Received: 11 December 2017 | Revised: 1 February 2018 | Accepted: 13 February 2018

DOI: 10.1111/jch.13272

ORIGINAL PAPER

WILEY

The impact of fixed-dose combination versus free-equivalent combination therapies on adherence for hypertension: A meta-analysis

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Nonadherence to antihypertensive medication is considered as a reason of inadequate control of blood pressure. This meta-analysis aimed to systemically evaluate the impact of fixed-dose combination (FDC) therapy on hypertensive medication adherence compared with free-equivalent combination therapies. Articles were retrieved from MEDLINE and Embase databases using a combination of terms "fixed-dose combinations" and "adherence or compliance or persistence" and "hypertension or antihypertensive" from January 2000 to June 2017 without any language restriction. A meta-analysis was performed to parallel compare the impact of FDC vs free-equivalent combination on medicine adherence or persistence. Studies were independently reviewed by two investigators. Data from eligible studies were extracted and a meta-analysis was performed using R version 3.1.0 software. A total of nine studies scored as six of nine to eight of nine for Newcastle-Ottawa rating with 62 481 patients with hypertension were finally included for analysis. Results showed that the mean difference of medication adherence for FDC vs free-equivalent combination therapies was 14.92% (95% confidence interval, 7.38%–22.46%). Patients in FDC group were more likely to persist with their antihypertensive treatment, with a risk ratio of 1.84 (95% confidence interval, 1.00–3.39). This meta-analysis confirmed that FDC therapy, compared with free-equivalent combinations, was associated with better medication adherence or persistence for patients with hypertension. It can be reasonable for physicians, pharmacists, and policy makers to facilitate the use of FDCs for patients who need to take two or more antihypertensive drugs.

1 | INTRODUCTION

Hypertension is the biggest risk factor for cardiovascular disease, with approximately one third of cardiovascular deaths attributed to uncontrolled hypertension.[1] Globally, hypertension affected 31.1% of the global population, or 1.4 billion people, worldwide in 2010[2] and resulted in 9.4 million deaths annually.[3] The control of high blood pressure (BP) by antihypertensive drugs is crucial for patients with hypertension, by reducing the risk of stroke and renal and cardiovascular disease.[4] A standardized reduction of 10/5 mm Hg systolic BP/diastolic BP reduces the of stroke by 36%, heart failure by 43%, coronary events by 16%, cardiovascular death by 18%, and all-cause mortality by 11%.[5] However, a worldwide study showed that only 32.5% of patients receiving antihypertensive treatment have controlled BP.[6]

Nonadherence to antihypertensive medication is considered one of the major contributors to inadequate control of BP.[7,8] A recent review including 28 studies from 15 countries demonstrated that 45.2% of patients with hypertension were nonadherent to medications and 83.7% of medication nonadherence was found in

patients with uncontrolled hypertension.[9] It was reported that approximately two thirds of the patients with hypertension required two or more antihypertensive drugs to control BP.[10] Compared with free-equivalent combinations, use of fixed-dose combination (FDC) therapies in patients who require combination medicines is believed to improve adherence to antihypertensive drugs as it reduces pill burden.[11] However, studies reported that the use of FDCs in patients taking two or more guideline-recommended antihypertensive medications was relatively low in clinical practices, from 10% to 50%.[12–14] This meta-analysis, which includes the latest studies, aimed to systemically evaluate the impact of FDCs on hypertensive medication adherence compared with free-equivalent combination therapies according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and Meta-Analysis of Observational Studies in Epidemiology (MOOSE) guidelines.[15,16]

2 | METHODS

2.1 | Search strategy

We performed a systematic literature search using MEDLINE and Embase databases using a combination of terms "fixed-dose combinations" and "adherence or compliance or persistence" and "hypertension or antihypertensive" from January 2000 to June 2017 without any language restriction. We also searched the articles from the related publications of the retrieved studies and review articles for potential additional studies. The authors were contacted in case further information was needed in selected articles. A screening of titles or abstracts was performed, followed by a full-text review.

2.2 | Data abstraction

Two investigators independently assessed literature eligibility. Any discrepancies were resolved by consensus or a third investigator. We included studies of patients with hypertension, which directly parallel-compared the impact of FDCs vs free-equivalent combinations on medication adherence or persistence. No single-arm studies were included. Relevant information from the selected studies was collected using a standard electronic form. We collected information about lead author, year of publication, patient characteristics, study design, drug therapy groups, measurements of adherence or persistence, and length of follow-up, as well as the study outcomes.

Medication adherence (also called compliance) was assessed by the medication possession ratio or proportion of days covered, which was measured by the sum of the days/medication supply for all fills of a given drug in a particular time period, divided by the number of days/medications in the time period. Medication persistence was defined as the percentage of patients who continuously refilled a prescription for either FDC or free-equivalent combinations during the follow-up period, and nonpersistence was assessed as the percentage of patients who, without authorization, stopped refilling prescribed medication without taking it up again.

The quality of the studies was assessed by the Newcastle-Ottawa rating on a scale of one to nine, which is a risk of bias assessment tool for observational studies recommended by the Cochrane Collaboration.[17] A study is judged on three broad perspectives by the Newcastle-Ottawa rating: (1) the selection of the study groups; (2) the comparability of the groups; and (3) the ascertainment of either the exposure or outcome of interest for case-control or cohort studies, respectively.

2.3 | Statistical analysis

Meta-analyses were performed using R version 3.1.0 software (R Foundation for Statistical Computing). Heterogeneity of the trial results was assessed by calculating the P value from the χ^2 test. Statistically significant heterogeneity was defined as a P value <.1 based on the χ^2 test or an I^2 statistic > 50%. In this case, a random effects model was used. Otherwise, a fixed-effects model was

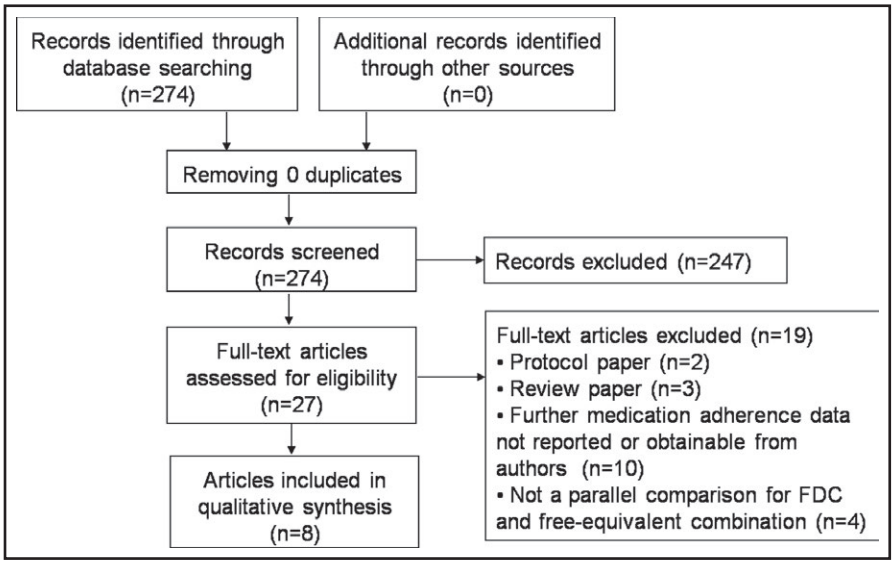

FIGURE 1 Flowchart describing the article selection process. FDC, fixed-dose combination

TABLE Characteristics of included studies

Authors	Sample size, No.	Age, y	Men, %	Follow-up, mo	Design	Contents of FDC
Dezii, 2000[18]	2268	–	–	12	Retrospective cohort	Lisinopril/hydrochlorothiazide
Dezii, 2000[18]	1674	–	–	12	Retrospective cohort	Enalapril/hydrochlorothiazide
Taylor, 2003[19]	5732	53	50	12	Retrospective cohort	Amlodipine besylate/benazepril HCl
Brixner, 2008[20]	2189	–	47.1	12	Retrospective cohort	Valsartan and hydrochlorothiazide
Dickson, 2008[21]	5704	76.0 ± 7.2	17.4	12	Retrospective cohort	Amlodipine besylate/benazepril HCl
Hess, 2008[22]	14449	62.5	43.1	12	Retrospective cohort	ARB/hydrochlorothiazide, ACEI/hydrochlorothiazide, ACEI/CCB
Hsu, 2015[23]	7348	55.2	55.6	24	Prospective cohort	ARB and thiazide diuretics
Tung, 2015[24]	16505	60.4	52.0	15.2	Retrospective cohort	ARB/CCB
Levi, 2016[25]	6612	67.1	48.2	6	Retrospective cohort	Olmesartan/amlodipine

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCB, calcium channel blocker; FDC, fixed-dose combination; HCl, hydrochloric acid; MPR, medication possession ratio; PDC, proportion of days covered.

chosen. The mean differences and risk ratio in adherence and persistence outcomes between the FDC and free-equivalent combination groups (as well as 95% confidence intervals [CIs]) were calculated for each study where possible. The pooled effect for each grouping of trials was derived from the point estimate for each separate trial weighted by the inverse of the variance.

3 | RESULTS

A total of 274 articles were yielded from the literature search, including 126 articles from Embase, 24 articles from MEDLINE, and 124 articles from both. After reviewing titles and abstracts and hand searching related citations, 27 potentially relevant articles were identified for full-text review. Of those, after review of the full-text articles, 19 studies were excluded for the following reasons: protocol papers (n = 2), review papers (n = 3), further medication adherence or persistence data not reported or obtainable from authors (n = 10), and not a parallel comparison of FDCs and free-equivalent combinations (n = 4). Finally, we included eight articles with nine studies[18–25] in our analysis (Figure 1).

In these nine studies, 62 481 patients with hypertension were included, with 30 103 patients taking FDCs and 32 378 patients taking free-equivalent combinations. The characteristics of the studies are elaborated in the Table. All of studies were retrospective cohort trials except one prospective study. Seven studies investigated the impact of FDCs on medication adherence, while five studies measured medication persistence. All contents of the FDCs or corresponding free combinations were renin-angiotensin system inhibitors with a diuretic or a calcium channel blocker. A study by Dezii and colleagues[18] involved two subgroups: one using an FDC of lisinopril and hydrochlorothiazide and the other using an FDC of enalapril and hydrochlorothiazide. These studies were scored as six of nine to eight of nine for the Newcastle-Ottawa rating.

Definition of Adherence or Persistence	Difference in Persistence	Difference in Adherence (MPR or PDC)	Newcastle-Ottawa Rating
Patients were regarded as persistent if they renewed their prescription within three times the number of days supplied by the previous prescription	68.7% vs 57.8%, $P < .05$	–	6 of 9
Patients were regarded as persistent if they renewed their prescription within three times the number of days supplied by the previous prescription	70.0% vs 57.5%, $P < .05$	–	6 of 9
Adherence was measured by the MPR during the study period	-	80.8% vs 73.8%, $P < .001$	8 of 9
Adherence was measured by calculating the MPRs for all patients with at least two prescription fills for dual therapy. MPR was defined as the total days supplied divided by the difference in days between the first fill and the last day of the last days supplied Patients were classified as persistent if they remained on dual therapy and did not discontinue therapy at 365 days.	54% vs 19%, $P < .001$	62.1% vs 53.0%, $P < .001$	7 of 9
Compliance defined as the MPR, which was the total days' supply of drug (excluding last prescription fill) divided by the length of follow-up	–	63.4% vs 49.0%, $P < .0001$	6 of 9
Compliance, defined as MPR, was measured over 12 mo Persistence was measured as the percentage of patients who did not experience a lapse in therapy of more than 30 d since their last prescription refill	58.3% vs 14.9%, $P < .001$ Regression-adjusted differences: 42.5% (40.6%–44.5%), $P < .001$	76.9% vs 54.4%, $P < .001$ Regression-adjusted differences: 22.1% (19.9%–24.1%), $P < .001$	7 of 9
Adherence was measured as the MPR, calculated as the number of days' supply of medication dispensed during a specified follow-up period divided by the number of days from the first dispensing to the end of the follow-up period Persistence was measured as continuously refilling the prescription for either an FDC or free combination during the follow-up period	26.1% vs 19.5%, $P < .001$	42.06% vs 32.45%, $P < .001$	8 of 9
Adherence was measured as PDC	–	80.35 ± 21.90% vs 72.57 ± 25.95%, $P < .001$	6 of 9
Adherence was estimated by calculating the PDC	–	55.1% vs 15.9%, $P < .001$	8 of 9

Among seven studies reporting medication adherence, the results showed that the mean difference of medication adherence for FDC vs free-equivalent combination therapies was 14.92% (95% CI, 7.38%–22.46%) with an I^2 estimate of 98% (Figure 2), indicating that the FDC significantly improved antihypertensive medication adherence. The largest differences were found in Levi's[25] and Hess's[22] studies, which were 39.20% and 22.10%, respectively.

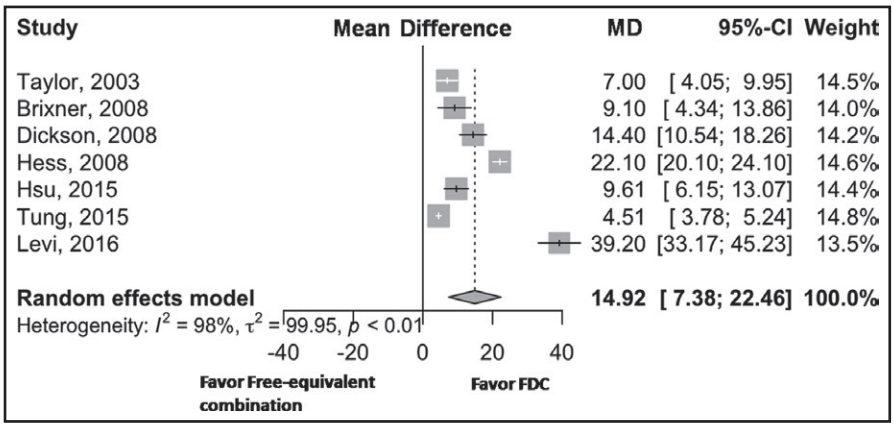

FIGURE 2 Forest plot for medication adherence. CI, confidence interval; FDC, fixed-dose combination; MD, mean difference

Five studies measured medication persistence for FDC vs free-equivalent combinations. The risk ratio was 1.84 (95% CI, 1.00–3.39) for the FDC with an I^2 estimate of 100% (Figure 3), which showed that FDCs improved medication persistence with a marginally statistical significance. The largest improvement was found in Hess's study,[22] with a risk ratio of 3.91.

4 | DISCUSSION

This study aimed to evaluate the impact of FDC vs corresponding free combination therapies on medication adherence or persistence of hypertensive medication use. Results showed that the use of an FDC was related to significantly better medication adherence or persistence. Compared with free-equivalent combinations, FDCs were associated with an additional 14.92% (95% CI, 7.38%–22.46%) of prescribed medicine taking and nearly a doubled number of patients (1.84-fold; 95% CI, 1.00–3.39) who continuously refilled the prescription during the follow-up period.

Although several recent studies were included, the results of this meta-analysis were consistent with previous similar reviews.[26,27] Gupta and colleagues[26] conducted a meta-analysis in 2009 to assess compliance and persistence associated with FDCs in comparison with their free-equivalent components. They found that the use of FDCs was associated with significantly better compliance (odds ratio, 1.21; 95% CI, 1.03–1.43 [P = .02]) and a nonsignificant improvement in persistence (odds ratio, 1.54; 95% CI, 0.95–2.49 [P = .08]) compared with corresponding free combinations. Another meta-analysis in 2011 by Sherrill and colleagues[27] showed that FDCs were related to a mean medication possession ratio difference of 13.31% and a 2.13 risk ratio for medication persistence compared with free-equivalent components, which were similar to our results. We found in recent studies that the two-class combination of antihypertensives––an angiotensin receptor blocker with a calcium channel blocker––was used more frequently compared with mainly a renin-angiotensin system inhibitor with diuretics in previous reviews. Despite having some combination class changes, the benefit of an FDC on medication compliance or persistence remained the same.

Evidence shows that BP control could be improved by better treatment compliance, but, in clinical practice, improving medication adherence remains a challenge.[4] Pill burden was significantly associated with decreased adherence to antihypertensive therapies in real-practice settings.[27] The number of prescribed pills was significantly related to adherence, with 55.3%, 40.4%, and 32.6% of patients having proportion of days covered ≥ 80% in the single-, double-, and triple-pill cohorts, respectively.[28] This is was why we found that FDCs always improved the adherence to antihypertensive drugs. The use of an FDC has been rapidly increasing in the past decade with evidence that the simpler the therapeutic regimen the better the patient's adherence and outcomes of disease.[25] It was reported in a German health insurance data analysis that in patients who started new antihypertensive therapy in 2007 or 2008 (n = 8,032), 10.8% of them started with an FDC of two drugs and only 8.2% started with a free combination of two drugs.[29] Single-pill therapy was associated with high medication adherence, and therapeutic simplification by the use of an FDC should be a nonignorable strategy to improve treatment adherence for hypertension.

5 | STUDY LIMITATIONS

There are some limitations in our study. First, nearly all of the data sources were retrospective studies. Although in most studies known confounding factors were adjusted for benefit of FDC, the patient characteristics of patients between the FDC group and the free-equivalent combination group may not be well balanced. Also, as in all retrospective studies, there may be recall bias for adherence assessment. Second, the definition and measurement of medication adherence is a key for our results, but we had a wide variety of measurement methods and definitions in our selected studies (Table). However, the results from different methods are consistent. Third, there was considerable heterogeneity among the included studies. Therefore, we used the random effects method to analyze the pooled data.

6 | CONCLUSIONS

This meta-analysis confirms that FDCs, compared with free-equivalent combinations, are associated with better medication adherence or

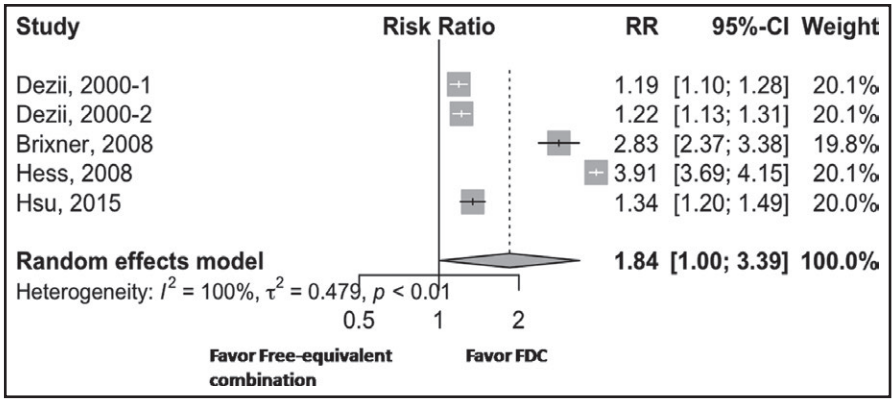

FIGURE 3 Forest plot for medication persistence. CI, confidence interval; FDC, fixed-dose combination; RR, risk ratio

persistence in patients with hypertension. It is reasonable for physicians, pharmacists, and policy makers to facilitate the use of FDCs for patients who need to take two or more antihypertensive drugs.

ACKNOWLEDGMENTS

The authors sincerely thank Quan Fang, MD, Professor and Director, Department of Cardiology, Peking Union Medical College Hospital, Beijing, China, for providing valuable literature and suggestions during the study.

CONFLICT OF INTEREST

The authors declare no potential conflicts of interest.

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How to cite this article: Du L-P, Cheng Z-W, Zhang Y-X, Li Y, Mei D. The impact of fixed-dose combination versus free-equivalent combination therapies on adherence for hypertension: A meta-analysis. *J Clin Hypertens*. 2018;20:902–907. https://doi.org/10.1111/jch.13272