18 years of adults with mild to moderate hypertension. In addition to RCTs, we separately reviewed six big Retrospective cohort studies involving 1,721,973 patients were conducted in USA three studies (37, 40, 41), Taiwan two studies (38, 39), and Germany one study (10). The population included in the retrospective studies were adults from national insurance databases. The results of RCTs and Cohort studies are discussed separately due to the difference in quality and nature of studies.

Three RCTs and all retrospective cohort studies revealed better adherence with FDC when compared with free drug combination or usual care. The result is consistent along a range from mild or moderate hypertension to hypertension in high cardiovascular disease risk patients. A randomized and controlled trial conducted in New Zealand (34), India and Europe (35), and Sir-Lanka(36) showed better adherence to FDC combination therapy when compared to their respective loose combinations. Similarly, Retrospective cohort studies in the USA (37, 40), Germany (10), and Taiwan (38, 39) showed excellent adherence to FDCs.

This is supported by evidence from different studies that reducing the pill burden is one of the strategies to improve adherence to treatment for patients taking more than one drug for a long period (42-44). This is in line with findings from different studies. For example, FDC increases the rate of treatment adherence and reduces the number of co-anti-hypertensive drugs (45). Fixed-dose combination decreased the risk of medication non-compliance by 24% compared with free-drug combination regimen (11, 46, 47). However, RCT conducted among hypertensive patients > 20 years of age in Japan showed no significant difference in adherence with FDC 98% (p = 0.89) (33). This may be due to the inclusion criteria and approach used for measuring adherence. Patients with complications and taking 4 and more drugs were excluded from the study. Therefore, reducing the pill burden may not have a significant change in adherence in this particular patient group.

Concerning blood pressure reduction, RCT conducted in India and Europe showed improvement in SBP control with FDC (35). Similarly, RCT conducted in Sir Lanka among adults ≥ 18 years with mild and moderate hypertension revealed better BP target achievement with FDCs than with usual care (36). Another RCT conducted among adults with hypertension and diabetes showed that the FDC group has better BP control (19). This is in line with the rationale of fixed-dose combination which showed that FDC therapy has a proven record of reducing BP (48). This view is also supported by evidence from a large population program study conducted in California by using FDC of a RAAS inhibitor and CCB, which demonstrated equal and significantly increased blood pressure control rates across a wide range of demographics, including sex, race, and ethnicity (17). However, a randomized controlled trial conducted in Japan revealed no significant difference in blood pressure reduction among FDC and lose combination users (33). Similarly, RCT conducted in New Zealand (34), retrospective study conducted in Germany (10), and retrospective cohort study conducted in the USA showed no significant effect on blood pressure reduction (40). This is in line with studies showing no significant improvement in BP in blood control with FDC (11, 49). This could be due to the type of patients involved and the study methodology. Patients involved in the New Zealand trial were hypertensive adults with a high risk for CVD which could contribute to treatment resistance.

Regarding microvascular and macrovascular complications, RCT conducted among adults with hypertension and diabetes showed a lower relative risk of micro and macrovascular complications, lower all-cause mortality, and mortality from CVD with FDCs (19). Similarly, a retrospective cohort study conducted among adult hypertensive patients in Taiwan showed a Lower risk of major cardiovascular events (MACE) and a lower rate of hospitalization for heart failure, malignant dysrhythmia, and percutaneous coronary intervention in the FDC group (38, 39). A retrospective cohort study conducted in the USA also showed a lower hospitalization rate in the FDC group (41). Fixed dose combinations are associated with survival free from major adverse cardiac

events. This is supported by evidence from other studies, which stated FDC minimizes the adverse effects of each agent (12-17).

Concerning cost-effectiveness, none of the RCTs included in this review compared the cost of FDC with free drug combinations or usual care treatment of hypertension. However, three retrospective cohort studies have shown some cost-benefit with FDCs when compared to free combination (10, 37, 41). A similar cohort study conducted among adult hypertensive patients in Taiwan showed a reduction in total healthcare costs in the FDC cohort (39). This is in line with other studies which showed the cost-effectiveness of FDC (50-52). However, unless the availability of FDCs is ensured through more generic production, particularly in resource-limited countries acceptance of FDCs is challenged by the cost of drugs. This is despite improved efficacy and minimizing the adverse effects (12-17). Increasing generic production could help to ensure availability and reduce the cost of FDCs.

Conclusion

Fixed-dose combination treatments offer several potential benefits, including simplification of the treatment regimen, improving efficacy, reducing clinical or therapeutic inertia in the control of hypertension improving adherence, and minimizing the adverse effects. They can be used as a good alternative for patients with a high risk of CVD and adherence problems. The role of fixed treatment outcomes like blood pressure reduction, CVD risk factor reduction, reduction in hospitalization rate, and the overall mortality rate was inconclusive. Likewise, there is insufficient evidence on the cost-effectiveness of FDC to recommend FDC as a first-line treatment option for hypertensive patients. Overall, there is insufficient evidence to recommend FDC as a first-line initial therapy for hypertensive patients. More strong multi-center trials involving patients with good adherence are required to see the true effect of FDCs on the treatment outcomes of hypertension patients. In addition to this, ensuring medicine availability and conducting economic evaluations from different perspectives are required to recommend FDC as a first-line treatment option for the treatment of hypertension in adults.

Abbreviations

ACEIs: Angiotensin Converting Enzyme Inhibitors
ARBs: Angiotensin Receptor, Blockers
CCBs: Calcium Channel Blockers
CHD: Coronary Heart Disease
CVD: Cardiovascular Diseases
FC: Free Combination
FDC: Fixed Dose Combination
IRR: Incidence Rate Ratio;
MACE: Major Adverse Cardiac Events
MD: Mean Difference
MeSH: Medical Subject Heading
PDC: Proportion of Days Covered
PPY: Per Patient Year
QALY: Quality Adjusted Life Year
RD: Risk Difference
RR: Relative Risk
SPC: Single Pill Combination
SSA: Sub-Saharan Africa
WHO: World Health Organization

Tables

Table 1: Quality appraisal of included Randomized Controlled Trials based on Delphi and CONSORT instruments that pertain to internal validity of Randomized Controlled Trials

S.No	Dimensions of Quality	Matsumura K. et al. 2012		Patel A. et al 2007		Selak V., et al, 2014		Thom S. et al., 2013		Webster R.et al., 2018	
		Yes	No	Yes	No	Yes	No	Yes	No	Yes	No
1	Randomization	√		√		√		√		√	
2	Masking	√		√		√		√		√	
3	Allocation Concealment		√	√		√		√		√	
4	Handling of Withdrawals and Dropouts	√		√		√		√		√	
5	Measures of Variability	√		√		√		√		√	
6	Pre-specified Analyses	√		√		√		√		√	
7	Stopping rules										
8	Statistical methods	√		√		√		√		√	
9	Baseline data	√		√		√		√		√	
10	Address Multiplicity	√		√		√		√		√	
	Total quality score in percent	90%		100%		100%		100%		100%	

Table 2: Quality of included cohort studies based on Quality appraisal tool adapted from national institute of health research (NHS), Health technology assessment

S.No	Criteria	References											
		Baser O, Andrews L, Wang L, Xie L., 2011		Bramlage P, Schmidt S, Sims H. , 2018		Tung YC, Huang YC, Wu LS, Chang CJ, Chu PH., 2017		Tung YC, Lin YS, Wu LS, Chang CJ, Chu PH., 2015		Xie L, Frech-Tamas F, Marrett E, Baser O., 2014		Yang W, Chang J, Kahler KH, Fellers T, Orloff J, Wu EQ, et al., 2010	
		Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No
1	Was the cohort drawn from the same community/source?	√		√		√		√		√		√	
2	Are the groups assembled/recruited at the same age (i.e. the measurement period)?	√		√		√		√		√		√	
3	Ascertainment of exposure: was the same measurement of attachment disorders used across the sample?	√		√		√		√		√		√	
4	Were the coders of the exposure blind to risk factors/predictive variables related to the exposure status?		√		√		√		√		√		√
5	Is there demonstration that outcome(s) of interest are not present at start of the study?		√		√		√		√		√		√
6	Is there a description of attachment classification across the entire sample	√		√		√		√		√		√	

S.No	Criteria	References											
		Baser O, Andrews L, Wang L, Xie L., 2011		Bramlage P, Schmidt S, Sims H. , 2018		Tung YC, Huang YC, Wu LS, Chang CJ, Chu PH., 2017		Tung YC, Lin YS, Wu LS, Chang CJ, Chu PH., 2015		Xie L, Frech-Tamas F, Marrett E, Baser O., 2014		Yang W, Chang J, Kahler KH, Fellers T, Orloff J, Wu EQ, et al., 2010	
		Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No
	at baseline?												
7	Were subsequent measures rated by blind coders who were not aware of the exposed /unexposed status?		√		√		√		√		√		√
8	Were there any significant differences at baseline between those lost at follow-up?		√		√		√		√		√		√
9	If significant differences at baseline are found did they do any analysis to compensate?	√		√		√		√		√		√	
10	Adequacy of follow-up: were the dropout rates/attrition adequately reported?	√		√		√		√		√		√	
11	Were dropout rates and reasons for dropout similar across the exposed/unexposed?	√		√		√		√		√		√	
12	Did the study declare conflicts of interest or identification of funding resources?	√		√		√		√		√		√	
13	Any other bias?		√		√		√		√		√		√
14	Overall quality in percent	78.6%		78.6%		78.6%		78.6%		78.6%		78.6%	

Table 3: Risk of bias of included RCTs based on Cochrane Risk of Bias Tool for Randomized Controlled Trials

S.No	Reference	Sample size	Selection bias	Performance bias(blinding)	Detection bias	Attrition bias	Other biases	Total
1	Matsumura K. et al. 2012	207	Low	Low	Low	Low	Low	Low
2	Patel A. et al 2007	11140	Low	Low	Low	Low	Low	Low
3	Selak V., et al, 2014	513	Low	Low	Low	Low	Low	Low
4	Thom S. et al., 2013	204	Low	Low	Low	Low	Low	Low
5	Webster R.et al., 2018	7000	Low	Low	Low	Low	Low	Low

Table 4: Rating risk bias of Retrospective Cohort studies included based on tools for assessment of risk of bias in cohort studies

. N	Criteria	References

		Baser O, Andrews L, Wang L, Xie L., 2011		Bramlage P, Schmidt S, Sims H. , 2018		Tung YC, Huang YC, Wu LS, Chang CJ, Chu PH., 2017		Tung YC, Lin YS, Wu LS, Chang CJ, Chu PH., 2015		Xie L, Frech-Tamas F, Marrett E, Baser O., 2014		Yang W, Chang J, Kahler KH, Fellers T, Orloff J, Wu EQ, et al., 2010	
		Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No
1	Was selection of exposed and unexposed drawn from same population?	√		√		√		√		√		√	
2	Can we be confident in assessment of exposure?	√		√		√		√		√		√	
3	Can we be confident that the outcome of the study is not present at start of the study		√		√		√		√		√		√
4	Do study match exposed and unexposed for all variables?		√		√		√		√		√		√
5	Can we be confident in the assessment of presence or absence of prognostic factors?		√		√		√		√		√		√
6	Can we be confident on the assessment of outcome?	√		√		√		√		√		√	
7	Was the follow-up of cohort adequate?	√		√		√		√		√		√	
8	Were co-interventions similar between groups?	√		√		√		√		√		√	
	Over all bias	Intermediate		Intermediate		Intermediate		Intermediate		Intermediate		Intermediate	

Table 5: Selected Randomized Controlled Trials Comparing Fixed dose combination (FDC) Versus Loose combination Therapies for treatment of hypertension

S.No	Study Reference	Country	Study type	**Cases**	**Controls**	**Population**	**Sample Size**	**Measured Outcome/s**	**No Total (%)**		**Treatment effect**	**95% CI**	**P-value**
									Cases	Controls			
1	Matsumura K. et al. 2012 (33)	Japan	RCT	FDC of Losartan and HCT	FC of Losartan and HCT	>20 years	207	Percentage Medication adherence	98%	98%		97-99%	0.89
								Mean SBP difference at 6 mons in mmHg	131	130	0..3(*SE=1.6)*		0.096
								Mean DBP difference at 6 months	75	75	0.1 (SE= 1.3)		0.096
								Serious adverse effect	1(1)	1(1)			0.99
								Mild side effect	6 (6)	10(10)			0.31
2	Patel A. 2007 (19)	20 countries	RCT	FDC of prindopril and Indapamide	Placebo matched on current therapy	Adults with hypertension and diabetes	11140	Mean reduction in SBP mmHg	5.6		SE=0.2	5·2–6·0	<0·0001
								Mean Reduction in DBP mmHg	2.2		SE= 0.1	2·0–2·4	<0·0001
								RR of Microvascular and Macrovascular complications	15.5%	16.8%	HR= 0·91	0·83–1·00	0·04
								RR of death from CVD	3.8%	4.6%	RR= 0·82	0·68–0·98	0·03
								All-Cause mortality	7.3%	8.5%	RR= 0·86	0·75–0·98	0·025
3	Selak V. et al, 2014 (34)	New Zealand	RCT	FDC of ASA+ S+ L+ A or HCT	FC of ASA+ S+ L+ A or HCT:	Adults with high risk of CVD	513	% of Adherence	81%	46%	RR= 1.75	1.52 - 2.03	0.001
								Difference in SBP reduction	4.5	2.3		-5.6 to 1.2	0.21
								Difference in DBP reduction	2.1	0.9		- 3.2 to 0.8	0.22
								Difference in LDL-C reduction in mmol/L	0.20	0.15		-0.17 to 0.08	0.46
								Number of patients CV events	16	18			0.73
								Number of Patients with Serious ADEs	99	93			0.56
4	Thom S. et al., 2013 (35)	India and Europe	RCT	FDC of ASA+ S+ L+ A or HCT		Adults with high risk of CVD	2004	Adherence to treatment	**86%**	**65%**	RR= 1.33	1.26-1.41	**< 0.01**
								Reduction in SBP	-2.6 mm Hg			-4.0 to -1.1	< .001
								Change LDL-C from Baseline	-4.2 mg/dL			-6.6 to -1.9	< .001
								Serious adverse events or CV events	**5%**	3.5%	RR= 1.45	0.94-2.24	.09
5	Webster R. et al., 2018 (36)	Sri Lanka	RCT	FDC of T/A/Chl	Usual Care	Adults ≥ 18 years with mild and moderate hypertension	7000	Achieving BP target at 6 mos.	69.5%	55.3%	RR= 1.23	1.09 to 1.39	< 0.001
								Adjusted Change in SBP at 6 mos.	-29.1	-20.3	MD, -8.8	-11.2 to -6.4	< 0.001
								Adjusted Change in DBP at 6 mos.	-13.9	-9.3	MD, -4.6	-6.0 to -3.1	< 0.001
								Self-reported adherence at 6 mos.	95.0	94.6	RR= 1.00	0.97-1.04	0.82
								Discontinuation due to ADE	6.6	6.8	RR= 0.97	0.56 - 1.70	0.92

Note: ADEs= Adverse Events, CCBs= Calcium channel Blockers, ARBs= Angiotension Receptor, Blockers, BP= Blood Pressure, SBP= Systolic Blood Pressure, DBP= Diastolic Blood Pressure, SPC= Single Pill combination, FDC= Fixed Dose Combination, FC= Free combination, IRR= Incidence Rate Ratio; R/A= Rampiril/Amilodipine, C/A= Condesartan/Amilodipine, HR= Hazard Ratio; T/A/R= FDC of Telmisartan, Amlodipine, and Rosuvastatin; T/A= telmisartan plus amlodipine; T/R= telmisartan plus rosuvastatin; RR= Relative Risk; A/P/A= Atorvastatin/Perindopril/Amlodipine; ASA+ S+ L+ A or HCT: Aspirin 75 mg, simvastatin 40 mg, and lisinopril 10 mg with either atenolol 50 mg or hydrochlorothiazide 12.5 mg; MACE= major adverse cardiac events; PDC= proportion of days covered; T/A/Chl= A once-daily fixed-dose triple combination pill (20 mg of telmisartan, 2.5 mg of amlodipine, and 12.5 mg of chlorthalidone),PPY = Per patient years; RD= Risk Difference, MD= mean difference

NB: Major Macrovascular and microvascular events: defined as death from cardiovascular disease, non-fatal stroke or non-fatal myocardial infarction, and new or worsening renal or diabetic eye disease

Table 6: Selected Retrospective Cohort Studies Comparing Fixed dose combination (FDC) Versus Loose combination Therapies for treatment of hypertension

S. No	Study Reference	Country	Study type	Cases	Controls	Population	Sample Size	Measured Outcome/s	No Total (%)		Treatment effect	95% CI	P-value
									Cases	Controls			
1	Baser O, Andrews L, Wang L, Xie L., 2011 (37)	USA	Retrospective Cohort	FDC of Valsartan/Amlodipine	FC of ARBs + CCBs	Adult hypertensive patients	12,628	Risk adjusted Adherence rate	46.8%	40.8%	OR=1.38	1.24-1.53	0.0000
								Likelihood of Rx discontinuation	53.2%	59.2%	HR= 0.87	0.83-0.92	<0.001
								% Emergency visits	7.62%	9.51%	Mean=7.48%	7.10-7.86	<0.01
								% Inpatient stay	8.66%	10.13%	Mean=8.41%	7.40-9.41	<0.05
								% physician office visits	97%	99%	Mean= 97.86%	97.75-97.97	<0.001
								% outpatient visit	54.12%	60.31%	Mean= 53.3%	52.8-53.8	<0.001
2	Bramlage P, Schmidt S, Sims H. , 2018 (10)	Germany	Retrospective	FDC of R/A	FC of R/A	Adult hypertensive patients	81, 958	Prescription of co-medication	2.7 ± 2.0	2.9 ± 2.2	OR = 0.78	0.72-0.8	< .001
								Rx discontinuation at 12 months	5.7%	48.6%	HR = 0.65	0.58-0.73	< .001
								Adherence	65.7%	48.6%	HR= 0.65	0.58-0.73	< .001
								Cost of treatment PPY	€230.20	€134.16	MD=€96.04		< .001
				FDC of C/A	FC of C/A			Prescription of co-medication	2.9 ± 2.0 3	.4 ± 2.3	OR= 0.55	0.48-0.61	< .001
								Rx discontinuation in 12 months	5.5%	43.1%,	HR = 0.82	0.80-0.84	< .001
								Adherence	55.5%	43.1%,	HR = 0.82	0.80-0.84	< .001
								Cost of treatment PPY	€339.61	€235.01	*MD*= €104.60		< .001
3	Tung YC, Huang YC, Wu LS, Chang CJ, Chu PH., 2017 (38)	Taiwan	Retrospective cohort study	FDC of ARB + CCB	FC of ARB + CCB	Adult hypertensive patients	5680	Excellent Adherence (≥80%)	64.97%	56.88%			<.001
								Medication persistence days	293.79±78.49	275.13±90.22		215.3-372.28	<.001
								Risk of Major Adverse Cardiac Events	1136	4544	HR= 0.72	0.54–0.95	0. 022
								Risk of new diagnosis of CKD	44	204	HR= 0.87	0.64–1.17	0.348
								Hospitalization for heart failure	1136	4544	HR= 0.71	0.51–0.99	0.041
4	Tung YC, Lin YS, Wu LS, Chang CJ, Chu PH., 2015 (39)	Taiwan	Retrospective Cohort	FDC of amlodipine/valsartan	FC of ARB+CCB	Adult hypertensive patients	16, 505	Healthcare costs	$1844	$2158	Coef= - 9063	- 13,316 to - 4811	<0.001
								Hospitalization rate	14.57%	18.43%			<.001
								% Adherence	80.35± 21.90	72.57± 25.95	HR=0.69	58.45-102.25	<.001
								Medication persistence days	266	225	OR=1.82	1.67–1.98	<.001
								Major Adverse Cardiovascular Event	171	1203	HR=0.83	0.73– 0.94	=.003
5	Xie L, Frech-Tamas F, Marrett E, Baser O., 2014 (40)	USA	Retrospective Cohort	Single Pill treatment ARB+ CCB+ HCT	Double and Triple pill	≥ 18 years	17,465	Adherence to FDC Compared to two drug therapy	55.31%	40.44%	OR: 0.45	0.42–0.48	<0.0001
								Adherence to FDC Compared three drug therapy	55.31%	32.61%	OR: 0.26	0.22–0.30	<0.0001
								Likelihood of Rx discontinuation of FDC Vs two Drugs	14.5%	18.86%	HR: 1.89	1.74–2.06	<0.0001
								Likelihood of Rx discontinuation of FDC Vs three drugs	14.5%	21.5%	HR= 2.49	2.14–2.88	<0.0001
6	Yang W, Chang J, Kahler KH, Fellers T, Orloff J, Wu EQ, et al., 2010 (41)	USA	Retrospective Study	FDC	FC	Adults	1, 587, 737	Adjusted Medication adherence rate	72.8%	61.3%	MD = 11.6%	11.4-11.7	0.0000
								Adjusted all case hospitalization	0.07	0.09	IRR=0.77	0.75-0.79	< 0.0001
								Adjusted Emergency Visits	0.13	0.15	IRR= 0.87	0.86-0.89	< 0.0001
								Difference in medical costs b/n 6-mon pre and Post-index period per patient	$-6	$202	MD= -208	-302 to -114	< 0.0001

Figures

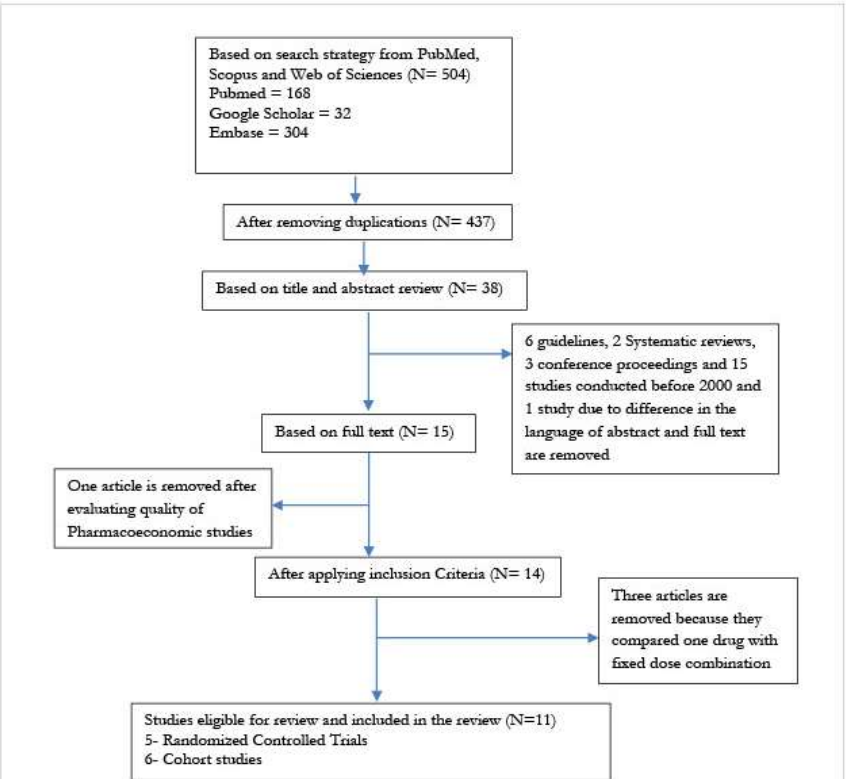

Figure 1: PRISMA Flowchart representing the result of search and the number of articles excluded and eligible for review

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