Journal of Applied Pharmaceutical Science Vol. 14(12), pp 001-026, December, 2024
Available online at http://www.japsonline.com
DOI: 10.7324/JAPS.2024.199087
ISSN 2231-3354

Economic evaluation of fixed-dose drug combinations: A systematic review

Toi Lam Phung[1*], Due The Ong[1], Nhi T. N. Ngo[2], Trang Thuy Pham[3], Ha Thi Nguyen[3], Khanh N.C. Duong[3,4], Mai Thi Ngoc Dang[5], Matthew James Alcusky[6], Daniel J. Amante[6], Hoa L. Nguyen[6]

[1]Department of Health Financing and Health Technology Assessment, Health Strategy and Policy Institute, Ministry of Health, Hanoi, Vietnam.
[2]Mahidol University Health Technology Assessment (MUHTA) Program, Mahidol University, Bangkok, Thailand.
[3]University of Health Sciences, Vietnam National University Ho Chi Minh (VNUHCM—UHS), Di An City, Vietnam.
[4]Department of Pharmacotherapy, College of Pharmacy, University of Utah, Salt Lake City, UT.
[5]Center of Clinical Pharmacology—Hanoi Medical University, Hanoi, Vietnam.
[6]Department of Population and Quantitative Health Sciences, University of Massachusetts Chan Medical School, Worcester, MA.

ARTICLE HISTORY

Received on: 25/04/2024
Accepted on: 13/06/2024
Available Online: 05/11/2024

Key words:
Economic evaluation, fixed-dose combinations, methodology, polypill, systematic review.

ABSTRACT

This study aimed to review the quality of published evidence on the cost-effectiveness of fixed-dose drug combinations (FDCs), summarize key methodologic assumptions, and make recommendations for future economic evaluations of FDCs. The search was conducted on four databases, namely Medline, Embase, Web of Science, and the International Network of Agencies for Health Technology Assessment. Studies were selected if they assessed the cost-effectiveness of FDCs compared to one or more single active ingredient dosage forms or placebo. The Consolidated Health Economic Evaluation Reporting Standards 2022 checklist was utilized for evaluating the quality of studies. The study protocol was registered in PROSPERO (CRD42021295388). A total of 39 studies were eligible for inclusion in the review. While most of the studies (n = 29) reported that FDCs are cost-effective, the comparator in the economic evaluations was not justified explicitly in most studies (n = 34). Modeling that examined cost-effectiveness did not incorporate medication adherence (n = 22), failing to consider a key advantage of FDCs. The majority of studies investigating FDCs reported that they were cost-effective interventions. However, further economic evaluations based on long-term clinical trials with larger populations are necessary. Also, future economic studies should incorporate superior treatment adherence with FDC into the model structure.

INTRODUCTION

Fixed-dose combinations (FDCs), also known as polypills, are defined as a combination of two or more active ingredients within a single form of pharmaceutical administration (i.e., dosage form) [1–6]. By simplifying medication administration they have been shown to improve treatment adherence, which is particularly important in patients with chronic diseases [7]. Patients with chronic diseases such as hypertension and diabetes often require multiple drugs to treat their conditions. Complicated drug regimens may pose accessibility and affordability challenges for patients, while the burden of taking multiple medicines daily may affect patient adherence and clinical outcomes. FDCs have the potential to reduce these difficulties.

In several countries, including Vietnam, FDCs are considered a new medicine, even though the single ingredients are quite familiar and covered by health insurance. The cost of FDCs is often more expensive than a single-ingredient drug, but less expensive than the sum cost of its constituent active ingredients when purchased separately when all drugs are either branded or generic. When the FDC is branded and the constituent single-ingredient drugs can be purchased separately as generics, the FDC is typically more expensive. Given the

*Corresponding Author
Toi Lam Phung, Department of Health Financing and Health Technology Assessment, Health Strategy and Policy Institute, Ministry of Health, Hanoi, Vietnam.
E-mail: toiphunglam @ gmail.com

controversies surrounding the use of FDCs, there is an urgent need to discuss both their advantages and disadvantages including their cost effectiveness. This is particularly important in low- and middle-income countries (LMICs) given their high prevalence of both infectious diseases and noncommunicable diseases (NCDs), their considerably limited resources, and the continued growth in both morbidity and mortality from NCDs [8].

Economic evaluations can inform decision-making regarding health resource allocation. In the pharmaceutical sector, cost-effectiveness analyses are considered when establishing drug coverage policies, pricing, and rebate negotiations. Some studies have found that FDCs may be cost-effective [9–12]. However, there are many variations between studies regarding the conditions studied, methodology, applied assumptions, and the comparators of choice. These might limit the generalizability and transferability of findings into other contexts. To the best of our knowledge, there has not been any specific guidance related to conducting economic evaluation of FDCs. This study aimed to review and assess the quality of published evidence on the cost-effectiveness of FDCs and summarize key methodologic assumptions. We also aim to provide recommendations for future economic evaluations of FDCs.

METHODS

This review was conducted in accordance with the proposal registered in PROSPERO (CRD42021295388). This review was also conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [13].

Location of studies

The literature search was conducted in MEDLINE (using PubMed), EMBASE, Web of Science, Health Technology Assessment database of INAHTA. The initial search was carried out in December 2021 and an updated search was done in October 2023. The search terms were combinations of the following terms and synonyms: "fixed dose combination," "FDC," "economic evaluation," "cost-effectiveness analysis," and "cost-utility analysis." The detailed search terms and search strategy for each database are described in Supplementary Material S1. Reference lists of included studies were explored. We also contacted experts in this field for potentially relevant studies.

Selection of studies

Two authors (T.L.P and T.T.T.P) independently selected studies. Separate authors (D.T.O and H.N.T) mediated all disagreements following discussion. Economic evaluation studies published in English were eligible if the intervention included FDCs of at least two active drugs and the comparators were either: 1) a regimen of two or more single active drug forms that together comprise the FDC, 2) a single active drug, or 3) a placebo. The main outcomes of interest included incremental cost-effectiveness ratio (ICER), cost per quality-adjusted life year (QALY), cost per disability-adjusted life year (DALY), and cost per life-year gained. Reviews, systematic reviews, meta-analyses; pilot studies, case reports/case series, open letters, editorials, commentaries, letters to the editor, research protocols, notes, book chapters, and conference abstracts not published in peer-reviewed journals were excluded. Research not published in the full text was also excluded.

Data abstraction

Two authors (T.L.P and N.T.N.N) independently abstracted data including author, year of publication, country, study design, the objective of the study, model characteristics (i.e., model type, model structure, and simulation technique; model assumptions, data sources for parameters, modeled complications/events, outputs from the model, results from sensitivity analyses, perspective, time horizon), name of FDCs and constituent ingredients, indications, comparators, types of costs included, total costs, year of costing, outcomes, and discount rate. Data abstraction was performed using a pre-designed data extraction form. Disagreements of data extraction between the two authors were resolved by discussion with the third-party authors (K.N.C.D, H.T.N).

Quality assessment

Two authors (D.T.O and K.N.C.D) independently performed the quality assessment using the Consolidated Health Economic Evaluation Reporting Standards (CHEERS 2022) statement checklist [14]. The CHEERS 2022 checklist specifies 28 items for assessing the quality of reporting economic evaluations. Each item was scored with 1 (fully completed), 0.5 (partially completed), or 0 points (not completed or not reported) based on the criteria. A percentage was calculated to compare scores between studies. The denominator was calculated by summing the number of applicable items per study, and the numerator was calculated by summing the scores. Studies were deemed to be of high (>75%), moderate (50%–75%), or low (<50%) reporting quality. After grading the studies, both authors (D.T.O and K.N.C.D) shared their results, and the final CHEERS grade was obtained as an average of both evaluations.

RESULTS

Selection of studies

A total of 1,563 records were identified from database searches and 28 articles were retrieved from other sources. 232 studies were removed as duplicated studies, and 1,359 studies were screened with titles and abstracts. 97 out of 1,359 studies were selected for full-text screening. Eventually, 39 studies met the eligibility criteria and were included in this systematic review. Figure 1 shows the PRISMA flowchart of study selection.

Characteristics of the eligible studies

A detailed description of the included studies and CHEERS assessment results are presented in Table 1. The studies were published between 1996 and 2023 with most study samples recruited from Europe (n = 19), America (n = 10), Asia (n = 5), Australia (n = 2), and Africa (n = 1). There are two

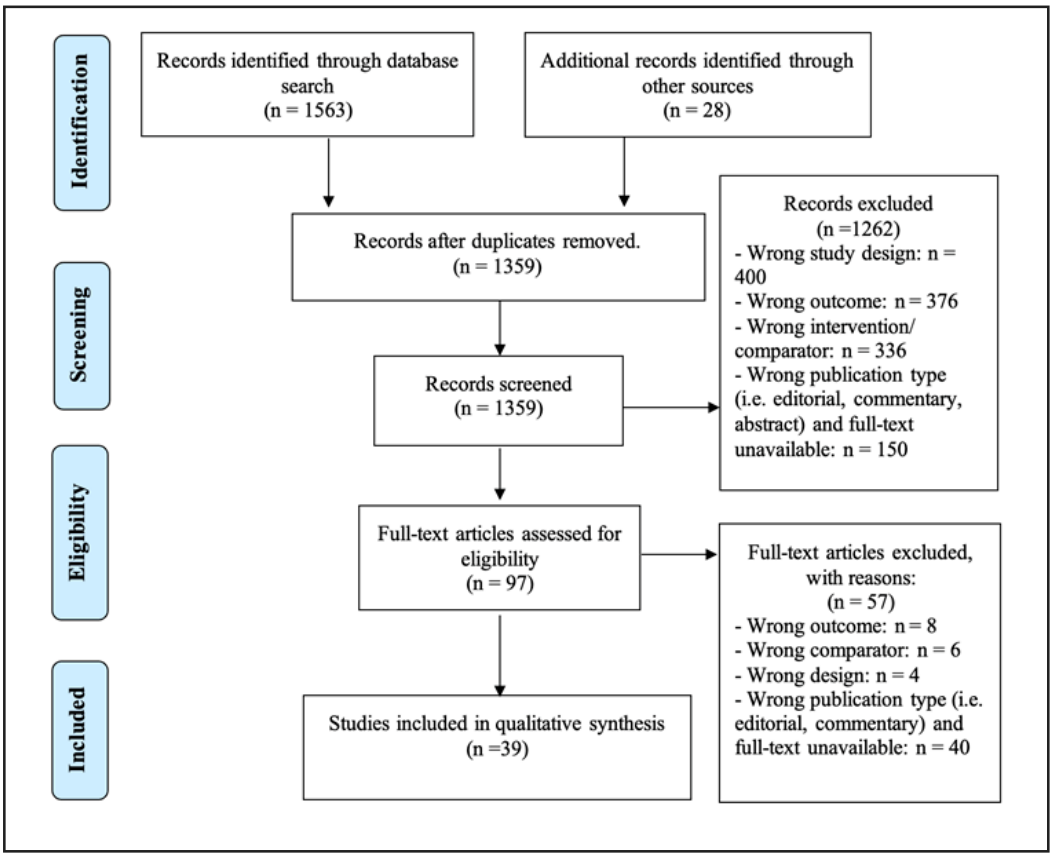

Figure 1. PRISMA flowchart of study selection.

studies conducted on a large scale which involved 20 countries [15] and five countries [16].

Most of the studies (n = 34) were of FDCs indicated for the treatment of chronic diseases. Of these, 11 studies investigated the cost-effectiveness of FDCs in chronic obstructive pulmonary disease (COPD) [9,10,17–26], one study in metabolic syndrome [27], two studies in type-2 diabetes [15,28], 21 studies in cardiovascular diseases including hypertension and heart failure [11,12,16,26,29–45], one study in rheumatoid arthritis [46], one study in benign prostatic hyperplasia [47], one study in cancer [48], and one study in preventing nausea and vomiting [49].

Most of the studies (n = 37) utilized cost-effectiveness analysis (CEA) and cost-utility analysis (CUA) approaches. One study by Price *et al.* [10] used the cost-minimization analysis (CMA) and one study used the cost-benefit analysis (CBA) [38]. The comparators of included studies can be categorized into three groups: (1) regimens of multiple separate components that belong to FDCs (n = 6), (2) mono-components that belong to FDCs with or without other drugs (n = 13), and (3) no treatment/placebo/usual care (n = 17). In studies comparing FDCs with usual care, seven studies specified that usual care involved separate medications, which were components of FDCs [16,32,38,41–43,49], and three studies indicated that usual care entailed either no treatment or the absence of FDC [33,34,40]. There are three studies [26,27,36] with two sets of comparators: the first comparator is a mono-component that belongs to FDCs and the second comparator is a regimen of multiple separate components that belong to FDCs.

Regarding the discount rate, 31 out of 39 studies were discounted for cost and effectiveness. Five studies analyzed the costs and outcomes within a short time horizon and did not apply discount rates [28,46]. The discount rate is generally identical between cost and outcomes, except for two studies by Van Boven *et al.* [19] and van Gils *et al.* [32], where the discount rates for costs and outcomes were 4% and 1.5%, respectively.

The majority of included studies (n = 19) were funded by the pharmaceutical industry. Other studies (n = 11) were funded by nonindustry sources such as a foundation, university, or research institution; two studies reported that they received funding from both industry and nonindustry sources [15,27]. Three studies reported that they received no funding [28,32,47] and three studies did not report the funding source [29,35,38].

In general, the methodological quality of included economic evaluations was classified as high (16 studies), although it varied across studies (Table 1). None of the studies fulfilled all 28 criteria. The maximum score was 98.2% [9,16,41], and the minimum score was 71.4% [28,49]. Two studies were graded as moderate quality [28,49]. These two studies did not report properly for 9 items of the CHEERS 2022 checklist. Three items in the CHEERS 2022 checklist have the lowest score (1) effect of engagement with patients and others affected

Table 1. General characteristics of included studies.

First author, year	Country	Study design	FDC/Polypill	Comparators	Perspectives	Time horizon	Discount rate	Funding from	Quality assessment
COPD and Asthma									
O'Connor *et al.* [17]	US	CEA	Fluticasone propionate/ Salmeterol	Fluticasone propionate + Montelukast	Third-party payer	12-week	NA	Industry	High
Ismaila *et al.* [18]	Canada	CUA	Salmeterol xinafoate/ Fluticasone propionate (SFC)	Fluticasone propionate (FP)	Canadian Public Healthcare	1 year	NA	Industry	High
Price *et al.* [10]	Swedish	CMA	Indacaterol/glycopyrronium	Indacaterol + glycopyrronium	Societal perspective	1, 3, 5, 10 years and lifetime	3% for both costs and outcomes	Industry	High
Van Boven *et al.* [19]	Netherlands	CUA	Tiotropium/olodaterol	Tiotropium	Healthcare payer	15 years	4% for cost and 1.5% for outcome	Industry	High
Ramos *et al.* [20]	Scotland	CUA	Aclidinium/formoterol	Aclidinium bromide	NHS Scotland	5 years	3.5% for both costs and outcomes	Industry	High
Selya-Hammer *et al.* [9]	Italy	CUA	Tiotropium/olodaterol	Tiotropium	NHS Italy	15 years	3% for both costs and outcomes	Industry	High
Rajagopalan *et al.* [21]	US	CUA	Indacaterol/glycopyrrolate	Placebo	The US payer	5 years	3% for both costs and outcomes	Industry	High
Hoogendoorn *et al.* [22]	France	CUA	Tiotropium/olodaterol	Tiotropium	Societal + National Sickness Fund	lifetime	4% in the first 30 years and at 2% thereafter. (Both costs and outcomes)	Industry	High
Hoogendoorn *et al.* [23]	Finland, Sweden, and the Netherlands	CEA	Tiotropium/olodaterol	Tiotropium	Societal (Swedish, Dutch), The Finnish payer's	lifetime	Finnish and Swedish: 3%. Netherlands: 1.5% For both costs and outcomes	Industry	High
Orlovic *et al.* [24]	England	CEA	Medium or high dose of Beclometasone dipropionate/ Formoterol fumarate/ Glycopyrronium	1. Medium or high dose of Beclometasone dipropionate/ Formoterol fumarate 2. High dose of Beclometasone dipropionate/ Formoterol fumarate + Tiotropium	England National Health Service (NHS)	Lifetime	3.5% for both costs and health outcomes	Industry	High
Lan *et al.* [25]	China	CEA	Tiotropium/Oldaterol	Tiotropium	Chinese health system	10 years	5% for both costs and health outcomes	Non-industry	High
Metabolic syndrome									

Continued

First author, year	Country	Study design	FDC/Polypill	Comparators	Perspectives	Time horizon	Discount rate	Funding from	Quality assessment
Zomer *et al.* [27]	Australia	CEA	FDC (three blood-pressure lowering, simvastatin, aspirin)	No treatment	Healthcare	10 years	5% for both costs and outcomes	Industry and non-industry	High
Type 2 diabetes									
Glasziou *et al.* [15]	20 countries	CEA	FDC (perindopril/ indapamide)	Placebo	The health care purchaser	4,3 years	0%, 3%, 5%, 10% for both costs and outcomes	Industry and non-industry	High
Vaidya *et al.* [28]	US	CUA	All available FDC for T2D	Free-dose combination (FRC)	A third-party payer	1 year	NA	None	Moderate
Cardiovascular diseases including hypertension and heart failure									
Angus *et al.* [12]	US	CEA	isosorbide dinitrate/hydralazine	Placebo	Societal perspective	12.8 months	3% for both costs and outcomes	Industry	High
Newman *et al.* [29]	US	CEA	Polypill (Simvastatin 40 mg/ Atenolol 25 mg/Captoprill 12.5 mg/Hydrochlorothiazide 12.5 mg)	No treatment	Healthcare	10-year	3% for both costs and health outcomes	NR	High
Rubinstein *et al.* [30]	Argentina	CEA	Polypill (thiazides 25 mg/ Enalapril 10 mg/Atorvastatin 10 mg/Aspirin 100 mg)	1. HBP lowering therapy (Chlorothiazide 25mg; Atenolol 50 mg; Enalapril 10 mg) 2. High-cholesterol lowering with statins (Atorvastatin 10 mg)	Payer	10-year	3% for both costs and health outcomes	Non-industry	High
Rubinstein *et al.* [31]	Argentina	CEA	Polypill (hydrochlorothiazide 25 mg/Enalapril 10 mg/ Atorvastatin 10 mg/Aspirin 100 mg)	No intervention	Purchaser	5-year	3% for both costs and outcomes	Non-industry	High
van Gils *et al.* [32]	Netherlands	CEA	Polypill: - A: Simvastatin 20 mg/ Thiazide 12.5 mg/Ramipril 5 mg/Atenolol 50 mg/Aspirin 100mg - B: Simvastatin 20 mg/ Thiazide 12.5 mg/Ramipril 5 mg/Atenolol 50 mg - C: Simvastatin 40 mg/ Thiazide 12.5 mg/Ramipril 5 mg/Atenolol 50 mg	Usual care	Healthcare payer	Lifetime	4% for costs and 1.5% for health outcomes	None	High
Ito *et al.* [33]	US	CEA	Polypill (Aspirin/β-blocker/ ACEI or ARB/Statin)	Usual care	Societal	Lifetime	3% for both costs and health outcomes	Non-industry	High
Khonputsa *et al.* [34]	Thailand	CEA	Polypill (Blood pressure lowering/Cholesterol-lowering)	Current practice	Health sector	Lifetime	3% for both costs and health outcomes	Non-industry	High

Continued

First author, year	Country	Study design	FDC/Polypill	Comparators	Perspectives	Time horizon	Discount rate	Funding from	Quality assessment
Bautista *et al.* [35]	Latin America	CEA	Polypill (Thiazide 12.5 mg/ Atenolol 50 mg/Ramipril 5 mg/ Simvastatin 20 mg/Aspirin 100 mg)	No polypill	NR	Lifetime	3% for both costs and health outcomes	NR	High
Megiddo *et al.* [36]	India	CEA	Polypill (aspirin, beta blockers, angiotensin-converting enzyme inhibitors, and statins)	Polypill's components (alone or in combination as free dose combination)	Provider	lifetime	3% for both costs and outcomes	Non-industry	High
Ong *et al.* [37]	Australia	CEA	Polypill (ACEI/β-blocker/ Calcium channel blocker/Statin)	No intervention (Null scenario)	Health sector	NR	NR	Non-industry	High
Becerra *et al.* [11]	UK	CEA	FDC (Aspirin, atorvastatin and ramipril)	multiple monotherapy	NHS and the Personal Social Services	10 years	3.5% for both costs and outcomes	Industry	High
Wald *et al.* [38]	UK	CBA	Polypill: Simvastatin 20 mg/ Amlodipine 2.5 mg/Losartan 25 mg/Hydrochlorothiazide 12.5 mg	Usual care	Healthcare payer	Lifetime	NR	NR	High
Barrios *et al.* [39]	Spain	CUA	FDC (Aspirin, atorvastatin, ramipril)	multiple monotherapy	The Spanish National Health System.	10 years	3% for both costs and outcomes	Industry	High
Ferket *et al.* [40]	UK	CEA	Polypill (Simvastatin 20 mg/ Amlodipine 2.5 mg/Losartan 25 mg/Hydrochlorothiazide 12.5 mg)	Current practice	UK Health system	Lifetime	3.5% for both costs and health outcomes	Non-industry	High
Jowett *et al.* [41]	UK	CUA	Polypill (Simvastatin 40 mg/ Amlodipine 2.5 mg/Lisinopril 5 mg/Hydrochlorothiazide 12.5 mg)	Usual care	National Healthcare System	10-year	3.5% for both costs and health outcomes	Non-industry	High
Gaziano *et al.* [42]	US	CEA	Polypill I (Aspirin 81 mg/ Atenolol 50 mg/Ramipril 5 mg/ Simvastatin 40 mg) Polypill II (Aspirin 81 mg/ Atenolol 50 mg/Ramipril 5 mg/ Atorvastatin 80 mg) Polypill III (Aspirin 81 mg/ Atenolol 50 mg/Ramipril 5 mg/ Rosuvastatin 40 mg)	Usual care	Healthcare and Societal	5-year	3% for both costs and heath outcomes	Non-industry	High
Lin *et al.* [16]	China, India, Mexico, Nigeria, South Africa	CEA	Polypill (Aspirin 75 mg/ Lisinopril 10 mg/Atenolol 50 mg/Simvastatin 40 mg)	Current practice (Polypill's components used in separate)	Healthcare sector	Lifetime	3% for both costs and health outcomes	Non-industry	High

Continued

First author, year	Country	Study design	FDC/Polypill	Comparators	Perspectives	Time horizon	Discount rate	Funding from	Quality assessment
Lung *et al.* [43]	Sri Lanka	CEA	Triple-pill (Amlodipine/ Telmisartan/Chlorthalidone)	Usual care	Health system	10-year	3% for both costs and health outcomes	Non-industry	High
Ren *et al.* [26]	China	CEA	FDC (Olmesartan /amlodipine)	(1) Olmesartan + amlodipine. (2) amlodipine;	Payer	20 years	3% for both costs and outcomes	Industry	High
Aguiar *et al.* [44]	Portugal	CEA	Polypill (aspirin, statin, angiotensin-converting enzyme inhibitors (ACEi))	Polypill's components administered concomitantly	Payer	Lifetime	4% for both costs and health outcomes	Industry	High
Gonzalez-Dominguez *et al.* [45]	Spain	CEA	Polypill (aspirin, statin, angiotensin-converting enzyme inhibitors (ACEi))	Polypill''s components administered separately	The Spanish National Healthcare System	Lifetime	3% for both costs and heath outcomes	Industry	High
Rheumatoid Arthritis									
Al *et al.* [46]	Netherlands	CEA	FDC (Misoprostol/ diclofenac)	Diclofenac	Societal perspective	3 months	NA	Industry	High
Benig prostatic hyperplasia									
Udeh *et al.* [47]	Nigeria	CEA	FDC (dutasteride /tamsulosin)	Dutasteride	The health service provider	10 or 15 years	6% for both costs and outcomes	None	High
Cancer									
Sussell *et al.* [48]	U.S.	CEA	FDC (Pertuzumab/ Trastuzumab/Hyaluronidase-zzxf) (PHESGO™)		US Health System	Lifetime	3% for both costs and health outcomes	Industry	High
Others									
Nilsson *et al.* [49]	Spain	CEA	FDC (Netupitant/palonosetron)	Multiple monotherapy	The Spanish Healthcare Payer	5 days	NA	Industry	Moderate

CEA, Cost-Effectiveness Analysis; CMA, Cost-Minimization Analysis; CUA. Cost-Utility Analsysis; CBA: Cost-Benefit Analysis; FDC, Fixed-Dose Combination; NA, Not Applicable; US, United States; UK, United Kingdom.

by the study (item No.25), (2) characterizing heterogeneity (item No.18), and (3) characterizing distributional effects (item No.19). Details of the quality assessment results were shown in **Supplementary Material S2**.

Methodological characteristics of included studies

The methodological characteristics of the included studies are presented in Table 2. The majority of studies were model-based economic evaluations in which the Markov model was most commonly applied. A few studies were economic evaluations alongside a clinical trial [12,15,17] or based on real-world data [28]. Regarding the costs, most studies used direct medical costs from the payer's perspective. Some studies [10,22,23] applied a societal perspective that required the include both direct costs and indirect costs. Ito *et al.* [33] also claimed that their study applied the societal perspective, but only the direct medical and direct nonmedical costs were included without involving the indirect cost. The sources of cost data were mainly from literature and local documents such as the regulated price of drugs and medical services, clinical guidelines, and local databases. Out of the majority of studies (n = 36), they explicitly specified the year of costing and adjusted for inflation, except for three studies [28,32,47].

The majority of studies used QALYs and life years (LYs) as the effectiveness outcomes. Clinical outcomes were also reported in some studies such as exacerbation rate in COPD [9,19,22,23], cardiovascular events prevented [11,39], or symptomatic ulcers [46]. The data sources for outcomes were mainly from literature and well-known clinical trials in the study's condition. For example, many studies [19,20,22,23] referred to the UPLIFT study as the source for outcome data in the COPD indication of FDCs. For studies that used QALY as the outcome, the EQ-5D was mentioned as the most popular tool to elicit the utility of patients [50].

The results of economic evaluations are dependent on their assumptions. The main assumptions in the included studies can be categorized into three groups: (1) assumptions relating to costs, (2) assumptions relating to drug efficacy, and (3) assumptions relating to treatment adherence. Due to the unavailability of cost or price information for FDCs in certain countries at the time of the studies, authors had to make assumptions regarding FDC prices based on available components or other FDCs. In their studies, Megiddo *et al.* [36] assumed that the costs of FDCs were less than the additive costs of every single drug in the free combination, and Zomer *et al.* [27] assumed that FDC's price was 25% less than the additive price of each drug in the free combination [27] and Bautista *et al.* [35] estimated the average cost of the FDC was $50 per subject per year. Selya-Hammer *et al.* [9] investigated the cost-effectiveness of a new FDC tiotropium/olodaterol (Respimat®) in COPD treatment. As this FDC was not marketed in Italy at the time of the study, the authors assumed that the price of the FDC was a parity price to other LAMA/LABA FDCs [9]. Jowett *et al.* [41] applied the cost of Trinomia1® for the cost of FDC used in their model, as the specific cost of the FDC used was not available in the UK at that time. Notably, Trinomia1® had different compositions compared to the FDC used in their study [41]. For the drug's efficacy, the assumption of equal efficacy between FDCs and the free combination was applied in two studies by Price *et al.* [10], Ito *et al.* [33], and Lin *et al.* [16]. Khonputsa *et al.* [34] assumed that the efficacy of three drugs in the FDC (in half standard dose) were 20% lower than those in standard doses and the FDC's effect was equal to the multiplication of the individual components' effects.

While the adherence rate is the main advantage of FDCs, it was poorly reported among many of the included studies. Some studies reported different assumptions regarding the adherence rate. Price *et al.* (2014) assumed that the adherence rate was similar between FDCs and comparators [10]. Six studies assumed the adherence rate was 100% among those treated with FDC [18,19,21,29,38,46]. Specifically, three studies indicated equal adherence rates between the FDC and the comparator group [18,19,21], while the remaining three studies did not provide information on adherence rates in the comparator group. Some studies cited data on the adherence rates which were different between FDCs and comparators. Barrios *et al.* [39] assumed based on prior research that 76% of patients treated with the FDC were adherent while only 49% of those adhered to regimens with the separate monocomponents. Becerra *et al.* [11] assumed an adherence rate of 86% in FDCs and 65% in regimens of separate monocomponents, based on results from the UMPIRE study. Ren *et al.* [26] assumed an adherence rate of 56.55% in FDC and 50.83% for a regimen of separate monocomponents based on prior research. Notably, two out of three studies which are trial-based economic evaluations reported a lower adherence rate for the FDC groups compared with placebo [12,15]. Angus *et al.* [12] reported that the adherence rate was 84.6% in FDCs and 85.2% in placebo based on the A-HeFT study. Glasziou *et al.* [15] used adherence rates of 73% in FDC and 74% in placebo. Other studies also reported that the adherence in the FDC group was 83% in Wald's study [38], 84% in Jowett's [41], and 85% in the first year in van Gils's study [32]. Gaziano *et al.* [42] reported that adherence was decreasing over time both in the FDC and usual care groups (from 81.9% to 37.8% in the FDC group and from 65% to 30% in usual care) [42]. Lin *et al.* [16] estimated an adherence rate based on a prior study of only 41%–55% in the compared group and 58% in the FDC group [16].

Cost-effectiveness results of fixed-dose combination drugs

The cost-effectiveness results of fixed-dose combination drugs are presented in Table 3. In these 39 studies, six studies did not report the cost of FDCs and/or comparators [18,31,32,36–38]. The overall cost of using FDCs was lower when the comparison group was a free combination of individual single substances as components in FDCs [10,26,28,30,48] (lower because the price of FDCs is lower than when taking combinations of individual drugs) and higher when the comparison group is a single substance (part of the FDCs) or placebo [9,11,15,19,21,23,25–27,35,45–47]. Two studies [12,39] reported total costs of treatment with FDC lower than comparators when the comparator is a single drug, placebo, or no treatment and one study reported cost of FDC was higher than usual care [33,40,43].

FDCs improved treatment efficacy compared to comparators which resulted in higher QALYs, and LYs, the

Table 2. Methodological characteristics of included studies.

First author, year	Type of model	Type of costs measured	Source for cost data	Outcomes	Source for outcome data	Outcome measure	Main assumptions	Adherance rate report
COPD								
O'Connor et all. [17]	NA (Trial based)	Direct medical costs	Literature and local databases	1. Proportion of successfully treated patients (achieving ≥12% increase FEV1 from baseline) 2. Proportion of symptom-free days	Clinical trial	NR	For proportion of symptom-free days: First scenario: All patients who prematurely withdrew from the study were symptom free from the time they withdrew. Second scenario: All patient who prematurely withdrew from the study were symptomatic from the time they withdrew.	Fluticasone propionate/ Salmeterol: 89% Fluticasone propionate + Montelukast: 87%
Ismaila *et al.* [18]	Decision model	Direct and indirect medical costs	Literatures and local databases	Symptom free days; QALYs	Meta-analysis	EQ-5D	100% adherence	NA
Price *et al.* [10]	Patient-level simulation model	Direct costs, Indirect costs	Drug list and local literature	QALY	BEACON study	NR	Treatment effect and adherance are similar between two group.	NR
Van Boven *et al.* [19]	Markov model	Direct medical costs	Local literature and database	QALY, LYs, COPD Exacerbation	UPLIFT study and TONADO study	EQ-5D	Same utility value in COPD mild and moderate state No drug's adverse event	Assume 100%
Ramos *et al.* [20]	Markov model	Direct medical costs	*Drug formulary* *Local database*	QALY	ACLIFORM study, AUGMENT study UPLIFT study, Karabis *et al.* Oostenbrink *et al.*	EQ-5D	Risk of pneumonia is similar between 2 groups. Same utility value between COPD mild and moderate.	NR
Selya-Hammer *et al.* [9]	Markov model	Direct medical costs	AIFA database and literatures,	QALY, LY, COPD Exacerbation	NR	NR	Assume study FDCs's price is equal price of another FDC (LAMA/ LABA)	NR
Rajagopalan *et al.* [21]	Markov model	Direct medical costs	Local database and regulation	LY, QALY	FLIGHT 1 study, FLIGHT 2 study.	EQ-5D.	100% adherance	NA
Hoogendoorn *et al.* [22]	Patient-level discrete event simulation model	Direct costs and indirect costs	Literatures and local databases	Exacerbation rate, QALYs.	UPLIFT, EXACTT, POET, TIOSPIR, TONADO study	Utility mapping from the St George's Respiratory Questionnaire	Treatment effect are constant by time of treatment	NR

Continued

First author, year	Type of model	Type of costs measured	Source for cost data	Outcomes	Source for outcome data	Outcome measure	Main assumptions	Adherance rate report
Hoogendoorn *et al.* [23]	Patient-level discrete event simulation model	Direct costs and indirect costs	Literature	FEV 1, total and severe exacerbations and pneumonias, QALY	UPLIFT, EXACTT, POET, TIOSPIR, TONADO study	NR	Treatment effects were assumed constant over the simulated lifetime horizon.	NR
Orlovic *et al.* [24]	Markov model	NR	Literatures and local databases	QALYs	Literatures	EQ-5D	The patients in each state of model are at risk of death.	NR
Lan *et al.* [25]	Markov model	Direct medical costs	Literatures and local databases	COPD exacerbations; LYs; QALYs	Literatures	Utility mapping from the St George's Respiratory Questionnaire	The maintenance measures, except for the dosage of the two interventions, were assumed to be consistent in the two groups.	NR
Metabolic syndrome								
Zomer *et al.* [27]	Markov model	Direct medical costs	Literature and local database	YoLs, QALY	TIPS study AusDiab study	EQ-5D	FDCs price are 25% less than the additive price of all individual drug.	NR
Type 2 diabetes								
Glasziou *et al.* [15]	NA (Trial based)	Direct medical costs	Local databases	LY, QALY	ADVANCE trial	EQ-5D	Proportional differences between US and UK in the costs according to the cost of 30 days medication.	Adherence rate were 73% in FDC and 74% in placebo
Vaidya *et al.* [28]	NA (Analysis based on MEPS database)	Direct medical costs	MEPS database 2010-2012	QALY	MEPS database 2010-2012	SF-6D, SF-36, SF-12	Comorbidity does not affect to utility of health state. FDC improve the adherance rate.	NR
Cardiovascular diseases including hypertension and heart failure								
Angus *et al.* [12]	NA (Trial based)	Direct medical costs	Medicare data	LY	A-HeFT study	NR	Resources used outside the A-HeFT study were similar in 2 groups	Adherance rate was 84.6% in FDC and 85.2% in placebo (A-HeFT study).
Newman *et al.* [29]	Markov model	Direct medical costs	Literatures	QALYs gained	Literatures	NR	All moderate side effects would lead to discontinuation of polypill. Adherence rate was 100%	NR

Continued

First author, year	Type of model	Type of costs measured	Source for cost data	Outcomes	Source for outcome data	Outcome measure	Main assumptions	Adherance rate report
Rubinstein *et al.* [30]	WHO-CHOICE	Direct medical costs	Literature and local databases, expert opinion	DALYs averted	NR	NR	1. For intervention of individual treatment of HBP: 40% population take one drug, 40% take at least two drugs and 20% take three or more drugs. 2. For intervention of Polypill strategies: 50% compliance rate in those with a 10 year risk of 5% and 10%, and 80% compliance in those with a 20% risk.	NA
Rubinstein *et al.* [31]	NR	Direct medical costs		DALYs averted	Literature	NR	1. At least 50% of the target population is reached by intervention. 2. 50% patient compliance rate with treatment and 70% provider compliance	NR
van Gils *et al.* [32]	Markov model	Direct and indirect medical costs	Literatures and local databases	LYs and QALYs gained	Literatures	NR	Patients already treated with drugs will not switch to the polypill. Cost and effect due to adverse event are captured by taking into account non-adherence and stopping taking the pill.	The average first year's adherence was 85%
Ito *et al.* [33]	Markov model	Direct medical and nonmedical costs	Literatures	QALYs gained	Literatures	NR	All the intervention were continued without crossover until patients died. The effectiveness of polypill was equivalent to four-drug regimen of combination.	NR

Continued

First author, year	Type of model	Type of costs measured	Source for cost data	Outcomes	Source for outcome data	Outcome measure	Main assumptions	Adherance rate report
Khonputsa *et al.* [34]	Markov model	Direct medical costs	Local databases	DALYs averted	NR	NR	60% adherence for polypill and 50% adherence for single drugs in full dose. The efficacy three drugs in the polypill (in half standard dose) were 20% lower than those in standard doses, and the polypill's effect was a multiplication of the individual components' effect.	NA
Bautista *et al.* [35]	Markov model	Direct and indirect costs	Literatures	QALYs gained	Literatures	Weighted disease-state values	The average cost of the polypill was estimated at $50 per subject per year. 23% patients with new case of coronary heart disease died before hospitalization.	NR
Megiddo *et al.* [36]	WHO-CHOICE	Direct medical costs	WHO, NCMH	DALY	TIPS study	NR	FDCs price are less than the additive price of all individual drug. The FDC was not assumed to increase adherence.	NR
Ong *et al.* [37]	Markov model	Direct medical and nonmedical costs	Literatures and local databases	DALYs adverted	NR	NR	For statin: only one general practitioner visit was required in the first year and followed by twice yearly visit.	NR
Becerra *et al.* [11]	Markov model	Direct medical costs	NHS cost and national drug formulary	CV events prevented; LY; QALY	Literature	NR	The model risk equations for CV events assumed that baseline risks and efficacy among adherent patients were equal for the polypill and its monocomponents in terms of health benefits.	Adherance rate was 86% in FDCs and 65% in free multiple drugs (UMPIRE study)
Wald *et al.* [38]	NR	Direct medical costs	Literatures	Total years of lifeainedd without a first MI or stroke	NR	NR	Polypill uptake and adherence rate were 100% for best case situation.	83%

Continued

First author, year	Type of model	Type of costs measured	Source for cost data	Outcomes	Source for outcome data	Outcome measure	Main assumptions	Adherance rate report
Barrios *et al.* [39]	Markov model	Direct medical costs	Literature and local database	Events avoided, LY, QALY	Meta-analysis	EQ-5D	All adherent patients were assumed to be adherent to the 3 drugs; nonadherent patients were considered to be nonadherent to all drugs.	76% of patients treated with the polypill were adherent vs only 49% of those treated with the separate monocomponents
Ferket *et al.* [40]	Microsimulation model (UK-PROMISE)	Direct medical costs	NICE, Literature and local databases	QALYs	Literature	EQ-5D	For annual follow up visits in case of diabetes, an uptake of 100% was used.	NR
Jowett *et al.* [41]	Markov model	Direct medical costs	WHO CHOICE database, Literature, Local databases	QALYs gained; Cardiovascular events	Literatures	EQ-5D	No reduction in QoL for any drugs. The cost of polypill in this study was in line of exiting secondary prevention polypill Trinomia	84%
Gaziano *et al.* [42]	Microsimulation model (CVD PREDICT)	For CEA: Direct and indirect medical costs	UHC database; Red book	QALYs gained	Literatures	NR	Aspirin initiation was independent of adherence to the other three classes of medications. All the drugs costs were in 2018.	Year 1: 81.9% Year 2: 50.4% Year 3: 37.8%
Lin *et al.* [16]	Markov model	Direct medical costs	WHO CHOICE website, Local databases, Literature	Adverted major adverse cardiovascular events, DALYs	Literatures	NR	Adverse event rate was the same in the two intervention. Patients derived identical benefit from a drug, regardless of whether it is received as an individual pill or as a part of the polypill.	Estimated 41-55%
Lung *et al.* [43]	Discrete-time simulation model	Direct medical costs	Literatures and local databases	DALY	Literatures	WHO and Global Burden of Disease Study methodology	No change to adherence or non-adherence of antihypertensive medication from the end of study measurements.	NR
Ren *et al.* [26]	Markov model	Direct medical costs	IMS databases	LY, QALY	Meta-analysis	Literature and IMS database	FDC improve the adherance rate.	Adherence rate was 56.55% in FDC and 50.83% in free combination

Continued

First author, year	Type of model	Type of costs measured	Source for cost data	Outcomes	Source for outcome data	Outcome measure	Main assumptions	Adherance rate report
Aguiar *et al.* [44]	Markov model	Direct medical costs	Literatures and local databases	LYs; QALYs; No. of subsequent/ recurrent events; CV death prevented	Literature	EQ-5D-3L	All patients entered the model in the stable secondary prevention state No death event in base case analysis WTP threshold was equal to €30,000	NR
Gonzalez-Dominguez *et al.* [45]	Markov model	Direct medical costs	Local databases	LYs; QALYs	Literature	NR	NR	NR
Rheumatoid arthritis								
Al *et al.* [46]	Mathematical model	Direct medical costs	Treatment guideline.	LY, symptomatic ulcers, deaths.	Literature	NR	100% adherance rate in FDCs Patients switch to treatment with diclofenac when stopping treatment with FDCs.	NR
Benign prostatic hyperplasia								
Udeh *et al.* [47]	Markov model	Direct medical costs	Local data	QALY	CombaT study	EQ-5D, TTO	Patient start the model with the mild disease.	NR
Cancer								
Sussell *et al.* [48]	Hybrid decision tree/ Markov model	Direct medical costs	Literatures and local databases	LYs; QALYs	KATHERINE trial; Literature	EQ-5D	Efficacy as demonstrated in clinical trials accurately characterized real-world effectiveness.	NR
Others								
Nilsson *et al.* [49]	Markov model	Direct medical costs	Literatures	QALDs	NR	NR	NR	NR

NR, Not reported; NA: Not applicable; FEV1: Forced expiratory volume in the first second; QALD: Quality-adjust life day; CV: Cardiovascular

; QALY, Qality-Adjusted Life Year; LY, Life-Year; DALY, Disability-Adjusted Life Year; EQ-5D, EuroQoL 5 Dimensions, TTO, Time Trade-Off; EQ-5D-3L: EuroQoL 5-Dimensions 3-Levels; SF-6D, Short-Form 6-Dimension, SF-36, 36-Item Short-Form; SF-12, 12-Item Short Form; WTP, Willingness-to-pay

Table 3. The cost-effectiveness results of fixed-dose combination drugs.

First author, year	Total costs		Total outcomes		ICER	Threshold	Conclusion of FDCs
	FDCs	Comparators	FDCs	Comparators			
COPD							
O'Connor *et al.* [17]	Mean per-patient daily cost: $3.64	Mean per-patient daily cost: $4.64	% successfully treated patients: 54% % symptom-free day: 31%	% successfully treated patients: 32% % symptom-free day: 27%	Daily cost per successfully treated patient (FP/salmeterol *vs.* FP + montelukast): Cost saving/Dominant	NR	Cost-saving
Ismaila *et al.* [18]	NR	NR	NR	NR	SFC200 versus FP200: $43,981 per QALY SFC500 versus FP400-500: $42,911 per QALY SFC1000 versus FP1000: $54,411 per QALY SFC200 versus FP400-500: $24,959 per QALY SFC500 versus FP1000: $3,432 per QALY	$50,000 per QALY	Cost-effective
Price *et al.* [10]	1 year: SEK 27,635 3 years: SEK 91,788 5 years: SEK 149,464 10 years: SEK 273,053 Lifetime: SEK 500,248	1 year: SEK 28,403. 3 years: SEK 93,906. 5 years SEK 152,772. 10 years: SEK 278,685. Lifetime: SEK 508,951	NR	NR	NR	NR	Cost-saving
Van Boven *et al.* [19]	€ 25,002	€ 24,494	QALY = 7.6231. LY = 11.184.	QALY = 7.5506. LY = 11.127.	€ 7,004 per QALY	€ 20,000 per QALY	Cost-effective
Ramos *et al.* [20]	Δ cost = £ 41		Δ QALY = 0.014		£ 2,976 per QALY	€ 20,000 per QALY	Cost-effective
Selya-Hammer *et al.* [9]	€ 27,597.77	€ 26,430.92	QALYs = 7.43 LYs = 12.24.	QALYs = 7.27 LYs = 12.07	€ 7,518 per QALY	€ 20,000 and € 30,000 per QALY	Cost-effective
Rajagopalan *et al.* [21]	$ 23,375	$ 9,365	LYs = 4.463; QALY = 3.294	LYs = 4.415; QALY = 3.093	$ 292,817 per LY $ 69,665 per QALY	50,000 $ –150,000 $/ QALY	Cost-effective
Hoogendoorn *et al.* [22]	Societal perspective: € 25,606 Payer perspective: € 22,161	Societal perspective: € 25,483 Payer perspective: € 22,433	QALY = 4.8	QALY = 4.76	Societal perspective: €2,900 per QALY	€10,000, 20,000, and 40,000 per QALY	Cost-effective

Continued

First author, year	Total costs		Total outcomes		ICER	Threshold	Conclusion of FDCs
	FDCs	Comparators	FDCs	Comparators			
Hoogendoorn *et al.* [23]	Finland: € 16,921. Sweeden: € 18,916 Netherlands: € 137,253	Finland: € 15,910 Sweeden: € 18,348 Netherlands: € 135,662	QALYs Finland: 6.159, Sweeden: 6.159 Netherlands: 6.832	QALYs Finland: 6.067 Sweeden: 6.067. Netherlands: 6.722	***Payer perspective:*** Finland: € 11,000 per QALY ***Societal perspective:*** Sweeden: € 6,200 per QALY Netherlands: € 14,400 per QALY.	Finland: €20,000 € per QALY Sweeden: €47,500 per QALY. Netherlands: € 50,000 per QALY	Cost-effective
Orlovic *et al.* [24]	Medium dose of BDP/FF/G: £44,454; High dose of BDP/FF/G: £44,769	Medium dose of BDP/FF: £40,842 High dose of BDP/FF: £43,45 High dose of BDP + Tiotropium: £47,092	Medium dose of BDP/FF/G: QALY = 15.27 High dose of BDP/FF/G: QALY = 15.27	Medium dose of BDP/FF: QALY = 14.98 High dose of BDP/FF: QALY = 15.18 High dose of BDP + Tiotropium: QALY = 15.25	Medium dose of BDP/FF/G versus Medium dose of BDP/FF: £12,224 per QALY gained High dose of BDP/FF/G versus High dose of BDP/FF: £15,587 per QALY gained High dose of BDP/FF/G versus High dose of BDP/FF + Tiotropium: Dominant	£20,000 - £30,000 per QALY gained	Cost-effective
Lan *et al.* [25]	$20,938.21	$18,670.04	QALY = 4.332 LY = 6.655	QALY = 4.325 LY = 6.667	$324,557.91 per QALY	$17,663.12 per QALY	Not cost-effective
Metabolic Syndrome							
Zomer *et al.* [27]	AUD 704 annual	AUD 42.50 annual	NR	NR	-Statin monotherapy: AUD 136,415 per QALY - Anti-hypertensive monotherapy AUD 233,306 per QALY - Aspirin+ Simvastatin: AUD 82,664 per QALY, - Aspirin + antihypertensive: AUD 157,071 per QALY - Antihypertensive and statin: AUD 253,520 per QALY) - FDCs: AUD 214,865 per QALY	AUD 50,000	Not cost-effective

Continued

First author, year	Total costs		Total outcomes		ICER	Threshold	Conclusion of FDCs
	FDCs	Comparators	FDCs	Comparators			
Type 2 diabetes							
Glasziou *et al.* [15]	Discount 3%: AUD 21,811 Discount 5%: AUD 21,001 Discount 10%: AUD 19,223	Discount 3%: AUD 21,281 Discount 5%: AUD 20,499 A$. Discount 10%: AUD 18,775	Total LYs: 14.97 Discount 3%: = 12.28 Discount 5%: = 10.88 Discount 10%: = 8.36	Total LYs: 14.88 Discount 3%: = 12.22. Discount 5%: = 10.84 Discount 10%: = 8.34	AUD 10,600 per QALY AUD 10,040 per LY (discount 5%) AUD 8,470 per LY (no discount).	NR	Cost-effective
Vaidya *et al.* [28]	$ 6,016,65 annual	$ 6,919.58 annual	QALY = 0.7214	QALY = 0.6811	Dominant	$ 50,000 per QALY	Cost-saving
Cardiovascular diseases including hypertension and heart failure							
Angus *et al.* [12]	$ 15,384.	$ 19,728.	- Mortality: 6.2%. - Survival: 403 days - Estimated mean survival: 5.33 years - Adherence: 84.6%. - Hospitalization related to heart failure: 0.33 - Length of stay: 6.7 days	- Mortality: 10,2%. - Survival: 380 days - Estimated mean survival: 5.07 years - Adherence: 85.2 %. - Hospitalization related to heart failure: 0.47 - Length of stay: 7.9 days	$16,600/LY (2 years time horizon), $37,100/LY (5 years), $41,800/LY (lifetime)	$10,000/LY and $ 50,000/LY	Cost-effective
Newman *et al.* [29]	$70,000	$93,000	QALY = 13.62	QALY = 12.96	Dominant	$50,000 per QALY gained	Cost-effective
Rubinstein *et al.* [30]	1. >5% CVD risk: ARS $63,893,600 2. >10% CVD risk: ARS $45,323,335 3. >20% CVD risk: ARS $23,533,467	1. HBP lowering therapy: ARS $37,478,853 2. High-cholesterol lowering with statins: ARS $40,253,626	1. >5% CVD risk: DALY = 14,095 2. >10% CVD risk: DALY = 11,263 3. >20% CVD risk: DALY = 6,539	1. HBP lowering therapy: DALY = 4,857 2. High-cholesterol lowering with statins: DALY = 567	1. Polypill for >5% CVD risk versus HBP lowering therapy: ARS $2,859 per DALY 2. Polypill for >10% CVD risk versus HBP lowering therapy: ARS $1,224 per DALY 3. Polypill for >20% CVD risk versus HBP lowering therapy: Dominant 4. Polypill for >5% CVD risk versus High-cholesterol lowering with statins: ARS $1,747 per DALY 5. Polypill for >10% CVD risk versus High-cholesterol lowering with statins: ARS $474 per DALY 6. Polypill for >20% CVD risk versus High-cholesterol lowering with statins: Dominant	3 x ARS $13,728	Cost-effective

Continued

First author, year	Total costs		Total outcomes		ICER	Threshold	Conclusion of FDCs
	FDCs	Comparators	FDCs	Comparators			
Rubinstein *et al.* [31]	I$ 23,489,613.55	NR	DALY = 12108.15	NR	I$ -246.45 per DALY saved	3 x I$13,728 (ARS $ 1.55 = 1 I$)	Cost-saving
van Gils *et al.* [32]	NR	NR	A: LY = 214,000; QALY = 266,000 B: LY = 291,000; QALY = 244,000 C: LY = 349,000; QALY = 296,000	NR	A: €9,000 per LY gained and €10,800 per QALY gained B: €8,200 per LY gained and €9,700 per QALY gained C: €7,600 per LY gained and €8,900 per QALY gained	€20000 per QALY gained	Cost-effective
Ito *et al.* [33]	Polypill: $107,077 Polypill plus mailed education: $107,075 Polypill plus disease management: $109,613	$102,767	QALY = 4.5080	QALY = 4.4756	Polypill: $133,000 per QALY gained. Polypill plus mailed education: $113,000 per QALY gained. Polypill plus disease management: $142,900 per QALY gained	$100,000 per QALY gained	Not cost-effective
Khonputsa *et al.* [34]	1. CVD risk: 5% - 9.9%: Baht (-12x10^9) 2. CVD risk: 10% - 19.9%: Baht (-16x10^9) 3. CVD risk: > 20%: Baht (-16 x10^9)	Baht 120 x10^9	1. CVD risk: 5% - 9.9%: DALYs adverted = 1,100,000 2. CVD risk: 10% - 19.9%: DALYs adverted = 910,000 3. CVD risk: > 20%: DALYs adverted = 720,000	DALYs adverted = 400,000	Dominant	Baht 110,000 - 330,000 per DALY adverted	Cost-effective
Bautista *et al.* [35]	***Women:*** Polypill for high-risk patients: $742 Polypill for abdominal obesity patients (WHO): $1,163 ***Men:*** Polypill for high-risk patients: $743 Polypill for abdominal obesity patients (LASO): $854	Women: $576 Men: $444	***Women:*** Polypill for high-risk patients: QALY = 23.696 Polypill for abdominal obesity patients (WHO): QALY = 23.849 ***Men:*** Polypill for high-risk patients: QALY = 22.166 Polypill for abdominal obesity patients (LASO): QALY = 22.198	Women: QALY = 23.076 Men: QALY = 21.660	***Women*** Polypill for high-risk patients versus no polypill: $268 per QALY gained Polypill for abdominal obesity patients (WHO) versus no polypill: $2,770 per QALY gained. ***Men:*** Polypill for high-risk patients versus no polypill: $1,041 per QALY gained Polypill for abdominal obesity patients (LASO) versus no polypill: $3,533 per QALY gained	GDP per capita in each country	Cost-effective

Continued

First author, year	Total costs		Total outcomes		ICER	Threshold	Conclusion of FDCs
	FDCs	Comparators	FDCs	Comparators			
Megiddo *et al.* [36]	NR	NR	DALY averted = 7,320,000	DALY averted - Aspirin:1,380,000 - Aspirin & beta blocker:3,460,000 - Aspirin & beta blocker & ACEI: 4,840,000 - Aspirin & beta blocker & ACEI & statin: 6,700,000	1,690 $ per DALY averted (80% coverage rate of FDC)	3 × GDP per DALY averted	Cost-effective
Ong *et al.* [37]	NR	NR	4,700 DALYs adverted	NR	Dominant	$50,000 per DALY adverted	Cost-effective
Becerra *et al.* [11]	£ 3,994,814	£ 3,752,473	QALY = 5278.46 LY = 6338.57	QALY = 5248.92 LY = 6307.69	£ 8,205 per QALY	£ 20,000 per QALY	Cost-effective
Wald *et al.* [38]	*For daily cost per patient:* - £0.5: Total costs £2.38 - £0.75: Total costs £3.57 - £1.00: Total costs £4.76 - £1.25: Total costs £5.94 - £1.50: Total costs £7.13	NR	Best case (100% uptake and adherence): 2,390,000 years of life gained without a first MI or stroke. Working case (50% uptake and 83% adherence): 990,000 years of life gained without a first MI or stroke.	NR	Net cost or saving according to daily cost per patient: - £0.5: saving (-£0.27) - £0.75 saving £0.92 - £1.00: saving £2.11 - £1.25: saving £3.29 - £1.50: saving £4.48	NR	If the cost of the program were £1 per person per day, the net cost per year of life gained without a first MI or stroke of £2120 (be cost-effective).
Barrios *et al.* [39]	€ 5,963,464.15	€ 6,473,325.79	Cost per LY: € 7,386.12 Cost per QALY: € 6147.32	Cost per LY: € 7,335.06 Cost per QALY: € 6,098.98	Cost per QALY gained: € 48.34. Cost per LY gained: € 51.06	€ 30,000 per QALY	Cost-effective
Ferket *et al.* [40]	Age 60+: £3,082 Age 55+: £3,331 Age 50+: £3,523 Age 45+: £3,645 Age 40+: £3,686	£1,854	Age 60+: QALY = 13.407 Age 55+: QALY = 13.406 Age 50+: QALY = 13.404 Age 45+: QALY = 13.401 Age 40+: QALY = 13.400	QALY = 13.367	Age 60+: £39,945 Age 40+ - 55+: Absolutely dominated	£20,000 - £30,000 per QALY	Not cost-effective

Continued

First author, year	Total costs		Total outcomes		ICER	Threshold	Conclusion of FDCs
	FDCs	Comparators	FDCs	Comparators			
Jowett *et al.* [41]	Men: from £1,878 to £2,459 Women: from £1,671 to £2,097	Men: from £1,625 to £2,457 Women: from £1,325 to £1,985	Men: QALY from 4.781 to 7.229 Women: QALY from 4.779 to 7.093	Men: QALY from 4.692 to 7.202 Women: QALY from 4.733 to 7.077	Men: from Dominant to £9,166 per QALY gained Women: from £1,870 to £21,798 per QALY gained	£20,000 per QALY	Polypill may be cost-effective in most people aged 50 and over with high cardiovascular risk on treatment. If cost of polypill lower than £150 per year, polypill becomes cost-effective for all sub-groups.
Gaziano *et al.* [42]	Healthcare perspective: $190,243 - $192,666 Societal perspective: (-$233,578) - (-$232,680)	Healthcare perspective: $186,493; Societal perspective: (-$229,653)	Healthcare and societal perspective: QALY from 8.31 to 8.38	QALY = 8.12	Healthcare perspective: $20,073 - $23,603 Societal perspective: Cost-saving	$50,000 - $150,000 per QALY	Cost-effective
Lin *et al.* [16]	China: I$ 2,430,000 India: I$ 658,000 Mexico: I$ 1,810,000 Nigeria: I$ 4,430,000 South Africa: I$ 2,140,000	China: I$ 2,280,000 India: I$ 541,000 Mexico: I$ 1,740,000 Nigeria: I$ 4,090,000 South Africa: I$ 2,080,000	China: DALY = 10,200 India: DALY = 10,300 Mexico: DALY = 10,600 Nigeria: DALY = 10,000 South Africa: DALY = 9,920	China: DALY= 11,100 India: DALY = 11,100 Mexico: DALY = 11,300 Nigeria: DALY = 10,900 South Africa: DALY = 10,800	China: I$ 168 per DALY adverted India: I$ 154 per DALY adverted Mexico: I$ 88 per DALY adverted Nigeria: I$ 364 per DALY averted South Africa: I$ 64 per DALY adverted	GDP per capita in each country	Cost-effective
Lung *et al.* [43]	$863.90	$516.15	DALY averted = 0.39	DALY averted = 0.51	$2842.79 per DALY averted	$6,100	Cost-effective
Ren *et al.* [26]	¥ 18,144	OM + AML: ¥ 23,584 AML: ¥ 11,615	LY: 14.5149. QALYs: 13.7776	OM+AML: - LY: 14.4630; -QALYs: 13.7045 AML: LY: 14.4483; QALYs: 13.6834	FDCs vs OM + AML: −¥104,968 FDCs vs AML: ¥ 98,173	¥193,563 ($28,163)	Cost-effective
Aguiar *et al.* [44]	€ 10,940,008	€ 10,888,206	QALY = 7371.46 LY = 9760.83	QALY = 7,338.20 LY = 9,721.80	€1557 per QALY €1327 per LY	€30,000 per QALY	Cost-effective
Gonzalez-Dominguez *et al.* [45]	€ 41,870,812	€ 42,151,487	QALY = 9,705.36 LY = 12,717.25	QALY = 12,704.03 LY = 9,693.73	Dominant	€25,000 per QALY	Cost-effective

Continued

First author, year	Total costs		Total outcomes		ICER	Threshold	Conclusion of FDCs
	FDCs	Comparators	FDCs	Comparators			
Rheumatoid arthritis							
Al *et al.* [46]	NLG 20,598	NLG 19,825	Symptomatic ulcers: 0.63 Death: 0.0189	symptomatic ulcers: 1.45 death: 0.0375	NLG 4,179 per LY. NLG 949 per symptomatic ulcer-free period gained.	NR	Cost-effective
Benign prostatic hyperplasia							
Udeh *et al.* [47]	Total costs $ 1.45 billions (10 years time horizon) and $ 2.19 billions (15 years time horizon)	$ 855 millions (10 years time horizon) $ 1.58 billion (15 years time horizon)	QALYs: 18.8 million (10 years) 23.9 million (15 years)	QALYs: 18.4 million (10 years) 20.9 million (15 years)	ICER: $ 1,481.92 per QALY (10 years) $ 908.13 per QALY (15 years)	$ 2,450 per QALY	Cost-effective
Cancer							
Sussell *et al.* [48]	$280,448	1. Strategy 2: $279,466 2. Strategy 3: $272,873 3. Strategy 4: $299,813 4. Strategy 5: $293,220 5. Strategy 6: $326,475 6. Strategy 7: $319,882	QALY = 14.585	1. Strategy 2: QALY = 14.493 2. Strategy 3: QALY = 14.493 3. Strategy 4: QALY = 14.585 4. Strategy 5: QALY = 14.585 5. Strategy 6: QALY = 13.687 6. Strategy 7: QALY = 13.687	1. Strategy 1 versus Strategy 2: $10,609 per QALY gained 2. Strategy 1 versus Strategy 3: $81,793 per QALY gained 3. Strategy 1 versus Strategy 4: Dominant 4. Strategy 1 versus Strategy 5: Dominant 5. Strategy 1 versus Strategy 6: Dominant 6. Strategy 1 versus Strategy 7: Dominant	$150,000	Cost-effective
Others							
Nilsson *et al.* [49]	€ 65.40	APR (PO) + OND (PO): €46.07 APR (PO) + PAL (IV): €78.92 FOS (IV) + GAR (IV): €95.03	QALDs = 4.272 QALYs = 0.0117	APR (PO) + OND (PO): QALDs = 4.117; QALYs = 0.0113 APR (PO) + PAL (IV): QALDs = 4.220; QALYs = 0.0116 FOS (IV) + GRA (IV): QALDs = 4.112; QALYs = 0.0113	- NEPA versus APR (PO) + OND (PO): Cost per avoided event: €33 Cost per QALD: €125 - - NEPA versus APR (PO) + PAL (IV): Cost per avoided event: Dominant Cost per QALD: Dominant - NEPA versus FOS (IV) + GRA (IV): Cost per avoided event: Dominant Cost per QALD: Dominant	NR	Cost-effective

I$: International Dollar; APR: aprepitant, OND: ondansetron, PAL: palonosetron, FOS: fosaprepitant, GRA: granisetron, dex dexamethasone, PO: per os (by mouth), IV: intravenous; OM/AML: olmesartan/amlodipine fixed-dose combination; OM+AM:, olmesartan and amlodipine free combination; AML: amlodipine; VM/AML: valsartan/amlodipine fixed-dose combination; ICER: incremental cost-effectiveness ratios; ICUR: incremental cost-utility ratios; LASO: Latin American Consortium of Studies in Obesity; CVD: Cardiovascular disease; HBP: High blood pressur; BDP/FF/G: beclometasone dipropionate/formoterol fumarate/glycopyrronium.

incidence and number of COPD exacerbations decreased, the number of ulcers and deaths decreased, and adverse events [9,11,15,19,21–23,26,28,36,39,46,47]. The study by Angus *et al.* [12] showed that FDCs improved treatment efficacy but adherence rates when using FDCs were lower than placebo, namely 84.6% versus 85.2%. FDCs could significantly increase the DALY adverted compared to current practice for primary prevention of cardiovascular disease in different classified risk populations [30,34]. In addition, 3 studies did not explicitly mention the total number of results on clinical efficacy between the 2 treatment or comparator groups [10,18,20,27,31,32,37,38]. FDC was cost-saving in four studies [10,17,28,31], suggesting that better outcomes can be obtained at a cheaper cost, four studies [25,27,33,40] showed that FDC was not cost-effective. Regarding FDCs for cardiovascular diseases including hypertension and heart failure, Wald *et al.* [38] reported FDCs will be cost-effective if the cost of the FDC program were £1 per person per day and Jowett suggested when FDC's price is lower than £150, it would be cost-effective for all population [41]. All 25 remaining studies showed that FDC was cost effective.

DISCUSSION

This systematic review aimed to review the methods and summarize key assumptions of previous economic evaluations of FDC drugs. A total of 39 studies across different health topics were included in the review. Economic evaluations of FDCs were relatively more common for the treatment of NCDs such as COPD or cardiovascular diseases. Two studies [28,49] were assessed to have moderate quality, while the remaining studies had high quality.

Most studies show that the FDC was cost-effective except for four studies [25,27,33,40]. All four studies concluded that FDCs could achieve cost-effectiveness with lower prices. Lan *et al.* [25] reported that both FDC and comparator prices were based on average bidding prices, with the FDC's price higher than other LABAs/LAMAs. Ito *et al.* used the price of the most expensive brand-name drug as the FDC's price, while comparator prices were sourced from generic drugs that had gone off-patent [33]. Ferket *et al.* [40] did not explicitly state prices, providing only annual costs, and notably, the FDC's annual cost (£382.64) was considerably higher than individual components. In Zomer *et al.* [27] study, they assumed the FDC cost was 25% less than the combined costs of its components. However, they expressed their concern about the WTP threshold in Australia, which was below the WHO's recommended threshold (A$ 92,123). However, even with an increased WTP of A$ 92,123, the FDC remained noncost effective, with an ICER of A$ 214,865 compared to no treatment [27]. Even though most studies suggest FDCs are cost-effective, there was substantial variation among the studies regarding methodological choices and assumptions applied.

Among included studies, the FDCs could be compared in one or more of three groups: (1) regimen of multiple separate components that belong to FDCs, (2) mono-component that belongs to FDCs with or without other drugs, and (3) no treatment/placebo/usual care. Only five studies explicitly indicated the selection of comparators in accordance with current treatment guidelines [18,20,40,41,49]. The selection of a comparator could be based on treatment guidelines such as the first-line treatment, second-line treatment, or combination therapy such as mono-therapy, dual- and triple therapy in some diseases such as diabetes. However, the rationale for comparator selection was not well reported in most of the included studies (n = 34). For best practices, the comparators for FDCs should consist of regimens with multiple separate components, similar to those included in the FDC as FDCs have demonstrated their ability to enhance adherence rates compared to multiple separate components [51,52].

For studies that compared FDCs to placebo/usual care or FDCs versus single component drugs, the efficacy of drugs could be predictable, i.e., FDC had higher efficacy while reducing adverse events [9,15,21,22]. The costs of FDCs were generally higher when compared to a placebo or single-component drug [9,11,15,19,21,23,25–27,35,45–47].

In their study, Khonputsa *et al.* [34] utilized an FDC comprising four blood pressure-lowering drugs, each administered at half the standard dose. They presumed that the efficacy of individual components at this reduced dosage in the FDC was 20% lower than that at the standard doses [34]. This assumption was derived from an analysis of 354 clinical trials that assessed the effectiveness of blood pressure-lowering drugs at half the standard dose compared to standard doses [53]. Another clinical trial consistently supported these findings when comparing two types of FDCs—one in the standard dose and the other in the half-standard dose. The results indicated that the standard dose FDC exhibited comparable tolerance but delivered a 25%–30% higher efficacy compared to the half-standard dose FDC [54]. For FDC's effect, Khonputsa *et al.* [34] assumed that it was equal to the multiplication of the individual components' effects. This assumption was different from other approaches in the included studies and may result in an overestimation of the effects of FDCs compared to multiple separate components.

For economic evaluations that compared FDCs to regimens of separate components of the FDC, there were three main groups of assumptions applied. The first assumption related to the costs of FDC as compared to the comparator while the second assumption was applied to the efficacy of FDCs, and the third assumption was about treatment adherence.

Some studies have assumed the costs of FDC were lower than the corresponding costs of comparators [9,27,35,36,41]. The costs of FDC were assumed to be generally lower [36] or 25% lower [27] than the additive cost of each single drug in the free combination. This assumption was made due to the unavailability of FDC's price in the countries where studies were conducted [9,41]. While the cost of FDC might be lower than the summation costs of multiple monotherapies in some situations, this depends on factors such as generic availability, pricing, and negotiation policies in a given country. In their study, Hong *et al.* [55] showed that the monthly cost of FDCs for antihypertensive drugs in the U.S. was higher than that of the separate components when generic FDCs were not available. In other words, the assumption of the cost advantage of FDCs over separate components might not be true when the separate components are generically available, particularly when the FDC is branded. Furthermore, a US-based study reported that

FDC antihypertensive drugs had higher out-of-pocket costs than did the sum of their components [56] but the total costs were lower for FDC drugs. This reflects an opportunity for a better value-based insurance design that reduces out-of-pocket costs for patients for higher value therapies. This also suggested that choosing analysis perspectives other than the third-party payer perspective such as the societal perspective would affect the conclusion of the cost-effectiveness of FDC.

Future guidance should be issued regarding the cost of intervention when the intervention is not marketed yet. This need is also applicable to the guidance of early health technology assessment which is conducted at earlier stages of the development of healthcare technology [57]. Guidance is crucial for successful health technology development and an efficient research and development system. This ensures innovations meet market demand, remain accessible to the target population, and contribute significantly to improving overall population health [58].

For the drug's efficacy, the assumption of equal efficacy between FDCs and the free combination was applied in a study by Price *et al.* [10], Ito *et al.* [33], and Lin *et al.* [16]. The adherence improvement of FDCs when compared to several monotherapies was highlighted in previous meta-analyses [59,60]. This is an important factor that contributes to the overall effectiveness of medical treatment, especially in chronic diseases. However, among the included studies, the adherence rate was not well reported and different assumptions were made about the relative adherence of FDCs versus alternatives. Most studies ($n = 22$) did not report the adherence rate. In model-based economic evaluations where adherence rate parameters were derived, the adherence rates were higher in FDCs as compared to free combination drugs [11,26,39]. Meanwhile, two trial-based economic evaluations [12,15] reported a lower adherence rate in the FDCs group compared to that of the placebo. Failure to consider adherence rate in economic evaluations of FDCs could result in the underestimation of the cost-effectiveness of FDCs. Furthermore, for some conditions such as asthma, ignoring adherence advantages with FDCs could lead to inaccurate conclusions regarding whether FDCs meet cost-effectiveness thresholds, with consequences for coverage and access. A systematic review by Chongmelaxme *et al.* [61] showed that few economic evaluations of asthma incorporated adherence in the analysis. Chongmelaxme *et al.* [61] also identified one method of incorporating adherence, which involved adjusting treatment effectiveness based on adherence levels. Moreover, further economic evaluations based on long-term clinical trials with larger populations are necessary. Future guidance is necessary to establish best practices on how to incorporate adherence into the economic evaluation of health technology, especially model-based economic evaluations.

According to the findings from the included studies, FDCs were deemed cost-saving [10,17,28,31] and cost-effective when compared to their comparators. These results provide substantial support for the integration and utilization of FDCs in clinical practice. Recent studies have demonstrated a high prevalence of FDC prescriptions in both primary and secondary healthcare settings, underscoring the proven efficiency of FDCs [62–64]. Improved adherence to treatment is a critical factor contributing to treatment effectiveness. Simplifying medication regimens by reducing the number of pills can enhance both uptake and adherence rates, particularly in chronic diseases that require lifelong medications. Nevertheless, the utilization of FDCs warrants careful consideration, especially in light of the observed high prevalence of irrational prescribing associated with FDCs [62,64,65]. This highlights the importance of involving pharmacists, who possess the most comprehensive knowledge of available dosage forms, to potentially enhance the prevalence of FDCs while mitigating the risk of irrational prescribing of FDCs.

Our study has limitations to consider. First, heterogeneity between studies including across clinical conditions and methodology made the pooling of data implausible. Second, publications in languages other than English or without full text were not included in this review.

CONCLUSION

In prior studies, FDCs were sometimes found to be cost-effective compared to regimens of separate components of the FDC. Whether an FDC was deemed cost-effective depended on the characteristics of the disease state, drugs under study, study design choices, and assumptions made in the economic evaluation. Variations among previous studies regarding methodological patterns and assumptions highlight an opportunity for guidance to promote the harmonization of methods. Future economic evaluations should comprehensively capture and report the costs and effectiveness of FDCs and justify the choice of comparators. In particular, the advantages of FDCs for enhancing adherence should be captured appropriately in future studies.

LIST OF ABBREVIATIONS

CBA, Cost-benefit analysis; CEA, Cost-effectiveness analysis; CHEERS, Consolidated Health Economic Evaluation Reporting Standards; CMA, Cost-minimization analysis; COPD, Chronic obstructive pulmonary disease; CUA, Cost-utility analysis; DALY, Disability-adjusted life year; FDCs, Fixed-dose drug combinations; INAHTA, International Network of Agencies for Health Technology Assessment; ICER, Incremental cost-effectiveness ratio; LY, Life-year; NCDs, Non-communicable diseases; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; QALY, Quality-adjusted life year.

AUTHOR CONTRIBUTION

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published. All authors reviewed, revised, and approved the final version of the manuscript.

FINANCIAL SUPPORT

The publication fees of this study were funded by the Fogarty International Center of the U.S. National Institutes of Health [D43 TW011394-01]. Dr. TLP received funding for the

post-doctoral fellow, supported by the Fogarty International Center of the U.S. National Institutes of Health [D43 TW011394-01].

CONFLICTS OF INTEREST

The authors report no financial or any other conflicts of interest in this work.

ETHICAL APPROVALS

This study does not involve experiments on animals or human subjects.

DATA AVAILABILITY

All data generated and analyzed are included in this research article.

PUBLISHER'S NOTE

All claims expressed in this article are solely those of the authors and do not necessarily represent those of the publisher, the editors and the reviewers. This journal remains neutral with regard to jurisdictional claims in published institutional affiliation.

USE OF ARTIFICIAL INTELLIGENCE (AI)-ASSISTED TECHNOLOGY

The authors declares that they have not used artificial intelligence (AI)-tools for writing and editing of the manuscript, and no images were manipulated using AI.

REFERENCES

1. Gautam CS, Saha L. Fixed dose drug combinations (FDCs): rational or irrational: a view point. Br J Clin Pharmacol. 2008;65(5):795–6. doi: https://doi.org/10.1111/j.1365-2125.2007.03089.x
2. Sreedhar D, Subramanian G, Udupa N. Combination drugs: are they rational. Curr Sci. 2006;91:406.
3. European Medicines Agency. Guideline on Clinical Development of Fixed Combination Medicinal Products. Amsterdam, The Netherlands: European Medicines Agency; 2017.
4. Auwal F, Dahiru MN, Abdu-Aguye SN. Availability and rationality of fixed dose combinations available in Kaduna, Nigeria. Pharm Pract (Granada). 2019;17(2):1470. doi: https://doi.org/10.18549/PharmPract.2019.2.1470
5. Sawicki-Wrzask D, Thomsen M, Bjerrum OJ. An analysis of the fixed-dose combinations authorized by the European Union, 2009-2014: a focus on benefit-risk and clinical development conditions. Ther Innov Regul Sci. 2015;49(4):553–9. doi: https://doi.org/10.1177/2168479014567322
6. Duconge J, Ruaño G. Fixed-dose combination products and unintended drug interactions: urgent need for pharmacogenetic evaluation. Pharmacogenomics. 2015;16(15):1685–8. doi: https://doi.org/10.2217/pgs.15.123
7. Bangalore S, Kamalakkannan G, Parkar S, Messerli FH. Fixed-dose combinations improve medication compliance: a meta-analysis. Am J Med. 2007;120(8):713–9. doi: https://doi.org/10.1016/j.amjmed.2006.08.033
8. Godman B, McCabe H, D Leong T, Mueller D, Martin AP, Hoxha I, *et al.* Fixed dose drug combinations—are they pharmacoeconomically sound? findings and implications especially for lower- and middle-income countries. Expert Rev Pharmacoecon Outcomes Res. 2020;20(1):1–26. doi: https://doi.org/10.1080/14737167.2020.1734456
9. Selya-Hammer C, Gonzalez-Rojas Guix N, Baldwin M, Ternouth A, Miravitlles M, Rutten-Van Mölken M, *et al.* Development of an enhanced health-economic model and cost-effectiveness analysis of tiotropium + olodaterol Respimat® fixed-dose combination for chronic obstructive pulmonary disease patients in Italy. Ther Adv Respir Dis. 2016;10(5):391–401. doi: https://doi.org/10.1177/1753465816657272
10. Price D, Keininger D, Costa-Scharplatz M, Mezzi K, Dimova M, Asukai Y, *et al.* Cost-effectiveness of the LABA/LAMA dual bronchodilator indacaterol/glycopyrronium in a Swedish healthcare setting. Respir Med. 2014;108(12):1786–93. doi: https://doi.org/10.1016/j.rmed.2014.09.015
11. Becerra V, Gracia A, Desai K, Abogunrin S, Brand S, Chapman R, *et al.* Cost-effectiveness and public health benefit of secondary cardiovascular disease prevention from improved adherence using a polypill in the UK. BMJ Open. 2015;5(5):e007111. doi: https://doi.org/10.1136/bmjopen-2014-007111
12. Angus DC, Linde-Zwirble WT, Tam SW, Ghali JK, Sabolinski ML, Villagra VG, *et al.* Cost-effectiveness of fixed-dose combination of isosorbide dinitrate and hydralazine therapy for blacks with heart failure. Circulation. 2005;112(24):3745–53. doi: https://doi.org/10.1161/CIRCULATIONAHA.105.563882
13. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med. 2009;6(7):e1000097. doi: https://doi.org/10.1371/journal.pmed.1000097
14. Husereau D, Drummond M, Augustovski F, de Bekker-Grob E, Briggs AH, Carswell C, *et al.* Consolidated Health Economic Evaluation Reporting Standards 2022 (CHEERS 2022) statement: updated reporting guidance for health economic evaluations. BMJ. 2022;376:e067975. doi: https://doi.org/10.1136/bmj-2021-067975
15. Glasziou PP, Clarke P, Alexander J, Rajmokan M, Beller E, Woodward M, *et al.* Cost-effectiveness of lowering blood pressure with a fixed combination of perindopril and indapamide in type 2 diabetes mellitus: an advance trial-based analysis. Med J Aust. 2010;193(6):320–4. doi: https://doi.org/10.5694/j.1326-5377.2010.tb03941.x
16. Lin JK, Moran AE, Bibbins-Domingo K, Falase B, Pedroza Tobias A, Mandke CN, *et al.* Cost-effectiveness of a fixed-dose combination pill for secondary prevention of cardiovascular disease in China, India, Mexico, Nigeria, and South Africa: a modelling study. Lancet Glob Health. 2019;7(10):e1346–e58. doi: https://doi.org/10.1016/s2214-109x(19)30339-0
17. O'Connor RD, Nelson H, Borker R, Emmett A, Jhingran P, Rickard K, *et al.* Cost effectiveness of fluticasone propionate plus salmeterol versus fluticasone propionate plus montelukast in the treatment of persistent asthma. Pharmacoeconomics. 2004;22(12):815–25. doi: https://doi.org/10.2165/00019053-200422120-00004
18. Ismaila AS, Risebrough N, Li C, Corriveau D, Hawkins N, FitzGerald JM, *et al.* Cost-effectiveness of salmeterol/fluticasone propionate combination (Advair(®)) in uncontrolled asthma in Canada. Respir Med. 2014;108(9):1292–302. doi: https://doi.org/10.1016/j.rmed.2014.06.005
19. Van Boven JFM, Kocks JWH, Postma MJ. Cost-effectiveness and budget impact of the fixed-dose dual bronchodilator combination tiotropium–olodaterol for patients with COPD in the Netherlands. Int J Chron Obstruct Pulmon Dis. 2016;11(1):2191–201. doi: https://doi.org/10.2147/COPD.S114738
20. Ramos M, Haughney J, Henry N, Lindner L, Lamotte M. Cost versus utility of aclidinium bromide 400 µg plus formoterol fumarate dihydrate 12 µg compared to aclidinium bromide 400 µg alone in the management of moderate-to-severe COPD. Clinicoecon Outcomes Res. 2016;8:445–56. doi: https://doi.org/10.2147/CEOR.S107121
21. Rajagopalan K, Bloudek L, Marvel J, Dembek C, Kavati A. Cost-effectiveness of twice-daily indacaterol/glycopyrrolate inhalation powder for the treatment of moderate to severe COPD in the US. Int J Chron Obstruct Pulmon Dis. 2018;13:3867–77. doi: https://doi.org/10.2147/COPD.S177097

22. Hoogendoorn M, Ramos IC, Baldwin M, Luciani L, Fabron C, Detournay B, *et al.* Long-term cost-effectiveness of the fixed-dose combination of tiotropium plus olodaterol based on the DYNAGITO trial results. Int J Chron Obstruct Pulmon Dis. 2019;14:447–56. doi: https://doi.org/10.2147/COPD.S191031
23. Hoogendoorn M, Ramos IC, Soulard S, Cook J, Soini E, Paulsson E, *et al.* Cost-effectiveness of the fixed-dose combination tiotropium/olodaterol versus tiotropium monotherapy or a fixed-dose combination of long-acting β2-agonist/inhaled corticosteroid for COPD in Finland, Sweden and the Netherlands: a model-based study. BMJ Open. 2021;11(8):e049675. doi: https://doi.org/10.1136/bmjopen-2021-049675
24. Orlovic M, Magni T, Lukyanov V, Guerra I, Madoni A. Cost-effectiveness of single-inhaler extrafine beclometasone dipropionate/formoterol fumarate/glycopyrronium in patients with uncontrolled asthma in England. Respir Med. 2022;201:106934. doi: https://doi.org/10.1016/j.rmed.2022.106934
25. Lan Y, Yang N, Wang Y, Yang Y, Xu M, He Q. Cost-effectiveness analysis of fixed-dose tiotropium/Olodaterol versus tiotropium for COPD patients in China. Int J Chron Obstruct Pulmon Dis. 2023;18:2093–103. doi: https://doi.org/10.2147/copd.S425409
26. Ren M, Xuan D, Lu Y, Fu Y, Xuan J. Economic evaluation of olmesartan/amlodipine fixed-dose combination for hypertension treatment in China. J Med Econ. 2020;23(4):394–400. doi: https://doi.org/10.1080/13696998.2019.1699799
27. Zomer E, Owen A, Magliano DJ, Ademi Z, Reid CM, Liew D. Predicting the impact of polypill use in a metabolic syndrome population: an effectiveness and cost-effectiveness analysis. Am J Cardiovasc Drugs. 2013;13(2):121–8. doi: https://doi.org/10.1007/s40256-013-0019-2
28. Vaidya V, Anupindi VR, Pinto S, Kaun M. Cost utility analysis of fixed-dose and free-dose combinations of oral medications in type 2 diabetes patients. J Pharm Health Serv Res. 2016;7(3):181–7. doi: https://doi.org/10.1111/jphs.12139
29. Newman J, Grobman WA, Greenland P. Combination polypharmacy for cardiovascular disease prevention in men: a decision analysis and cost-effectiveness model. Prev Cardiol. 2008;11(1):36–41. doi: https://doi.org/10.1111/j.1520-037x.2007.06423.x
30. Rubinstein A, García Martí S, Souto A, Ferrante D, Augustovski F. Generalized cost-effectiveness analysis of a package of interventions to reduce cardiovascular disease in Buenos Aires, Argentina. Cost Eff Resour Alloc. 2009;7:10. doi: https://doi.org/10.1186/1478-7547-7-10
31. Rubinstein A, Colantonio L, Bardach A, Caporale J, Martí SG, Kopitowski K, *et al.* Estimation of the burden of cardiovascular disease attributable to modifiable risk factors and cost-effectiveness analysis of preventative interventions to reduce this burden in Argentina. BMC Public Health. 2010;10:627. doi: https://doi.org/10.1186/1471-2458-10-627
32. van Gils PF, Over EA, Hamberg-van Reenen HH, de Wit GA, van den Berg M, Schuit AJ, *et al.* The polypill in the primary prevention of cardiovascular disease: cost-effectiveness in the Dutch population. BMJ Open. 2011;1(2):e000363. doi: https://doi.org/10.1136/bmjopen-2011-000363
33. Ito K, Shrank WH, Avorn J, Patrick AR, Brennan TA, Antman EM, *et al.* Comparative cost-effectiveness of interventions to improve medication adherence after myocardial infarction. Health Serv Res. 2012;47(6):2097–117. doi: https://doi.org/10.1111/j.1475-6773.2012.01462.x
34. Khonputsa P, Veerman LJ, Bertram M, Lim SS, Chaiyakunnaphruk N, Vos T. Generalized cost-effectiveness analysis of pharmaceutical interventions for primary prevention of cardiovascular disease in Thailand. Value Health Reg Issues. 2012;1(1):15–22. doi: https://doi.org/10.1016/j.vhri.2012.03.019
35. Bautista LE, Vera-Cala LM, Ferrante D, Herrera VM, Miranda JJ, Pichardo R, *et al.* A 'polypill' aimed at preventing cardiovascular disease could prove highly cost-effective for use in Latin America. Health Aff (Millwood). 2013;32(1):155–64. doi: https://doi.org/10.1377/hlthaff.2011.0948
36. Megiddo I, Chatterjee S, Nandi A, Laxminarayan R. Cost-effectiveness of treatment and secondary prevention of acute myocardial infarction in India: a modeling study. Global Heart. 2014;9(4):391–8.e3. doi: https://doi.org/10.1016/j.gheart.2014.07.002
37. Ong KS, Carter R, Vos T, Kelaher M, Anderson I. Cost-effectiveness of interventions to prevent cardiovascular disease in Australia's indigenous population. Heart Lung Circ. 2014;23(5):414–21. doi: https://doi.org/10.1016/j.hlc.2013.10.084
38. Wald NJ, Luteijn JM, Morris JK, Taylor D, Oppenheimer P. Cost-benefit analysis of the polypill in the primary prevention of myocardial infarction and stroke. Eur J Epidemiol. 2016;31(4):415–26. doi: https://doi.org/10.1007/s10654-016-0122-1
39. Barrios V, Kaskens L, Castellano JM, Cosin-Sales J, Ruiz JE, Zsolt I, *et al.* Usefulness of a cardiovascular polypill in the treatment of secondary prevention patients in Spain: a cost-effectiveness study. Revista Espanola de Cardiologia. 2017;70(1):42–9. doi: https://doi.org/10.1016/j.recesp.2016.05.011
40. Ferket BS, Hunink MG, Khanji M, Agarwal I, Fleischmann KE, Petersen SE. Cost-effectiveness of the polypill versus risk assessment for prevention of cardiovascular disease. Heart. 2017;103(7):483–91. doi: https://doi.org/10.1136/heartjnl-2016-310529
41. Jowett S, Barton P, Roalfe A, Fletcher K, Hobbs FDR, McManus RJ, *et al.* Cost-effectiveness analysis of use of a polypill versus usual care or best practice for primary prevention in people at high risk of cardiovascular disease. PLoS One. 2017;12(9):e0182625. doi: https://doi.org/10.1371/journal.pone.0182625
42. Gaziano TA, Pandya A, Sy S, Jardim TV, Ogden JM, Rodgers A, *et al.* Modeling the cost effectiveness and budgetary impact of Polypills for secondary prevention of cardiovascular disease in the United States. Am Heart J. 2019;214:77–87. doi: https://doi.org/10.1016/j.ahj.2019.04.020
43. Lung T, Jan S, de Silva HA, Guggilla R, Maulik PK, Naik N, *et al.* Fixed-combination, low-dose, triple-pill antihypertensive medication versus usual care in patients with mild-to-moderate hypertension in Sri Lanka: a within-trial and modelled economic evaluation of the TRIUMPH trial. Lancet Glob Health. 2019;7(10):e1359–e66. doi: https://doi.org/10.1016/S2214-109X(19)30343-2
44. Aguiar C, Araujo F, Rubio-Mercade G, Carcedo D, Paz S, Castellano JM, *et al.* Cost-effectiveness of the CNIC-Polypill strategy compared with separate monocomponents in secondary prevention of cardiovascular and cerebrovascular disease in Portugal: the MERCURY Study. J Health Econ Outcomes Res. 2022;9(2):134–46. doi: https://doi.org/10.36469/001c.39768
45. González-Domínguez A, Durán A, Hidalgo-Vega Á, Barrios V. Cost-effectiveness of the CNIC-Polypill versus separate monocomponents in cardiovascular secondary prevention in Spain. Rev Clin Esp (Barc). 2023;223(7):414–22. doi: https://doi.org/10.1016/j.rceng.2023.06.007
46. Al MJ, Michel BC, Rutten FFH. The cost effectiveness of diclofenac plus misoprostol compared with diclofenac monotherapy in patients with rheumatoid arthritis. PharmacoEconomics. 1996;10(2):141–51. doi: https://doi.org/10.2165/00019053-199610020-00006
47. Udeh EI, Ofoha CG, Adewole DA, Nnabugwu II. A cost effective analysis of fixed-dose combination of dutasteride and tamsulosin compared with dutasteride monotherapy for benign prostatic hyperplasia in Nigeria: a middle income perspective; using an interactive Markov model. BMC Cancer. 2016;16(1):405. doi: https://doi.org/10.1186/s12885-016-2431-x
48. Sussell JA, Roth JA, Meyer CS, Fung A, Hansen SA. Assessment of the cost-effectiveness of HER2-targeted treatment pathways in the neoadjuvant treatment of high-risk HER2-positive early-stage breast cancer. Adv Ther. 2022;39(3):1375–92. doi: https://doi.org/10.1007/s12325-022-02047-y

49. Nilsson J, Piovesana V, Turini M, Lezzi C, Eriksson J, Aapro M. Cost-effectiveness analysis of NEPA, a fixed-dose combination of netupitant and palonosetron, for the prevention of highly emetogenic chemotherapy-induced nausea and vomiting: an international perspective. Support Care Cancer. 2022;30(11):9307–15. doi: https://doi.org/10.1007/s00520-022-07339-1
50. EuroQol. EQ-5D [cited 2023 13 November]. Available from: https://euroqol.org/.
51. Memon RA, Raveena Bai B, Simran F, Kumari M, Aisha F, Sai Kiran K, *et al.* Effect of the Polypill on adherence and prevention of cardiovascular diseases in patients with or at high risk of cardiovascular diseases: a meta-analysis of randomized controlled trials. Cureus. 2023;15(1):e34134. doi: https://doi.org/10.7759/cureus.34134
52. Baumgartner A, Drame K, Geutjens S, Airaksinen M. Does the Polypill improve patient adherence compared to its individual formulations? a systematic review. Pharmaceutics. 2020;12(2):190. doi: https://doi.org/10.3390/pharmaceutics12020190
53. Law MR, Wald NJ, Morris JK, Jordan RE. Value of low dose combination treatment with blood pressure lowering drugs: analysis of 354 randomised trials. BMJ. 2003;326(7404):1427. doi: https://doi.org/10.1136/bmj.326.7404.1427
54. Yusuf S, Pais P, Sigamani A, Xavier D, Afzal R, Gao P, *et al.* Comparison of risk factor reduction and tolerability of a full-dose Polypill (With Potassium) versus low-dose Polypill (Polycap) in individuals at high risk of cardiovascular diseases. CircCardiovasc Qual Outcomes. 2012;5(4):463–71. doi: https://doi.org/10.1161/CIRCOUTCOMES.111.963637
55. Hong SH, Wang J, Tang J. Dynamic view on affordability of fixed-dose combination antihypertensive drug therapy. Am J Hypertens. 2013;26(7):879–87. doi: https://doi.org/10.1093/ajh/hpt035
56. Rabbani A, Alexander GC. Out-of-pocket and total costs of fixed-dose combination antihypertensives and their components. Am J Hypertens. 2008;21(5):509–13. doi: https://doi.org/10.1038/ajh.2008.31
57. Ijzerman MJ, Koffijberg H, Fenwick E, Krahn M. Emerging use of early health technology assessment in medical product development: a scoping review of the literature. PharmacoEconomics. 2017;35(7):727–40. doi: https://doi.org/10.1007/s40273-017-0509-1
58. Wang Y, Rattanavipapong W, Teerawattananon Y. Using health technology assessment to set priority, inform target product profiles, and design clinical study for health innovation. Technol Forecast Soc Change. 2021;172:121000. doi: https://doi.org/10.1016/j.techfore.2021.121000
59. Gupta AK, Arshad S, Poulter NR. Compliance, safety, and effectiveness of fixed-dose combinations of antihypertensive agents: a meta-analysis. Hypertension. 2010;55(2):399–407. doi: https://doi.org/10.1161/hypertensionaha.109.139816
60. Santo K, Kirkendall S, Laba TL, Thakkar J, Webster R, Chalmers J, *et al.* Interventions to improve medication adherence in coronary disease patients: a systematic review and meta-analysis of randomised controlled trials. Eur J Prev Cardiol. 2020;23(10):1065–76. doi: https://doi.org/10.1177/2047487316638501
61. Chongmelaxme B, Chaiyakunapruk N, Dilokthornsakul P. Incorporating adherence in cost-effectiveness analyses of asthma: a systematic review. J Med Econ. 2019;22(6):554–66. doi: https://doi.org/10.1080/13696998.2019.1572014
62. Pradhan S, Panda A, Sahu S, Behera JP. An evaluation of prevalence and prescribing patterns of rational and irrational fixed dose combinations (FDCs): a hospital based study. Int J Med Public Health. 2017;6:58–62. doi: https://doi.org/10.5455/ijmsph.2017.19062016555
63. Poudel A, Mohamed Ibrahim MI, Mishra P, Palaian S. Assessment of utilization pattern of fixed dose drug combinations in primary, secondary and tertiary healthcare centers in Nepal: a cross-sectional study. BMC Pharmacol Toxicol. 2017;18:69. doi: https://doi.org/10.1186/s40360-017-0176-z
64. Balat JD, Gandhi AM, Patel PP, Dikshit RK. A study of use of fixed dose combinations in Ahmedabad, India. Indian J Pharmacol. 2014;46(5):503–9. doi: https://doi.org/10.4103/0253-7613.140581
65. Nigam MP, Fernandes VLG, Rataboli PV. Fixed dose combinations-to prescribe or not to prescribe: a dilemma of medical profession. Int J Basic Clin Pharmacol. 2014;3:105–13. doi: https://doi.org/10.5455/2319-2003.IJBCP20140212

How to cite this article:
Phung TL, Ong DT, Ngo NTN, Pham TT, Nguyen HT, Duong KNC, Dang MTN, Alcusky MJ, Amante DJ, Nguyen HL. Economic evaluation of fixed-dose drug combinations: A systematic review. J Appl Pharm Sci. 2024;14(12):001–026.