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SYSTEMATIC REVIEW

Novel Treatment Strategies for Secondary Prevention of Cardiovascular Disease: A Systematic Review of Cost-Effectiveness

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Abstract

Background New pharmacological therapies for the treatment of cardiovascular disease (CVD) have emerged in recent years. The high rates of CVD and the need for long-term treatment to decrease risk factors makes cost-effectiveness crucial for their successful long-term implementation.

Objective This study assessed cost-effectiveness studies of novel pharmacological treatments (ezetimibe, proprotein convertase subtilisin/kexin type 9 [PCSK9] inhibitors, omega-3 polyunsaturated fatty acids [n-3 PUFAs], and the cardiovascular polypill) compared with standard care for the secondary prevention of CVD.

Methods We searched seven databases and the reference list of selected literature reviews for eligible cost-effective analyses (CEA) published between January 2009 and January 2020 that evaluated the above novel treatments versus standard care. Two independent reviewers performed the screening and evaluation in accordance with the Consolidated Health Economic Evaluation Reporting Standards statement. Cost results were adapted to 2018 US dollars (US$) to facilitate comparisons between studies. Consideration of cost-effectiveness was based on the original study criteria.

Results Thirty-two studies were included in this review, most of them adopting a healthcare perspective. Studies evaluating ezetimibe, PCSK9 inhibitors and n-3 PUFAs assessed their addition to standard care compared with standard care alone, while studies analysing the polypill evaluated the replacement of multiple monotherapies for a fixed-dose combination. Ten studies reported on ezetimibe, fifteen evaluated PCSK9 inhibitors, five focused on n-3 PUFAs and seven on the polypill. From a healthcare perspective, ezetimibe was cost effective in 62.5% of the studies (incremental cost-effectiveness ratios [ICERs] ranged from US$27,195 to US$204,140), n-3 PUFAs in 60% (ICERs from US$57,128 to US$139,082) and the cardiovascular polypill in 100% (ICERs from dominant to US$30,731) compared with standard care. Conversely, only 10% of the studies considered PCSK9 inhibitors cost effective compared with standard care from a healthcare perspective (ICERs ranged from US$231,119 to US$1,223,831). Additionally, ezetimibe was cost effective in 50% of the studies, PCSK9 inhibitors in 33% and the polypill in 50% of the studies adopting a societal perspective. The key model-related parameters predicting cost-effectiveness included drug cost, time horizon, and the baseline risk of cardiovascular events.

Conclusions Based on current pricing and willingness-to-pay thresholds, most CEA studies considered ezetimibe, n-3 PUFAs and the polypill to be cost effective compared with standard care but not PCSK9 inhibitors for secondary prevention of CVD.

1 Introduction

Although rates of cardiovascular disease (CVD) have decreased over the last 30 years, it remains the leading cause of mortality worldwide, accounting for more than 30% of all global deaths in 2017 [1]. People with established CVD are at higher risk of experiencing life-threatening cardiovascular events, and their quality of life is significantly reduced [2]. Moreover, due to the high prevalence of CVD and the high costs associated with its management, understanding of the cost-effectiveness of treatments is crucial to inform decision making about healthcare spending.

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Key Points for Decision Makers

Ezetimibe, proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, omega-3 polyunsaturated fatty acids (n-3 PUFAs), and the cardiovascular polypill can reduce the residual cardiovascular risk in statin-treated patients with established CVD. However, their cost-effectiveness remains unclear.

This systematic review found that in most CEAs, the addition of ezetimibe and n-3 PUFAs to statin therapy was found to be good value for money, when adopting a healthcare system perspective. The cardiovascular polypill was also cost effective in all the studies, suggesting it as a solid option for the secondary prevention of CVD. Conversely, most studies found PCSK9 inhibitors to be not cost effective. These overall results were consistent after adaptation to a US setting.

The decision models were most influenced by the time horizon projected, the baseline cardiovascular risk, and the cost of the drugs.

CVD encompasses multifactorial disorders with well described modifiable risk factors including high blood pressure, smoking, and dyslipidaemia [2]. High plasma levels of low density lipoprotein cholesterol (LDL-C) is considered one of the most important modifiable risk factors for CVD [2], and recent meta-analyses undertaken by the Cholesterol Treatment Trialists' (CTT) Collaboration of statin trials on primary and secondary prevention populations revealed that a 1-mmol/L reduction in plasma LDL-C was associated with a 10% reduction in all-cause mortality (relative risk [RR] 0.90, 95% confidence interval [CI] 0.87–0.93) and a 24% reduction in major coronary events (RR 0.76, 95% CI 0.73–0.79) [3, 4]. Despite the success of statins in decreasing plasma cholesterol levels, many patients, especially those with established CVD, are unable to reach desirable LDL-C targets even with the maximum doses of statins [5], and there is a significant on-treatment residual risk, with 5-year major cardiovascular event rates of 22% among secondary prevention patients [3]. Hence, there is a significant interest in additive therapies to minimise this residual risk. In recent years, two novel agents—proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors and ezetimibe—have been included as second-line treatments. PCSK9 inhibitors are human monoclonal antibodies that bind human PCSK9-reducing plasma LDL-C concentrations by decreasing the degradation rates of the LDL-C hepatocyte receptor [6]. The effectiveness of PCSK9 inhibitors at lowering the risk of non-fatal cardiovascular events has been shown in several randomised controlled trials (RCTs) [7], but their cost-effectiveness has been widely debated [8, 9]. Ezetimibe reduces intestinal absorption of cholesterol by blocking the internalisation of the cholesterol transport protein Niemann–Pick C1-like 1 (NPC1L1) to the enterocytes [10]. Several RCTs analysing ezetimibe versus statins have shown a reduction in cardiovascular events [11], but cost-effectiveness results have been inconsistent [12, 13].

Mixed dyslipidaemia, including hypertriglyceridaemia, is also associated with a higher risk of CVD even after adjusting for LDL-C levels [14–16]. Omega-3 polyunsaturated fatty acids (n-3 PUFAs) have been shown to reduce plasma levels of triglycerides by downregulating very-low-density lipoprotein production and increasing β-oxidation of fatty acids in different tissues [16]. Several RCTs have shown n-3 PUFAs to be effective at reducing the risk of CVD [17, 18], and its cost-effectiveness has been analysed in several studies.

The complexity of these disorders usually requires people with established CVD, or at high risk, to take multiple medications, which tends to decrease adherence [19]. The cardiovascular polypill, consisting of three or four active ingredients in a fixed-dose combination, has been shown to increase adherence, which has a direct impact on subsequent cardiovascular events [20, 21]. Several studies have analysed the cost-effectiveness of the polypill for secondary prevention in different settings [22].

In the present study, we systematically reviewed recent literature on the cost-effectiveness of novel treatment strategies (ezetimibe, PCSK9 inhibitors, n-3 PUFAs and the cardiovascular polypill) for secondary prevention of CVD, adapted the results to a common cost-effectiveness plane and identified the factors driving their cost-effectiveness.

2 Methods

The present study was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) reporting guidelines [23] and the quality of reporting was assessed using the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement [24]. The PRISMA checklist is available in Appendix 1 (see Electronic Supplementary Material [ESM]). The study protocol was pre-registered in PROSPERO (ID 152196).

2.1 Eligibility Criteria for Study Selection

Studies were selected based on the following criteria: the target population were adults (age ≥ 18 years) with established CVD (atherosclerotic disease or any previous acute cardiovascular event), with no restrictions set for co-morbidities or co-treatment strategies. Studies that reported results for

mixed populations (i.e. including patients with high risk but no established CVD) were excluded. The focus of the analysis was on novel lipid-lowering strategies and the cardiovascular polypill. We considered novel lipid-lowering strategies as those developed and approved after statins, including n-3 PUFAs, ezetimibe and PCSK9 inhibitors. The cardiovascular polypill was defined as a fixed-dose combination of three or four components: aspirin, an angiotensin converting enzyme (ACE) inhibitor, a statin and in some cases an anticoagulant. We did not set any restrictions on the definition of 'standard therapy'; rather, this was as defined by the individual studies. The main outcome of interest was the incremental cost-effectiveness ratio (ICER) in terms of net costs divided by net benefits. Benefits were reported as quality-adjusted life-years (QALYs), disability-adjusted life-years (DALYs) averted or cardiovascular events averted. We included cost-effectiveness studies published in peer-reviewed journals, comprising a full economic evaluation involving any type of decision model that reported an ICER. We excluded within-trial cost effective studies with the aim to capture long-term cost-effectiveness and budget impact studies and value-based price valuations.

2.2 Search Strategy

Two reviewers (CM, ZA) developed the search strategy using Medical Subject Heading (MeSH) terms based on the concepts of CVD, economic evaluation and the interventions of interest (n-3 PUFAs, ezetimibe, PCSK9 inhibitors and the polypill). The literature search was conducted in MEDLINE via Ovid, EMBASE via Ovid, Scopus, the Cochrane Library, the Economic Literature Database (EconLit) via EBSCOHost, the NHS Economic Evaluation Database (EED), and the Database of Abstracts of Reviews of Effects (DARE). We searched for studies published between January 2009 and 31 January 2020 (full search strategies are available in Appendix 2, see ESM). No language restrictions were applied. Limiting the search period to the past 10 years reflected the focus on novel treatments. The reference lists of included studies and previous reviews of interest were also screened for additional studies. One reviewer (CM) screened titles and abstracts, and two reviewers screened the full text of selected studies (CM, SV). Disagreements about the inclusion of studies were resolved by consultation with a third reviewer (ZA). Conference abstracts and reports not published in peer-reviewed journals were excluded.

2.3 Data Extraction and Synthesis

Data extraction was performed using a data extraction template adapted for the outcomes of interest. Collected data included author, year, country of setting, objective of the study, general characterisation of the model (model type, perspective, time horizon, treatment arms, discount rate and currency year), baseline risks and treatment effectiveness and their sources, types of costs included, total costs, total outcomes, ICERs and results from sensitivity analyses. Studies were grouped by treatment strategies in data extraction summaries. Treatments were defined as cost effective based on the author's conclusion.

2.4 Quality Assessment

Reporting quality was assessed independently by two reviewers (CM and SV) using the 24-item checklist provided in the CHEERS statement. Each item was scored with 0, 0.25, 0.5, 0.75 or 1 point based on criteria. After grading the studies, both reviewers (CM, SV) shared their results and the final CHEERS grade was obtained as an average of both evaluations. In addition, the results for each CHEERS item were summarised in a colour histogram with 'yes', 'no' and 'unclear' categories, depending on the criteria fulfilment. Information regarding funding sources was also collected and reported in the results.

2.5 Cost Adjustments Methods

To be able to compare ICERs in a common currency and cost-effectiveness plane, all costs were adapted to 2018 US dollars (US$) using the cost-adjustment method described by Ademi et al. [25]. Briefly, reported costs were adjusted for the level of healthcare resource utilisation, the prices of healthcare in each country and finally adjusted for US inflation. Further details for the cost adaptation process can be found in Appendix 3 (see ESM). Studies that did not report the cost year [26–30] were excluded for adaptation. Authors from studies not reporting cost year were contacted by e-mail in an effort to complete the missing data. In addition, results from Permpanich et al. [31] and Yang et al. [32] could not be adapted due to the lack of data on purchasing power parities. Korman and Wisloff [33] reported cost results in Euros but the study was based in Norway, and Lin et al. [34] reported costs in international dollars but the study was set in five low- and medium-income countries (LMIC), and both studies were excluded from cost adjustment. Additionally, results from studies that reported costs in 2018 US$ were not adapted and the original results were used.

3 Results

3.1 Search Results

The literature search yielded 5923 unique records after duplicate removal. After screening the titles, 700 studies were selected for abstract screening, of which 142 studies

were selected for full-text screening. Only 35 studies were included for data extraction and quality assessment. Four studies were excluded due to their not reporting ICERs as an outcome of interest, one was excluded due to being a within-trial analysis, and two studies were included after review of the references of the selected studies. In total, 32 studies were included in this systematic review. The searching, screening and inclusion procedure is summarised in the PRISMA flowchart in Fig. 1.

3.2 Quality Appraisal

Results from the CHEERS assessment can be found in Appendix 4 (see ESM). Briefly, the overall average score was 0.75 points (out of a total of 1 point). Ezetimibe studies had the highest average score (0.85 points), followed by PCSK9 inhibitors (0.80 points), n-3 PUFAs (0.78 points) and studies analysing the polypill (0.74 points).

Overall, 16 out of the 32 included studies declared specific funding for the project, and from those, 10 studies declared industry support. Three out of 10 studies [13, 35, 36] were funded by industry for ezetimibe (30%), five out of 15 [26, 29, 37–39] for PCSK9 inhibitors (33%), one out of five (20%) [40] for n-3 PUFAs, and one out of seven (14%) [41] for the polypill. Granular information on funding sources can be accessed in Appendix 5 (see ESM).

3.3 General Characteristics of the Included Studies

The general characteristics of the included articles organised by treatment strategies are summarised in Table 1. Of the selected studies, ten evaluated ezetimibe [12, 13, 32, 33, 35, 36, 42–45], 15 PCSK9 inhibitors [12, 26, 28–30, 33, 37–39, 43–48], five n-3 PUFAs [31, 40, 49–51], and seven the polypill [27, 34, 41, 52–55]. Four out of the 15 studies focusing on PCSK9 inhibitors also reported the ICERs of ezetimibe versus statins, but considering ezetimibe as a comparator [12, 33, 43, 44], and those results have also been included and reported in this review. Of note, the study by Dressel et al. [28] used ezetimibe as a comparator, but did not report the ICER for ezetimibe. Only five out of 32 studies [31, 32, 34, 45, 53] were set in LMICs, and only seven [31, 32, 34, 45, 46, 49, 53] were based in non-Western countries. Most of the studies analysed lifetime horizons (28 studies) [12, 13, 25–29, 31–40, 42–52, 55], and the majority used Markov models (29 studies) [12, 13, 26, 28–33, 35–52, 54, 55]. QALYs were the preferred outcome to report health benefits (29 studies) [12, 13, 26–29, 31–33, 35–52, 54, 55].

3.3.1 Ezetimibe

Among the ten studies evaluating the cost-effectiveness of ezetimibe versus standard therapy, five were set in the US [12, 13, 42–44] and the rest in Finland [36], the UK [35],

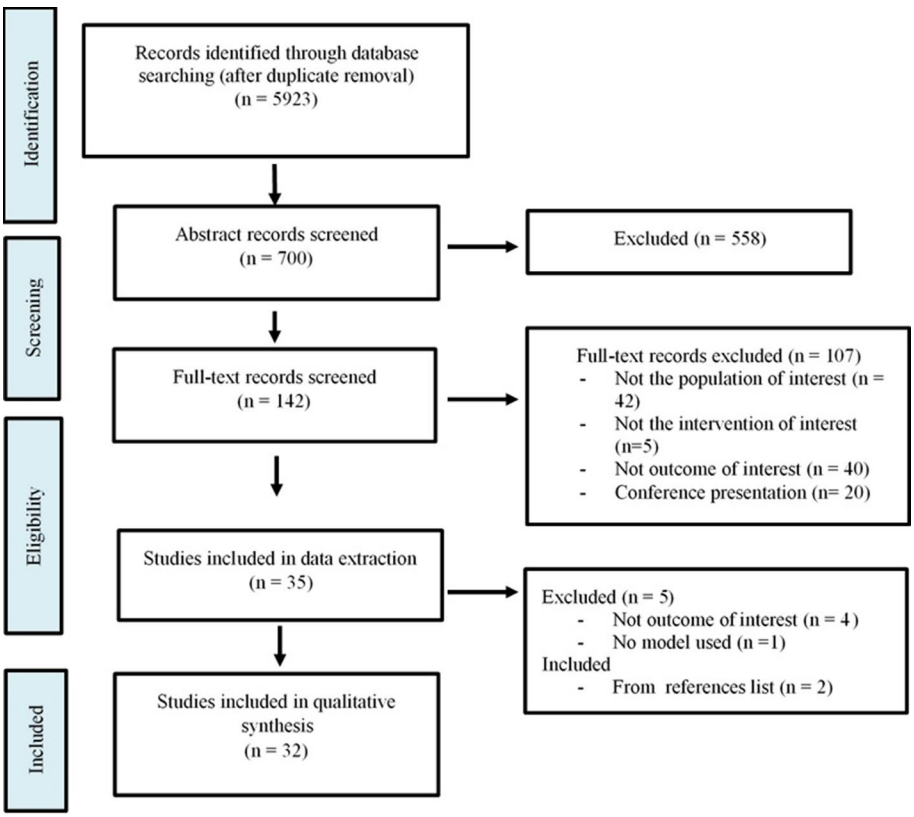

Fig. 1 PRISMA flow diagram. *PRISMA* Preferred Reporting Items for Systematic Reviews and Meta-Analyses

Table 1 General characteristics of the included studies

Study	Country of setting	Intervention	Comparator	Model approach	Horizon	Perspective	Main effects
Ezetimibe							
Reckless et al. (2010) [35]	UK	EZT + simvastatin	Doubling statin dose	Markov	Lifetime	Healthcare	QALYs
Soini et al. (2010) [36]	Finland	EZT + simvastatin	Atorvastatin/rosuvastatin/simvastatin	Markov	Lifetime	Societal	QALYs, LY
Kazi et al. (2016) [12]	US	EZT + statins/PCSK9i + statins	Statins/EZT + statins	CVD Policy Model	Lifetime	Healthcare	QALYs, MACE, NNT, LY
Davies et al. (2017) [13]	US	EZT + statins	Statins	Markov	Lifetime	Payer	QALYs, LY
Kazi et al. (2017) [44]	US	EZT + statins	Statins	CVD Policy Model	Lifetime	Healthcare	QALYs, MACE, NNT, LY
Almalki et al. (2018) [42]	US	EZT + simvastatin	Simvastatin	Markov	3.2, 5 and 10 years and lifetime	Healthcare	QALYs
Korman and Wisloff, 2018) [33]	Norway	EZT + statins	Statin + EZT	Markov	Lifetime	Healthcare	QALYs
Kazi et al. (2019) [43]	US	PCSK9i + statins + EZT	Statins/statins + EZT	CVD Policy Model	Lifetime	Healthcare	QALYs, MACE, NNT, LY
Kongpakwattana et al. (2019) [45]	Thailand	EZT + statins	Statins	Markov	Lifetime	Societal & healthcare	QALYs, events averted
Yang et al. (2020) [32]	China	EZT + rosuvastatin	High-dose rosuvastatin	Markov	Lifetime	Healthcare	QALYs
PCSK9 inhibitors							
Gandra et al. (2016) [26]	US	SoC + evolocumab	Statins	Markov	Lifetime	US payer	QALYs, LY
Kazi et al. (2016) [12]	US	EZT + statins/PCSK9i + statins	Statins/EZT + statins	CVD Policy Model	Lifetime	Healthcare	QALYs
Arrieta et al. (2017) [48]	US	PCSK9i + statins	Statins	Markov	Lifetime	Payer & healthcare	QALYs, LY
Fonarow et al. (2017) [37]	US	Evolocumab + statins	Standard therapy	Markov	Lifetime	Societal	QALYs
Kazi et al. (2017) [44]	US	PCSK9i + statins + EZT	Statins + EZT	CVD Policy Model	Lifetime	Healthcare	QALYs, MACE, NNT, LY
Toth et al. (2017) [29]	US	PCSK9i	Standard therapy	Markov	Lifetime	Payer	QALYs, LY
Villa et al. (2017) [39]	Spain	Evolocumab + SoC	Statins	Markov	Lifetime	Healthcare	QALYs
Kodera et al. (2018) [46]	Japan	PCSK9i + statins	Statins monotherapy	Markov	Lifetime	Healthcare	QALYs
Korman and Wisloff, 2018) [33]	Norway	Evolocumab/alirocumab	SoC + EZT	Markov	Lifetime	Healthcare	QALYs

Table 1 (continued)

Study	Country of setting	Intervention	Comparator	Model approach	Horizon	Perspective	Main effects
Kumar et al. (2018) [47]	Australia	PCSK9i	Statins	Markov	Lifetime	Healthcare	QALYs
Olry de Labry Lima et al. (2018) [30]	Spain	PCSK9i	Standard therapy	Decision tree & Markov	26 months and 10 years	Healthcare	Averted events
Dressel et al. (2019) [28]	Germany	PCSK9i	Statins + EZT	Markov	Lifetime	NR	QALYs
Fonarow et al. (2019) [38]	US	PCSK9i	Statins	Markov	Lifetime	Societal	QALYs
Kazi et al. (2019) [43]	US	PCSK9i + statins + EZT	Statins/statins + EZT	CVD Policy Model	Lifetime	Healthcare	QALYs
Kongpakwattana et al. (2019) [45]	Thailand	PCSK9i + statins/ EZT + statins	Statins	Markov	Lifetime	Societal & healthcare	QALYs
n-3 PUFAs							
Cowie et al. (2011) [40]	UK	n-3 PUFA + standard therapy	Standard therapy	Markov	Lifetime	Healthcare	QALYs
Permpanich et al. (2015) [31]	Thailand	n-3 PUFA + standard therapy	Standard therapy	Markov	Lifetime	Healthcare	QALYS
Kodera et al. (2018) [49]	Japan	EPA + statin	Statin	Markov	Lifetime	Healthcare	QALYs
Gao et al. (2019) [51]	Australia	Icosapent ethyl + statin therapy	Statins	Markov	Lifetime	Healthcare	QALYs
Ademi et al. (2020) [50]	Australia	Icosapent ethyl + statin therapy	Statins	Markov	Lifetime	Healthcare	QALYs
Polypill							
Ito et al. (2012) [52]	US	Fixed-dose combination (aspirin, atorvastatin, ramipril, atenolol)	Aspirin, atorvastatin, ramipril, atenolol	Markov	Lifetime	Societal	QALYs
Megiddo et al. (2015) [53]	India	Fixed-dose combination (aspirin, atorvastatin, ramipril, atenolol)	Aspirin, atorvastatin, ramipril, atenolol	Deterministic model	NR	NR	DALYs
Becerra et al. (2015) [41]	UK	Fixed-dose combination (aspirin, atorvastatin, ramipril)	Aspirin, atorvastatin, ramipril	Markov	10 years	Healthcare	QALYs
Barrios et al. (2017) [54]	Spain	Fixed-dose combination (aspirin, atorvastatin, ramipril)	Aspirin, atorvastatin, ramipril	Markov	10 years	Healthcare	QALYs
Barth et al. (2017) [55]	Germany	Fixed-dose combination (aspirin, atorvastatin, ramipril)	Aspirin, atorvastatin, ramipril	Markov	Lifetime	Healthcare	QALYs

Table 1 (continued)

Study	Country of setting	Intervention	Comparator	Model approach	Horizon	Perspective	Main effects
Gaziano et al. (2019) [27]	US	Fixed-dose combination (aspirin, atenolol, ramipril, simvastatin/atorvastatin/rosuvastatin)	Aspirin, atenolol, ramipril, simvastatin/atorvastatin/rosuvastatin	CVD PREDICT model	5 years and lifetime	Healthcare & societal	QALYs
Lin et al. (2019) [34]	5 LMICs	Fixed-dose combination (aspirin, simvastatin, lisinopril and atenolol)	Aspirin, simvastatin, lisinopril and atenolol	Micro-simulation	Lifetime	Healthcare	Averted events, DALYs & NNT

CVD cardiovascular disease, *DALYs* disability-adjusted life-years, *EPA* eicosapentaenoic acid, *EZT* ezetimibe, *LMICs* low- and medium-income countries, *LY* life-years, *MACE* major adverse cardiovascular events, *NNT* number needed to treat, *NR* not reported, *n-3 PUFA* omega-3 polyunsaturated fatty acid, *PCSK9i* proprotein convertase subtilisin/kexin 9 inhibitor, *QALYs* quality-adjusted life-years, *SoC* standard of care

Norway [33], Thailand [45] and China [32]. All the studies analysed the addition of ezetimibe 10 mg/day to statin therapy. Additionally, Korman and Wisloff [33] analysed ezetimibe alone versus no treatment for statin-intolerant patients. The mean age of the population ranged from 53 to 67 years, and all studies with the exception of Kongpakwattana et al. [45] and Almalki et al. [42] reported mean plasma LDL-C levels > 70 mg/dL, which reflects current guideline recommendations for the prescription of ezetimibe (i.e. patients with established CVD not meeting lipid targets).

All the included studies used Markov models with yearly cycles and lifetime horizons [12, 13, 32, 33, 35, 36, 42–45]. There was a variety of model structures, with studies modelling between three [45] and 28 [13] health states. All the studies [12, 13, 32, 33, 35, 36, 42–45] included fatal and non-fatal coronary heart disease, and all studies but two [35, 36] included fatal and non-fatal stroke. Three studies also modelled unstable angina [35, 36, 42] and Almalki et al. [42] also considered coronary revascularisation. Three studies [12, 43, 44] used the CVD Policy Model, a computer-simulation Markov model developed and validated for the US context that simulates the incidence, prevalence, mortality and costs of stroke and chronic heart failure in the whole population aged ≥ 35 years using age- and sex-specific data. Seven studies [12, 32, 33, 35, 42–44] analysed a healthcare system perspective, Soini et al. [36] adopted a societal perspective, Kongpakwattana et al. [45] analysed both healthcare system and societal perspectives, and Davies et al. [13] considered a US payer perspective. Costs and health benefits were discounted with rates ranging between 3% and 4%. All the studies [12, 13, 32, 33, 35, 36, 42–45] reported health benefits in terms of QALYs. Three studies [12, 43, 44] modelled adverse events as penalties, and Yang et al. [32] included costs due to adverse events. Further details on the characteristics are provided in Appendix 6 (see ESM).

3.3.2 Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9) Inhibitors

Among the 15 selected studies evaluating PCSK9 inhibitors, three were updates from previous published models incorporating new clinical or pricing data [38, 44, 48], and the rest were original research articles. Eight studies were set in the US [12, 26, 29, 37, 38, 43, 44, 48], two in Spain [30, 39], and the rest in Japan [46], Norway [33], Australia [47], Germany [28] and Thailand [45]. The comparator was statins or statins plus ezetimibe. The mean age of the population was > 60 years in all the included studies and baseline LDL-C levels ranged from 70 to 150 mg/dL.

All the studies used a Markov model with yearly cycles except Kumar et al. [47], who modelled 5-year cycles, and all used lifetime horizons with the exception of Olry de Labry Lima et al. [30], who used a 10-year time horizon

[30]. The model structure varied, with studies simulating from three [45] to eleven [39] health states, and important differences in the variety of the included cardiovascular events, with fatal and non-fatal myocardial infarction and fatal and non-fatal stroke modelled in 13 studies [12, 26, 28, 33, 37–39, 43–48]. Three of the studies [12, 43, 44] used the CVD Policy Model. Two studies [37, 38] adopted a societal perspective, Kongpakwattana et al. [45] used both a healthcare system and a societal perspective, Arrieta et al. [48] a healthcare and a payer perspective, Gandra et al. [26] used a US payer perspective, and two studies [28, 29] did not report the perspective adopted for the analysis. The rest of the studies [12, 30, 33, 39, 43, 44, 46–48] adopted a healthcare system perspective. All the studies with the exception of Olry de Labry Lima et al. [30] applied annual discount rates to costs and benefits, ranging from 2 [46] to 5% [47]. Health benefits were mostly reported as QALYS, but Olry de Labry Lima et al. [30] reported averted cardiovascular events. Three studies [12, 43, 44], included adverse events derived from injection of PCSK9 inhibitors as a small penalty in the utility values, but such penalty was not included in the costs or risk of events. Additional information on the characteristics of the models used are available in Appendix 6 (see ESM).

3.3.3 Omega-3 Polyunsaturated Fatty Acids (n-3 PUFAs)

Five of the 32 included studies evaluated the cost-effectiveness of n-3 PUFAs added to statin therapy. Two studies were set in Australia [50, 51], and the other three in the UK [40], Thailand [31] and Japan [49]. Two studies [31, 40] analysed the addition of 1 g/day of highly purified n-3 PUFAs, and one study [49] analysed the addition of 18 g/day of eicosapentaenoic acid (EPA), which is a specific subclass of n-3 PUFA. The last two [50, 51] evaluated statins plus 4 g/day of icosapent ethyl, a highly purified and stable EPA ethyl ester. The average age of the modelled populations was > 60 years in the five studies [31, 40, 49–51]. Two studies [31, 49] specifically targeted patients with previous myocardial infarction, Cowie et al. [40] focused on patients with chronic heart failure, and the two studies set in Australia specified patients with established CVD and hypertriglyceridaemia [50, 51].

All the studies [31, 40, 49–51] used a Markov model with yearly cycles and a lifetime horizon and the number of health states ranged between three [50] and six [40, 49]. Myocardial infarction and stroke, both fatal and non-fatal, were included in all the models [31, 40, 49–51]. Kodera et al. [49] also included stable angina, while Ademi et al. [50] also modelled coronary revascularisation and hospitalisations due to atrial fibrillation. All studies [31, 40, 49–51] adopted a healthcare system perspective, discounted costs and benefits, with annual discount rates between 2% [49] and 5% [50], and all [31, 40, 49–51] evaluated health outcomes in terms of QALYs. Only Ademi et al. [50] modelled the health outcomes and costs of adverse events. Further information on the models can be accessed in Appendix 6 (see ESM).

3.3.4 Polypill

Among the seven selected studies evaluating the polypill strategy, two were set in the US [27, 52], and the rest in India [53], the UK [41], Spain [54], Germany [55], and Lin et al. [34] analysed the polypill in five different LMICs. Three studies [41, 54, 55] analysed three-component polypills (aspirin, an ACE inhibitor and a moderate-potency statin), the other three [34, 52, 53] analysed a four-component polypill (aspirin, an ACE inhibitor, a beta-blocker and a moderate- or low-potency statin) and Gaziano et al. [27] analysed four-component polypills with three different statins of different potencies. All the studies used multiple monotherapies as a comparator. The populations modelled had a mean age of > 60 years in most of the studies [27, 41, 52, 54, 55]. Five of the studies [41, 52–55] targeted patients with previous myocardial infarction, Lin et al. [34] considered patients with previous ischaemic heart disease or stroke, and Gaziano et al. [27] described patients with established CVD.

Four of the seven studies [41, 52–55] used a Markov model, Megiddo et al. [53] used a deterministic model, Lin et al. [34] used a micro-simulation model and Gaziano et al. [27] used the CVD PREDICT model. The CVD PREDICT is a micro-simulation model developed to predict the risk of cardiovascular events based on the Framingham risk equations, extrapolating risk profiles from US demographic trends and rates of medication [56]. The number of included health states varied between nine [27] and five [52], with six out of seven studies [27, 34, 41, 52, 54, 55] including myocardial infarction and stroke, both fatal and non-fatal. All the studies included CVD death. The time horizon of the analysis was lifetime for three studies [34, 52, 55], 10 years for two studies [41, 54], Gaziano et al. [27] evaluated both 5 years and a lifetime horizon, and Megiddo et al. [53] did not report the time horizon. Four studies [34, 41, 54, 55] adopted a healthcare system perspective, Ito et al. [52] used a societal perspective, and Gaziano et al. [27] analysed both perspectives using different time horizons for each of them. The study by Megiddo et al. [53] did not report the perspective used in the analysis. All the studies [27, 34, 41, 52–55] discounted cost and benefits using rates between 3 and 3.5%. The outcomes of interest were mostly reported as QALYs [27, 41, 52, 54, 55], while Megiddo et al. [53] and Lin et al. [34] used DALYs averted. Only Lin et al. [34] and Gaziano et al. [27] included the impact of adverse events in the model. Further details on the model characteristics can be accessed in Appendix 6 (see ESM).

3.4 Baseline Risks and Treatment Effects

3.4.1 Ezetimibe

Six out of ten studies profiled the model population after local registries and databases [12, 13, 33, 36, 43, 44], three studies [32, 35, 42] after the patient characteristics of clinical trials, and Kongpakwattana et al. [45] used patient profiles from a meta-analysis of RCTs. To model baseline risks, four studies [12, 36, 43, 44] used local observational data, five studies [13, 32, 35, 42, 45] used baseline data from clinical trials and meta-analyses, and Korman and Wisloff [33] used both observational and clinical data. Two studies [35, 36] used the Framingham risk score and two studies [13, 33] applied risk reduction estimates from the CTT Collaboration meta-analyses. Eight out of the ten studies [12, 13, 33, 35, 36, 43–45] applied age-related trends to baseline risk for fatal and non-fatal events.

Six studies [12, 13, 33, 35, 36, 44] used surrogate markers to model the treatment effect, estimating the relative reduction of cardiovascular risk from LDL-C changes reported from clinical trials and meta-analyses. As for baseline events, cardiovascular risk was modelled using the Framingham risk score or risk reduction values from CTT Collaboration meta-analyses. The other four studies [32, 42, 43, 45] used event rates from clinical trials with cardiovascular event endpoints to model the treatment effect. All the studies [12, 13, 32, 33, 35, 36, 42–45] modelled the intervention and the treatment effect to last for the duration of the model.

The most used clinical trial was the IMProved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) trial, the largest RCT with hard outcomes to date that analysed ezetimibe + simvastatin versus simvastatin. It included more than 18,000 patients with established CVD and showed a hazard ratio (HR) of 0.93 (95% confidence interval [CI] 0.89–0.99) for ezetimibe/simvastatin versus simvastatin for a composite of fatal and non-fatal cardiovascular events at 7 years' follow-up [11]. Further details regarding model input sources are available in Appendix 7 (see ESM).

3.4.2 PCSK9 Inhibitors

Eleven out of the 15 studies [12, 26, 28, 29, 33, 37–39, 43, 44, 46] used observational data from registries and local databases to profile the model populations. Three studies [47, 48, 57] incorporated patient characteristics from the same clinical trial (FOURIER [Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk] [7, 37]), and Kongpakwattana et al. [45] used data from a meta-analysis of RCTs. To estimate the baseline risk of cardiovascular events, twelve studies [12, 26, 28, 29, 33, 37–39, 43, 44, 46, 48] used observational data from local registries and databases while the other three [33, 45, 47] used data from clinical trials. Eleven out of the 15 studies [12, 26, 29, 33, 37, 38, 43–45, 47, 48] applied age-related trends to the event rates in the model, for both fatal and non-fatal events.

Eight studies [12, 26, 29, 33, 37–39, 44] used clinical trials with surrogate markers to model the treatment effect, while four studies [43, 46, 47, 57] incorporated event rates from clinical trials with fatal and non-fatal cardiovascular events as endpoints, and Kongpakwattana et al. [45] used event rates from a meta-analysis of RCTs. In addition, Arrieta et al. [48] included both event rates from a clinical trial for the duration of the trial, and surrogate markers beyond the trial duration. Dressel et al. [28] modelled the treatment effect of PCSK9 inhibitors assuming relative risk reductions for cardiovascular events ranging from 10 to 50% compared with statin therapy. All the studies incorporated the intervention and the treatment effect to last as long as the model time horizon.

Several different clinical trials and meta-analyses were used as sources for the treatment effects. The most used was the FOURIER trial, which was used in seven studies [30, 37, 38, 44, 47–49]. The FOURIER trial was an RCT involving more than 27,000 patients analysing PCSK9 inhibitors, with a primary composite endpoint of non-fatal and fatal cardiovascular events. The results showed a reduction in the primary endpoint with an HR of 0.85 (95% CI 0.79–0.92) when compared with statin monotherapy [7]. More information on model input sources can be accessed in Appendix 7 (see ESM).

3.4.3 n-3 PUFAs

Four out of the five included studies [40, 49–51] used data from clinical trials to profile the model populations, while Permpanich et al. [31] used data from a local registry. To model baseline risks, two studies [31, 40] used local demographic data and registries, while the other three studies [49–51] extracted baseline event rates from clinical trials. Only Ademi et al. [50] adjusted the event rates for increasing age, using local demographic data.

All the studies [31, 40, 49–51] used clinical trials with composites of cardiovascular events, or cardiovascular events plus all-cause mortality to model the treatment effect. Three of the five studies [31, 49, 50] modelled the intervention effects for the duration of the model. The other two studies, Cowie et al. [40] and Gao et al. [51], modelled the intervention for a duration of 4 and 5 years, respectively. However, while Cowie et al. [40] did not consider the treatment effect to extend beyond the intervention period, Gao et al. [51] assumed the health benefits to extend up to 10 years.

Only one trial was used as a treatment effect source in more than one study. The two most recent studies, Gao et al. [51] and Ademi et al. [50], used data from the Reduction of Cardiovascular Events with Icosapent Ethyl–Intervention (REDUCE-IT). The REDUCE-IT trial was an RCT including 8179 patients, analysing the effectiveness of icosapent ethyl on cardiovascular event rates [18]. Results from the REDUCE-IT trial showed a 0.75 HR (95% CI 0.68–0.83) for the primary endpoint (a composite of fatal and non-fatal cardiovascular events). More details about model input sources can be consulted in Appendix 7 (see ESM).

3.4.4 Polypill

Three studies [41, 54, 55] used assumptions from experts to model the characteristics of the study populations, while the other four studies used profiles from local demographic data [27, 34, 52, 53]. Baseline risks were estimated from local registries [27, 34, 41, 53, 55] or from the statin arm of clinical trials [52, 54] and two studies used the Framingham study to model cardiovascular risk [27, 53]. Two studies modelled an increase in cardiovascular risk with increasing age [27, 34].

Regarding the treatment effect, six studies [27, 34, 41, 52, 54, 55] incorporated different adherence rates to both treatment arms, with the polypill having higher compliance over a longer period. The remaining study did not model changes in adherence to treatment between the polypill and multiple monotherapies [53]. Five studies [27, 34, 41, 54, 55] used data from the UMPIRE (Use of a Multidrug Pill In Reducing cardiovascular Events) trial. The UMPIRE trial was an open-label trial with a median follow-up of 15 months, including 2004 participants with established CVD in India and Europe [21]. The results showed increased adherence, from 65% in multiple monotherapy users to 86% in polypill users, and parallel reductions in blood pressure levels and LDL-C levels. Details regarding model input sources are available in Appendix 7 (see ESM).

3.5 Perspective and Costs

Granular information on included costs and perspective is provided in Appendix 8 (see ESM). The majority of the studies adopted a healthcare perspective, therefore the main costs captured were direct medical costs (hospitalisation, medication and outpatient appointments). Studies that included a societal perspective captured travelling, caregiver time and future consumption as additional costs. Only Gaziano et al. [27] reported the inclusion of productivity costs defined as labour market earnings lost.

Willingness-to-pay (WTP) thresholds were set according to different criteria. Five studies [31–33, 45, 50] used the criteria recommended by local health technology assessment (HTA) bodies, four studies [12, 27, 43, 44] used the criteria set by the American College of Cardiology/American Heart Association and four studies used the criteria set by WHO [26, 34, 37, 38]. Seven studies [39, 42, 46, 47, 49, 51, 52] cited other published sources, Toth et al. [29] used the recommendation of the Second Panel on Cost-effectiveness, and finally, 11 studies [13, 28, 35, 36, 40, 41, 48, 53–55, 57] did not report the source used to set the WTP threshold and defined it as the commonly accepted threshold.

3.6 Cost-Effectiveness of Original Results and Key Drivers of Cost-Effectiveness

3.6.1 Ezetimibe

Five out of eight studies (62.5%) [32, 33, 35, 42, 43] from a healthcare perspective and Soini et al. [36] from a societal perspective considered ezetimibe to be cost effective compared with statins. In addition, Davies et al. [13] considered ezetimibe to be cost effective from a US payer perspective assuming a 90% price reduction due to patent expiration. Of the five studies set in the US, three studies (60%) reported an ICER below the WTP threshold, from a healthcare [42, 43] or a payer's perspective [13]. The original results from the two earliest studies by Kazi et al. [12, 44] reported ezetimibe to be above the US$100,000/QALY threshold commonly used. Of note, one study was an update [44], so differences between studies were minimal. The most recent study by Kazi et al. [43], using the same model but published after patent expiration, reported the ICER of ezetimibe to be below the mentioned threshold. Finally, the study by Kongpakwattana et al. [45] did not consider ezetimibe to be cost effective from a healthcare or societal perspective according to the WTP threshold in Thailand. The results for total health outcomes and total costs are summarised in Table 2.

All the studies reported increased health benefits with the addition of ezetimibe to statins versus statin monotherapy, with incremental QALYs ranging from 0.10 in Kongpakwattana et al. [45] to 0.62 in the oldest study by Kazi et al. [12]. Interestingly, in the three studies by Kazi et al. [12, 43, 44], the health benefits (incremental QALYs) were lower in the most recent study [43] compared with previous ones [12, 44], but the ICER is also lower, reflecting the price reduction of the drug after patent expiration. Detailed information on health benefits, original costs, and adapted costs are summarised in Table 2.

Three studies did not report sensitivity analyses for ezetimibe [33, 35, 44] while the remaining seven studies [12, 13, 32, 36, 42, 43, 45] had undertaken both deterministic and probabilistic sensitivity analyses. Additionally, four studies [12, 42, 43, 45] reported scenario and threshold analyses and three studies [13, 36, 43] also included sub-group analyses.

There was a variety of drivers of cost-effectiveness. Cost of ezetimibe was identified by three studies [12, 13, 43] and time horizon by another three [12, 32, 42]. Non-fatal coronary heart disease rates were identified as an important parameter by Davies et al. [13], and Kongpakwattana et al. [45] identified the treatment effect on mortality as the essential parameters for cost-effectiveness. Additionally, Soini et al. [36] reported the results of sub-group analysis, showing that changes in baseline LDL-C levels, gender and diabetes status had no significant influence in the model. Although Reckless et al. [35] did not report results from sensitivity analysis, the authors mentioned the risk coronary heart disease as the main driver for cost-effectiveness, with highest risk rates giving lower ICERs.

3.6.2 PCSK9 Inhibitors

From the healthcare system perspective, one out of ten studies (10%) [39] considered PCSK9 inhibitors to be cost effective compared with statins. Additionally, Gandra et al. [26] and Fonarow et al. [38] considered PCSK9 inhibitors to be cost effective versus statins, from a US payer and a societal perspective. From the eight studies set in the US [12, 26, 29, 37, 38, 43, 44, 48], two studies (25%) considered PCSK9 inhibitors to be cost effective, one from a payer [26] perspective, and one from a societal perspective [38]. Of note, the ICERs of PCSK9 inhibitors versus statins were generally lower than when compared with statins plus ezetimibe. Health benefits, total costs, and adapted costs are summarised in Table 2.

In all the studies [12, 26, 28, 30, 33, 37–39, 43–48], the cost-effective analysis of PCSK9 inhibitors for patients with a history of CVD and LDL-C levels > 70 mg/dL yielded additional QALYs per person, ranging between 0.17 [45] and 1.12 [26].

Eight studies [12, 26, 37, 39, 43, 45, 46, 57] performed deterministic sensitivity analyses, and nine studies [12, 26, 33, 37, 39, 43, 45, 46, 57] also conducted probabilistic sensitivity analyses.

The cost of PCSK9 inhibitors was identified as the main driver of cost-effectiveness in five of the included studies [12, 43, 46–48]. Three studies [26, 37, 39] considered the effect of the reduction of plasma LDL-C on cardiovascular risk as the most influential parameter and Kongpakwattana et al. [45] reported treatment effect on mortality risks to be the key drivers of cost-effectiveness. Time horizon was mentioned in one study [12], with longer time horizons producing better ICERs. Three studies [30, 44, 57] did not explore key influences in their analysis. Interestingly, in one study by Fonarow et al. [37], the authors used the same model with two different sources for the baseline risks, US claims data and data from the FOURIER trial. Results showed that the ICERs obtained with data from FOURIER were much higher, and thus less cost effective than those obtained with US claims.

3.6.3 n-3 PUFA

Out of the five studies, all from a healthcare perspective, three (60%) [40, 49, 50] considered the addition of n-3 PUFAs to statin therapy to be a cost-effective strategy versus statin monotherapy, while the other two studies, Permpanich et al. [31] and Gao et al. [51], did not consider the intervention to be cost effective. None of the studies analysing n-3 PUFAs were set in the US. The five studies reported a gain in health benefits from the intake of n-3 PUFAs ranging from 0.08 additional QALYs per person in Cowie et al. [40] to 2.01 QALYS per person in Permpanich et al. [31]. Total and adapted costs and health benefits are summarised in Table 2.

All the studies performed deterministic and probabilistic sensitivity analyses [31, 40, 49–51], two studies reported scenario and threshold analyses [49, 50] and Gao et al. [51] reported results for the expected value of perfect information.

Time horizon was an important driver in four of the studies [40, 49–51], the cost of n-3 PUFAs was identified in three studies [31, 50, 51] and population mortality rates due to CVD were also identified in three studies [49–51]. In addition, discounting rates were described as influential in two of the studies [31, 51] but were not influential in two other studies [40, 50]. In scenario analyses, the study by Kodera et al. [49] noted that the results were no longer cost effective when compared with high-potency statin treatment instead of low to medium potency. The study by Permpanich et al. [31] highlighted that the ICER decreased as age increased, making it a more cost-effective strategy for older patients. In addition, Ademi et al. [50] showed that the intervention was no longer cost effective if age-related population trends were not applied into the model.

3.6.4 Polypill

All the studies adopting a healthcare perspective considered the polypill to be cost effective [34, 41, 53, 55] or cost saving [54] compared with multiple monotherapies. Additionally, Gaziano et al. [27] reported the polypill to be cost saving from a societal perspective. From the two studies [27, 52] set in the US, one study (50%) considered the polypill to be cost saving from a healthcare perspective [27], while the other did not consider it cost effective from a societal perspective [52]. Total costs, total health benefits and adjusted costs are summarised in Table 2.

All the studies reported a small increase in health benefits with the polypill compared with multiple monotherapies, with gained QALYs per person ranging from 0.02 [52] to 0.05 [54].

Table 2 Health benefits, total costs and adapted costs. The adopted perspective is healthcare for all studies unless specified otherwise (highlighted in bold)

Study	Currency, year	Benefits (per person)		Total costs (per person)		Adapted total costs (2018 US dollars)		Original ICERs (Cost/QALY)	WTP thresholds	Adapted ICERs (2018 US dollars)
		Treatment	Comparator	Treatment	Comparator	Treatment	Comparator			
Ezetimibe										
Reckless et al. (2010) [35][a]	GBP 2009	7.17	6.94	7398	4763	33,048	21,277	11,571	20,000–30,000	51,178
Soini et al. (2010) [36] Societal (men/women)[b]	EUR 2007	10.85/14.31	10.48/14.07	21,410/24,936	13,032/13,814	68,327/79,580	41,590/44,085	22,841/46,686	30,000–50,000	72,853/149,136
Kazi et al. (2016) [12]	USD 2015	0.62	0	94,817	0	100,449	0	154,000	100,000	163,055
Davies et al. (2017) [13] Payer	USD 2017	11.80	11.63	101,525	99,994	109,429	107,779	9149	20,000–30,000	9707
Kazi et al. (2017) [44]	USD 2017	0.49	0	98,529	0	100,933	0	199,000	100,000	204,140
Almalki et al. (2018) [42]	USD 2016	16.96	16.84	42,346	36,819	44,303	38,520	45,046	50,000–100,000	48,187
Korman and Wisloff (2018) [33][c]	EUR 2015	8.05	7.55	42,110	38,594			6969	67,165	
Kazi et al. (2019) [43][d]	USD 2018	0.21	0	16,730	0			81,000	100,000	
Kongpakwattana et al. (2019) [45] Health care/Societal[d]	USD 2018	11.05	10.95	16,556/18,834	13,954/16,217			27,195/27,361	4994	
Yang et al. (2020)[e]	CNY 2017	6.98	6.63	84,780	68,322			47,102	56,660	
PCSK9 inhibitors										
Gandra et al. (2016) [26] Payer, vs statins[f]	USD NR	10.51	9.39	381,499	223,192			141,699	55,000–165,000	
Kazi et al. (2016) [12], vs statins + EZT	USD 2015	0.93	0	384,097	0	407,551	0	414,000	100,000	439,026
Arrieta et al. (2017) [48], vs statins	USD 2016	0.36	0	120,361	0	125,924	0	337,729	100,000	349,789
Fonarow et al. (2017) [37] Societal, vs statins	USD 2017	7.62	7.23	340,275	234,877	348,577	240,608	268,637	150,000	276,845
Kazi et al. (2017) [44], vs statin + EZT	USD 2017	0.62	0	279,380	0	399,765	0	450,000	100,000	460,674

Table 2 (continued)

Study	Currency, year	Benefits (per person)		Total costs (per person)		Adapted total costs (2018 US dollars)		Original ICERs (Cost/QALY)	WTP thresholds	Adapted ICERs (2018 US dollars)
		Treatment	Comparator	Treatment	Comparator	Treatment	Comparator			
Toth et al. (2017) [29] Payer, vs statins[f]	USD NR	9.91	9.23	362,792	235,863			187,538	100,000–200,000	
Villa et al. (2017) [39], vs statins	EUR 2016	6.57	5.64	76,596	34,330	389,524	174,586	45,340	30,000–45,000	231,119
Kodera et al. (2018) [46], vs statins	JPY 2018	8.95	8.47	13,224,836	7,174,489	289,764	157,197	13,454,814	5,000,000	276,181
Korman and Wisloff, 2018) [33], vs statins + EZT[c]	EUR 2015	8.69	8.05	124,366	42,110			128,191	67,165	
Kumar et al. (2018) [47], vs statins	AUD 2017	9.13	8.82	93,895	20,948	141,911	31,661	308,558	50,000	467,162
Olry de Labry Lima et al. (2018) [30] (averted events)[e,f]	EUR NR	8.38	8.08	471,418	13,948			1,531,434	NR	
Dressel et al. (2019) [28] (men/women)[f]	EUR NR	14.91/15.50	13.67/14.27					108,660/112,530	100,000–150,000	
Fonarow et al. (2019) [38], Societal, vs statins	USD 2018	7.62	7.23	257,105	234,877	NA	NA	56,655	50,000–150,000	NA
Kazi et al. (2019) [43] vs statins/vs statins + EZT[d]	USD 2018	0.27/0.07	0/0	84,567/67,846	0/0	NA	NA	308,000/997,000	100,000	NA
Kongpakwattana et al. (2019) [45], vs statins, Healthcare/Societal[d]	USD 2018	11.12	10.95	105,061/107,351	13,954/16,217	NA	NA	1,223,831/1,223,995	4994	NA
n-3 PUFAs										
Cowie et al. (2011) [40]	GBP 2009	3.99	3.84	15,011	14,017	68,156	63,643	12,636	30,000	57,128
Permpanich et al. (2015) [31][e]	THB 2013	15.06	13.05	2,600,348	2,001,572			256,199	160,000	
Kodera et al. (2018) [49]	JPY 2018	18.1	17.9	6,551,407	5,281,864	143,545	115,729	5,450,831	5,000,000	139,082
Gao et al. (2019) [51]	AUD 2018	10.57	10.28	83,258	66,453	112,887	98,083	59,036	50,000	85,530

Table 2 (continued)

Study	Currency, year	Benefits (per person)		Total costs (per person)		Adapted total costs (2018 US dollars)		Original ICERs (Cost/QALY)	WTP thresholds	Adapted ICERs (2018 US dollars)
		Treatment	Comparator	Treatment	Comparator	Treatment	Comparator			
Ademi et al. (2020) [50]	AUD 2018	7.82	7.54	89,333	76,311	131,854	112,633	35,935	50,000	63,990
Polypill										
Ito et al. (2012) [52], Societal	USD 2010	4.51	4.47	107,075	102,767	123,299	118,336	133,000	100,000	153,178
Megiddo et al. (2014) [53] (DALYS), NR	USD 2010	7,320,000	0	NR	NR			1760	<3 × per capita GDP	
Becerra et al. (2015) [41]	GBP 2014	5.28	5.25	3995	3752	14,964	14,056	8205	20,000	30,731
Barrios et al. (2017) [54]	EUR 2014	6.15	6.10	5963	6473	32,871	30,282	Dominant	NR	Dominant
Barth et al. (2017) [55]	EUR 2015	3.96	3.94	8579	8376	20,988	20,489	9228	NR	22,572
Gaziano et al. (2019) [27] Healthcare/ Societal[g]	USD, NR	8.38	8.12	190,243/−39,925	186,493/0			20,073/Dominant	50,000–150,000	
Lin et al. (2019) [34] (DALYs) China/India/ Mexico/ Nigeria/ South Africa[e,f]	Int$ 2017	https://doi.org/10.2/https://doi.org/10.3/https://doi.org/10.6/10/9.9	11.1/11.1/11.3/10.9/10.8	2280/541/1740/4090/2080	2430/658/1810/4430/2140			168/154/88 364/64	1 × per capita GDP	

DALYs disability-adjusted life-years, *EZT* ezetimibe, *GDP* gross domestic product, *ICERs* incremental cost-effectiveness ratios, *n-3 PUFA* omega-3 polyunsaturated fatty acids, *NR* not reported, *PCSK9* proprotein convertase subtilisin/kexin 9, *QALY* quality-adjusted life-years, *WTP* willingness to pay

Currency: *AUD* Australian dollar, *EUR* Euro, *GBP* Great British pound, *Int$* International dollar, *JPY* Japanese yen, *THB* Thai baht, *USD* United States dollar

[a]Results from pooled data (statins of different potency as comparators)

[b]Results from the comparison between simvastatin versus ezetimibe plus simvastatin

[c]Results from "Miscellaneous High-Risk sub-group" reported by Korman and Wisloff

[d]Total costs and ICERs not adapted since the original results are already reported in 2018 USD

[e]Total costs and ICERs not adapted due to lack of information on purchasing power parities

[f]Total costs and ICERs not adjusted due to lack of information regarding the currency year

[g]Results from the best polypill analysed versus standard therapy

All the studies [27, 34, 41, 52–55] reported deterministic and probabilistic sensitivity analyses and five out of seven studies [34, 41, 53–55] also performed scenario analyses.

Three studies [41, 54, 55] reported utility values as the most influential parameter for cost-effectiveness [41, 54, 55], followed by adherence rates to polypill [27, 34, 41], and rates of cardiovascular events, particularly myocardial infarction. In addition, Gaziano et al. [27] reported the polypill cost as a determinant of cost-effectiveness.

3.7 Adaptation of Cost-Effectiveness Studies to 2018 US Dollars

Four out of six studies (66%) [35, 42, 43, 45] that evaluated ezetimibe from a healthcare perspective had ICERs below US$100,000 after adapting costs to 2018 US dollars (Fig. 2). The value of the ICERs ranged from US$27,195 in Kongpakwattana et al. [45] to US$204,140 in Kazi et al. 2017 [44] in studies adopting a healthcare perspective. The results from the two studies adopting a societal perspective [36, 45] ranged from US$149,136 for women in the study by Soini et al. [36] to US$27,361 in Kongpakwattana et al. [45].

After adapting costs to 2018 US dollars, none of the PCSK9 inhibitor studies adopting a healthcare perspective had ICERs below US$100,000 (Fig. 2). There was an important variation in the values of the ICERs for PCSK9 inhibitors, from US$231,119 in Villa et al. [39] to US$1,223,831 in the study by Kongpakwattana et al. [45], in both cases from a healthcare perspective. From a societal perspective, ICERs ranged from US$56,655 in the most recent study by Fonarow et al. [38] incorporating new pricing and diagnosis guidelines, to US$1,223,995 in the study by Kongpakwattana et al. [45].

Three out of four studies (75%) [40, 50, 51] analysing n-3 PUFAs had ICERs below US$100,000 after cost adaptation (Fig. 2). The adapted ICERs for n-3 PUFAs versus statin therapy had a smaller range, from US$57,128 in the oldest

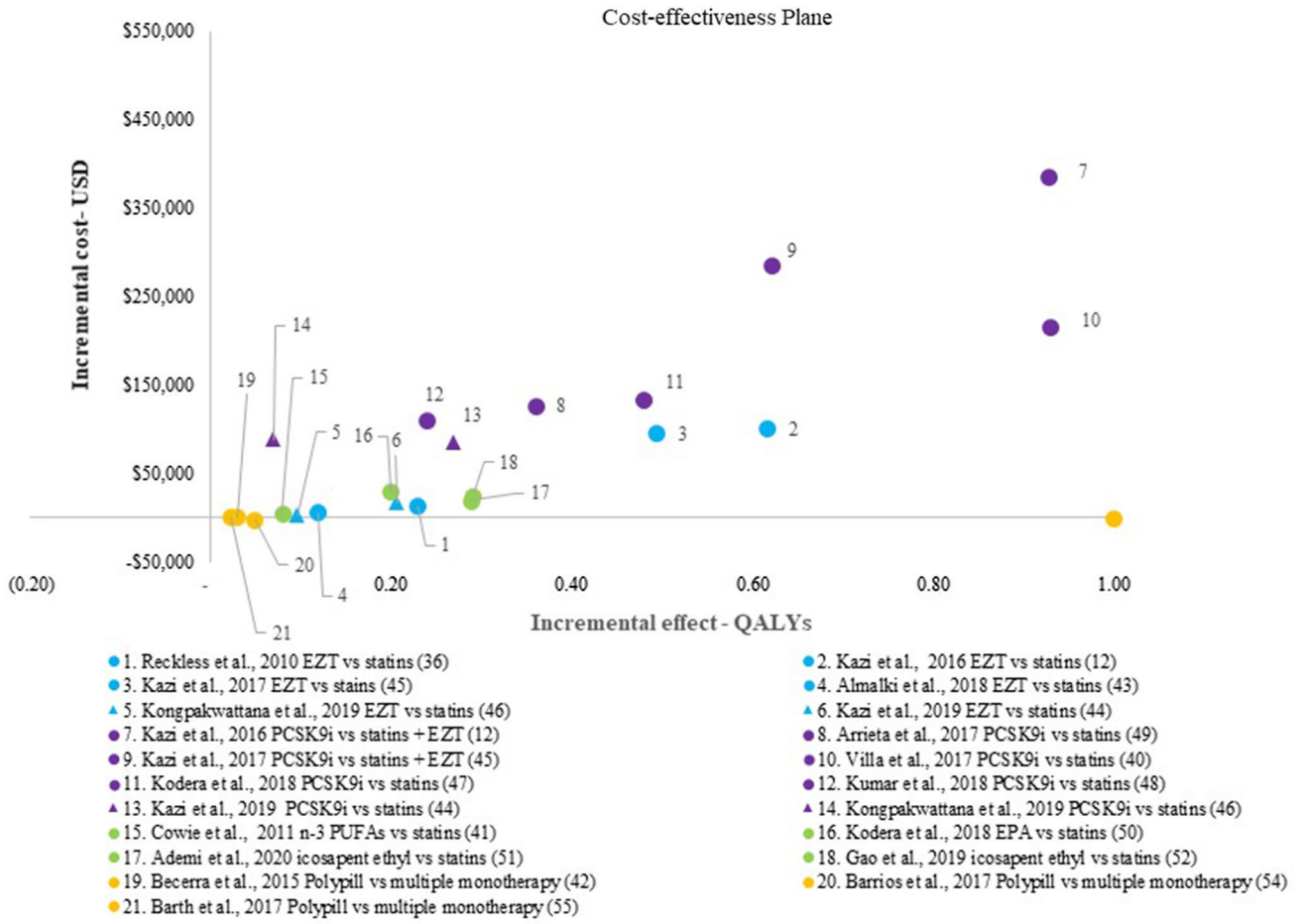

Fig. 2 Cost-effectiveness plane, displaying costs adapted to 2018 US dollars and original effect estimates for studies adopting a healthcare perspective. All studies used a lifetime horizon, except for Barrios et al. [53] and Becerra et al. [52]. Circles represent data after cost adjustment, and triangles non-adjusted data (originally reported in 2018 USD). *EZT* ezetimibe, *QALY* quality-adjusted life years

study [40] to US$139,082 in the study by Kodera et al. [49], all being from a healthcare perspective.

For the polypill, three out of the four studies (75%) [41, 54, 55] adjusted to 2018 US dollars had ICER values below US$100,000 (Fig. 2).The polypill had important variations as well in the results from the adapted ICERs, ranging from being dominant (i.e. cost saving) in Barrios et al. [54] to US$133,000 in the oldest study by Ito et al. [52].

The results of the studies using a healthcare perspective and adjusted to 2018 US dollars are included in a common cost-effectiveness plane (Fig. 2). Cost-effectiveness planes for studies using a societal perspective are available in Appendix 3 (see ESM).

4 Discussion

In general, ezetimibe, n-3 PUFAs and the polypill are cost effective compared with standard therapy (statin monotherapy for ezetimibe and n-3 PUFAs and multiple monotherapies for the polypill), while most studies analysing PCSK9 inhibitors considered them not cost effective when compared with statins or statins plus ezetimibe.

Our results revealed that seven out of the ten included studies [12, 13, 32, 33, 35, 36, 42] considered ezetimibe plus statins to be cost effective or reported an ICER below the usual WTP threshold for their setting when compared with statin monotherapy, in patients with established CVD and LDL-C levels > 70 mg/dL despite statin treatment. These results are in accord with a previous systematic review by Suh et al. [58], who indicated that ezetimibe was cost effective for patients intolerant to statins, with chronic kidney disease or not reaching plasma LDL-C therapeutic levels. For ezetimibe, the main cost-effectiveness drivers were cost of the drug [12, 13], baseline cardiovascular risks [35, 42] and treatment effect related to cardiovascular and non-cardiovascular mortality [13, 45]. These parameters were also identified as crucial drivers for cost-effectiveness in a recent systematic review analysing pharmacological treatments for heart failure [59].

Twelve out of 15 studies [12, 28–30, 33, 37, 43–48] indicated that PCSK9 inhibitors were not cost effective with current pricing and WTP thresholds compared with statin monotherapy or statins plus ezetimibe for patients with established CVD. The reported ICERs were significantly higher when compared with ezetimibe plus statins. Similar results have been published in previous systematic reviews [58, 60], although these reviews were not specific for secondary prevention. Drug cost was the main driver of cost-effectiveness in five studies [12, 43, 44, 47, 48]. Most of the studies that used LDL-C levels to extrapolate cardiovascular risk identified this parameter as one of the main drivers of cost-effectiveness.

The analysis of cost-effectiveness studies on n-3 PUFAs showed that three out of five studies [40, 49, 50] considered the addition of n-3 PUFAs to statins to be cost effective when compared with statin monotherapy. Similar results were reported by Sadler et al. [61], although their results were not specific to secondary prevention. The time horizon was the main driver of cost-effectiveness for n-3 PUFA. The relatively small health benefits of the intervention versus standard therapy make time horizon a pivotal element, since the cost will only be offset in the long term.

The cost-effectiveness results of the polypill showed that it was cost saving/cost effective compared with multiple monotherapies for secondary prevention populations. Although there is no other specific review on the cost-effectiveness of fixed-dose combinations for patients with established CVD, other systematic reviews of interventions that aimed to increase adherence [62] have shown similar results, and it was shown to be cost effective for primary prevention in LMICs [22, 63]. Interestingly, two of the analysed studies [34, 41] mentioned the need for synergistic approaches to improve adherence to guideline-based prescription and treatment together with the polypill.

4.1 Limitations of the Present Systematic Review

Our review has several limitations. The generalisation of the cost-effectiveness results is debatable, since most of the clinical effectiveness data emanates from Western countries, with only a small percentage of clinical data coming from studies undertaken in Asia, and none in Africa or South America. Moreover, most of the studies are set in high-income countries, which determines the costs of long-term treatment and prescriptions and reflects the need for more studies using data from LMICs [63]. In addition, the differences between the healthcare systems in different countries and the discrepancies in WTP thresholds also make generalisation difficult. The exclusion of non-peer-reviewed publications, such as publications by health technology assessment bodies, means that we may have missed some important models.

The structural variation among the studies can also increase the uncertainty of the overall conclusions, as seen for primary prevention in hypertensive patients [64]. The lack of publicly available models limits the capacity to compare between settings and countries, since many model features remain obscure [65].

The estimates derived from the adaptation of cost results cannot be directly interpreted as ICERs for the US, only as an approximation of cost-effectiveness levels to be expected for the US. Nevertheless, the overall cost-effectiveness results in the four analysed strategies were consistent when adapted to the US setting. Of note, original consideration of cost-effectiveness from LMIC was less likely to be consistent after adaptation to the US setting.

4.2 Limitations of the Reviewed Cost-Effectiveness Studies

The cost-effectiveness studies analysed also had some limitations. Lower adherence rates have been shown to lead to worse health outcomes and increased costs for healthcare systems [66]; however, adherence was only modelled in six out of seven studies evaluating the cost-effectiveness of the polypill [27, 34, 41, 52, 54, 55] and in none of the studies analysing other interventions in this systematic review. In many cases, assumptions were made about utility values to derive QALYs gained due to lack of evidence.

Health technology agencies recommend the use of clinical endpoints instead of surrogate markers [67]. The use of surrogate markers (i.e. lipid levels to estimate the relative risk reduction in cardiovascular events), in most cases due to lack of clinical trials describing hard outcomes, increased the uncertainty of the models. Some studies showed that LDL-C poses a cumulative risk and that decreases in LDL-C levels will not necessarily mean an immediate decrease in cardiovascular risk [68]. Most of the studies did not explore the effect of starting the treatment at different age ranges, which can have a significant influence given the focus on populations with established CVD. In addition, some models used data from the statin arm of clinical trials to model baseline risk of cardiovascular events while others used local demographic data. The use of clinical trials to model event rates could lead to an underestimation of the baseline risk and the treatment effect [69]. In our study, we were not able to observe any clear trend on whether the use of clinical trials data generated improved cost-effectiveness results compared with using observational studies with regards to baseline risk and treatment effect.

Only Ademi et al. [50], Gaziano et al. [27] and Lin et al. [34] considered adverse events and subsequent costs, although another four studies [12, 32, 43, 44] incorporated adverse events as a decrement utility or as an extra cost. The majority of the cost-effectiveness studies undertook a healthcare perspective, highlighting the gap in evidence and the need for analysing results from a societal perspective. While most patients included in these studies were beyond typical working age, since the mean age for almost all studies was > 60 years, out-of-pocket payments and caregiver time should have been considered, which would likely improve the cost-effectiveness.

5 Conclusions

Ezetimibe and n-3 PUFAs represent cost-effective strategies for the secondary prevention of CVD compared with statin monotherapy. Similarly, the polypill is cost saving or cost effective compared with multiple monotherapies. PCSK9 inhibitors did not meet cost-effectiveness thresholds in most of the studies reviewed. Time horizon and cardiovascular risks were the main drivers for n-3 PUFAs and the cardiovascular polypill. Drug cost, time horizons and cardiovascular risks were the main drivers for ezetimibe and the ICERs for PCSK9 inhibitors were mainly influenced by the cost of the drugs and the relative reduction of cardiovascular risk.

Author Contributions ZA designed the scope of this systematic review, supervised the quality appraisal, data extraction and cost-adaptation processes and contributed to the writing of the first manuscript and to the editing of all subsequent versions. CM contributed to the quality appraisal, data extraction, cost adaptation and writing of the first manuscript. SVT contributed to the quality appraisal and data extraction as well as the editing process. EZ contributed to the editing of the manuscript. ROA, SZ and DL contributed to the editing of the manuscript.

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Compliance with ethical standards

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