Cost effectiveness analysis of a fixed dose combination pill for primary prevention of cardiovascular disease from an individual participant data meta-analysis

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Summary

Background Cardiovascular disease (CVD) continues to impart a large burden on the global population, especially in lower income countries where affordability limits the use of cardiovascular medicines. A fixed dose combination strategy of at least 2 blood pressure lowering medications and a statin with aspirin in a single pill has been shown to reduce the risk of incident CVD by 38% in primary prevention in a recent meta-analysis. We report the in-trial (median follow-up: 5 years) cost-effectiveness of a fixed dose combination (FDC) pill in different income groups based on data from that meta-analysis.

Methods Countries were categorized using World Bank economic groups: Lower Middle Income Countries (LMIC), Upper Middle Income Countries (UMIC) and High Income Countries (HIC). Country specific costs were obtained for hospitalized events, procedures, and non-study medications (2020 USD). FDC price was based on the cheapest equivalent substitute (CES) for each component.

Findings For the CES-FDC pill versus control the difference in cost was $346 (95% CI: $294–$398) per participant in Lower Middle Income Countries, $838 (95% CI: $781–$895) in Upper Middle Income Countries and $42 (95% CI: –$155 to $239) (cost-neutral) in High Income Countries. During the study period the CES-FDC pill was associated with incremental gain in quality-adjusted life years of 0.06 (95% CI: 0.04–0.08) resulting in an incremental cost-effectiveness ratio (ICER) of $5767 (95% CI: 5735–$5799), $13,937 (95% CI: $13,893–$14,041) and $700 (95% CI: $662–$738) respectively. In subgroups analyses, the highest 10 years CVD risk subgroup had ICERs of $2033, $7322 and –$6000/QALY.

Interpretation A FDC pill produced at CES costs is cost-neutral in HIC. Governments of LMI and UMI countries should assess these results based on the ICER threshold accepted in their own country and own specific health care priorities but should consider prioritizing this strategy for patients with high 10 years CVD risk as a first step.

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Research in context

Evidence before this study

A search on Pubmed was performed on February 21, 2024 with the terms: (((((cardiovascular disease) OR (hypertension) OR (hyperlipidemias) OR (primary prevention))) AND (((polypill) OR (policap) OR (polycap) OR (quintapill) OR (fixed-dose combination)))) AND (((cost-effectiveness [Title/Abstract]) OR (cost [Title/Abstract]) OR (economic [Title/Abstract]))) AND ((("2017/01/01" [Date–Publication]: "2024/02/21" [Date–Publication])))). We identified two previous studies in this time frame that evaluated the cost-effectiveness of a polypill for primary prevention of cardiovascular disease. Both studies adopted the perspective of the United Kingdom; one with a 10 year time horizon the other with a lifetime. The former found that over a 10 year period, the polypill would be either cost-effective, cost-saving or cost-neutral for most age groups while the latter concluded that the polypill would only become cost-effective compared to current practice if polypill prices were reduced.

Added value of this study

We add to the limited recent literature related to the use of a fixed dose combination (FDC) pill for primary prevention of cardiovascular disease by providing the in-trial costs and cost-effectiveness of a FDC pill comprised of a statin, three blood pressure lowering agents and aspirin from the healthcare system perspective of three different income groups (lower-middle, upper-middle and high income). This analysis was performed using patient-level data collected for a meta-analysis of the three largest fixed dose combination clinical trials published to date; HOPE-3, TIPS-3 and PolyIran. We also used an approach that considers the cheapest therapeutic equivalent component in each region which should represent the price most patients can access currently.

Implications of all the available evidence

Integrating a FDC pill containing a statin, three blood pressure lowering agents and aspirin sold at a cost equivalent to the sum of the cheapest available substitutes into a primary prevention strategy could be a cost-effective method in many populations, which could contribute to the UN Sustainable Development Goals of reducing premature mortality from noncommunicable diseases.

Introduction

Cardiovascular disease (CVD) accounts for a large amount of morbidity and deaths globally every year.[1–3] As most events associated with CVD occur in individuals with no prior history of vascular disease, primary prevention is essential in reducing the burden of CVD in all populations.

One strategy for preventing CVD is through fixed dose combination (FDC) therapy, also referred to as a "polypill". This concept gained momentum in the early 2000s with a proposed formulation of a statin, three blood pressure lowering drugs (at half standard dose), folic acid and aspirin.[4,5] More recently a FDC therapy consisting of at least 2 blood pressure lowering medications and a statin in a single pill together with aspirin has demonstrated its benefits in clinical trials and more conclusively in a recently published meta-analysis of 3 of these trials.[6–9]

In 2023 the World Health Organization (WHO) added fixed dose combinations for prevention of atherosclerotic cardiovascular disease to its 23rd Model List of Essential Medicines.[10] As such the cost-effectiveness of such a strategy is important to document, especially in regions with limited resources. In this study we report the in-trial cost effectiveness of a single FDC pill strategy plus aspirin using individual participants data (IPD) from a meta-analysis of the three largest FDC primary CVD prevention trials. Based on our previous work in TIPS-3, we hypothesize that a FDC pill with aspirin would cost more in the LMIC and UMIC groups but would be cost-saving or cost-neutral in the HIC group.

Methods

Meta analysis

Our analysis used IPD from a published meta-analysis of large, long-term randomized trials that evaluated the efficacy and safety of a FDC treatment strategy versus a control for primary CVD prevention.[9] The meta-analysis found three trials between September 2016 and April 2021 that tested a FDC strategy comprised of multiple blood pressure lowering agents and a statin (with or without aspirin), enrolled at least 1000 patients, and had a follow-up of at least 2 years.

To briefly summarize each trial in the meta-analysis, the Heart Outcomes Prevention Evaluation (HOPE) –3 trial was a 2-by-2 factorial, large, long-term, double-blinded, randomized, placebo-controlled trial that compared rosuvastatin 10 mg, candesartan 16 mg plus HCT 12.5 mg or both daily with a placebo. The trial recruited 12,705 participants from 21 countries and had a median participant follow-up of 5.6 years.[6,11,12] Of those, 6348 participants randomized to either the double

active group (testing the polypill concept) or to the double placebo group were included in the meta-analysis. The PolyIran study was a two-group, pragmatic, cluster randomized trial of 6838 participants within the larger Golestan cohort study in Iran. Participants in this study received either minimal care or a once daily polypill consisting of either enalapril 5 mg, atorvastatin 20 mg, HCT 12.5 mg and ASA 81 mg or, if participants developed cough during the follow-up period, valsartan 40 mg instead of enalapril 5 mg. Participants were followed for 60 months.[8] However, 6101 participants from the PolyIran study did not have a prior history of CVD and were included in this IPD meta-analysis. Lastly, the International Polycap Study –3 (TIPS-3) was a 2-by-2-by-2 factorial, double blinded, randomized, placebo-controlled trial evaluating the benefits of a daily polypill comprised of simvastatin 40 mg, atenolol 100 mg, HCT 25 mg and ramipril 10 mg. This study randomized 5713 participants from nine countries and had a mean follow-up of 4.6 years.[7,13] All participants enrolled in TIPS-3 were included in the IPD meta-analysis.

In a more recent published meta-analysis of polypill trials[14] only one trial would satisfy the original meta-analysis criteria but this trial utilized a Zelen design which can introduce significant bias post randomization and so would not be included as part of the meta-analysis our study is based on.[15]

Analysis of participant data from these trials found that the FDC strategy reduced the occurrence of the primary outcome (time to first occurrence of CV death, MI, stroke or arterial revascularization; 3.0% in the FDC group versus 4.9% in control (HR: 0.62; 95% CI: 0.53–0.73, $p < 0.001$). The FDC strategy also reduced the occurrence of the individual components of the primary outcome (Supplementary Table S1).

Healthcare utilization and unit costs

This in-trial analysis counted all cases of HF, MI, stroke, angina and revascularization recorded in the meta-analysis; not just those relevant to the first event (Supplementary Table S2). Physician visits, outpatient tests and other resources consumed outside of the hospital were not recorded in any study in the meta-analysis. The cost for events, procedures and non-study medication were estimated using costs from all three trials. Countries from each trial were grouped into their appropriate income group based on World Bank classifications (Table 1).[16] These costs were adjusted to 2020 USD using average inflation data for each income group and then averaged to yield an average income group specific unit cost. All costs were originally collected through standardized questionnaires sent to National Study leaders, who obtained these costs from local DRGs or hospital databases at the time the initial economic analyses were conducted and have since been published.[17,18]

Country	Studies (# of participants[a])	World bank income group
Lower middle income		**(Mean GDP/Capita: $2945)**
Bangladesh	TIPS-3 (295)	$2122
India	HOPE-3 (1824), TIPS-3 (2739)	$2050
Philippines	HOPE-3 (571), TIPS-3 (1676)	$3414
Tunisia	TIPS-3 (107)	$3478
Ukraine	HOPE-3 (333)	$3661
Upper middle income		**(Mean GDP/Capita: $7905)**
Argentina	HOPE-3 (1459)	$9964
Brazil	HOPE-3 (551)	$8845
China	HOPE-3 (3677)	$10,144
Colombia	HOPE-3 (1463), TIPS-3 (489)	$6437
Ecuador	HOPE-3 (397)	$6233
Indonesia	TIPS-3 (118)	$4151
Iran	PolyIran (6838)	$3850
Malaysia	HOPE-3 (87), TIPS-3 (119)	$11,074
Russia	HOPE-3 (190)	$11,287
South Africa	HOPE-3 (211)	$7068
High income		**(Mean GDP/Capita: $40973)**
Australia	HOPE-3 (45)	$57,274
Canada	HOPE-3 (1156), TIPS-3 (131)	$46,374
Czech Republic	HOPE-3 (70)	$23,424
Hungary	HOPE-3 (263)	$16,425
Netherlands	HOPE-3 (117)	$53,044
South Korea	HOPE-3 (14)	$33,447
Sweden	HOPE-3 (117)	$54,589
UK	HOPE-3 (69)	$43,204

[a]All participant numbers are based on each trial's original recruitment. All participants in the TIPS-3 trial, 6348 (50%) from the HOPE-3 trial and 6101 (89%) from PolyIran. LMI, Lower Middle Income; UMI, Upper Middle Income; HI, High Income.

Table 1: **Countries, their respective studies and their World Bank income group classifications included in the meta-analysis.**

The cost of stroke used in our analysis is costed differently compared to other events in our analysis. Unlike myocardial infarction, heart failure or angina, strokes typically require more care beyond the acute hospitalization. To reflect this increased resource utilization, we used a cost of stroke that better reflects care over a 1-year period by including costs beyond the initial hospitalization such as rehabilitation, nursing home costs and outpatient visits. Since the TIPS-3 and HOPE-3 trials did not use an aggregate cost of revascularization, we used an average of CABG and PCI costs, weighted for the incidence of each using data from TIPS-3 and HOPE-3 to estimate the cost of revascularization used in our analysis.

Economic analysis

Using all participant data from the FDC meta-analysis, we estimated in-trial costs (median follow-up: 5 years) incurred from a third-party payer perspective of three different income groups: Lower Middle-Income countries (LMIC), Upper Middle Income countries (UMIC) and High Income countries (HIC). Participant costs were comprised of two components: healthcare

utilization and the associated unit costs for resources consumed. Concomitant non-study medication utilization and cardiovascular events and procedures (MI, stroke, angina, heart failure and revascularization) were available in the meta-analysis dataset. Costs reflecting each income group were applied to concomitant non-study medication used and each cardiovascular events and procedures that occurred for all participants in the meta-analysis (Supplementary Table S3).

Since the meta-analysis did not focus on a specific formulation of FDC pill, in our analysis we assumed a FDC pill similar in composition that was used in the TIPS-3 RCT (i.e.,: a statin, ACE inhibitor or ARB, beta blocker and hydrochlorothiazide) plus aspirin. The price of this FDC pill was estimated using the cheapest equivalent substitute (CES) approach we used in our cost-analysis of the TIPS-3 and HOPE-3 trials.[17,18] This method considered generic pharmacological equivalents for each component and assumed a hypothetical CES-FDC pill consisting of the lowest priced component for each income group.

Study drug adherence was recorded in all trials. A polynomial curve of best fit was applied to these data and the corresponding equation was used to estimate the percentage of patients on study medication for each year of the meta-analysis.

In our previous work reporting on the cost implications of the TIPS-3 trial, we found that a polypill plus aspirin was more expensive in both lower and upper middle income countries and cost neutral in high come countries.[17] Based on this we hypothesized that a FDC pill with aspirin would cost more in the LMIC and UMIC groups but would be cost-saving or cost-neutral in the HIC group. If the incremental cost was within a window defined as ± 5% of the total cost of the control, the FDC pill would be considered cost-neutral. If it was above this, it would be considered more expensive and cost-saving if below. If our hypothesis is rejected, we would report the incremental cost-effectiveness ratios for the applicable income groups.

The cost-effectiveness outcome was expressed as the incremental cost-effectiveness ratio (ICER) and reported in terms of net costs per quality-adjusted life-years (QALY) gained. The Restricted Mean Survival Times (RMST) were used to estimate in-trial life years both within and between each treatment group.[19,20] Life-year estimates were based on cardiovascular mortality since between 60% and 66% of all deaths were due to non-cardiovascular causes which was not expected to be influenced by CES-FDC pill treatment. Utility scores were calculated based on EQ-5D data collected from the HOPE-3 and TIPS-3 trials. These data were collected at baseline and the penultimate visit in HOPE-3 and in TIPS-3, at baseline, 2 year and at the end of the study. No quality of life (QoL) data was collected in PolyIran. For the purposes of pooling between studies, only baseline and penultimate (HOPE-3)/End of Study (TIPS-3) EQ-5D data were considered in our analysis. Utility scores for these timepoints were calculated using a US population value set.[21] Once utilities were obtained, they were applied to life year data to calculate QALYs.

Although a perspective that considers the impact to society as well as direct healthcare costs may be preferred, as these costs were not collected in any of the trials in the meta-analysis, they were not available for our analysis.[22] All costs and effects were discounted at 1.5% per year as the median follow-up of the meta-analysis was 5 years.

Sensitivity and subgroup analysis

While there are several polypill formulations currently available in different markets, no polypill is currently marketed with the same composition and strength as the one in our analysis using cheapest equivalent doses. Therefore, a sensitivity analysis was performed on the daily price of the CES-FDC pill used in our analysis. In this analysis the daily cost of the CES-FDC pill was altered by ±50%. All other costs in these analyses were the same as the base case and the analysis itself was performed in the same manner as the base case. The line of best fit for each income group was determined and the resulting equation of the line used to estimate the mean difference in cost across a range of daily CES-FDC pill costs. As an additional sensitivity analysis a discount rate of 3.5% for both cost and effect was also used. We also performed subgroup analyses on all clinical subgroups published in the meta-analysis: age (>66 years, 60–66 years, ≤60), systolic blood pressure (SBP) (>144 mm Hg, >130–144 mm Hg, ≤130 mm Hg), low-density lipoprotein (LDL) cholesterol (>135 mg/dL, >101–135 mg/dL, ≤105), body mass index (BMI) (≥30 kg/m^2, <30 kg/m^2), smoking status (Prior, Never), diabetes (No, Yes), hypertension (No, Yes), gender (male, female) and 10-year CVD risk (>22%, >12%–22%,≤12%) as estimated by Framingham risk score.[23]

Statistics

In this analysis categorical data are reported as frequencies and continuous data as means. Total costs are reported as mean costs per participant including the 95% Confidence Intervals (CIs). Since cost data are not likely to be normally distributed, bootstrapping (5000 samples) was used to calculate 95% CIs.[24] The bias corrected and accelerated methods were used for these analyses.[25] All analyses were performed with Stata (StataCorp. 2017. Stata Statistical Software: Release 15. College Station, TX: StataCorp LLC.).

Role of funding source

The Population Health Research Institute funded the meta-analysis our work is based on. The original trials included in the meta-analysis had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

	LMIC			UMIC			HIC		
	FDC pill	Control	Difference FDC pill-placebo (95% CI)	FDC pill	Control	Difference FDC pill-placebo (95% CI)	FDC pill	Control	Difference FDC pill-placebo (95% CI)
Non-study drug costs									
Events/Procedures	$204	$345	−$141 (−$192 to −$90)	$215	$373	−$158 (−$211 to −$105)	$727	$1261	−$534 (−$731 to −$337)
Concomitant non-study medications	$49	$84	−$35 (−$40 to −$30)	$148	$241	−$93 (−$108 to −$78)	$53	$88	−$35 (−$40 to $30)
Total non-study drug costs	**$253**	**$429**	**−$176 (−$228 to −$124)**	**$363**	**$614**	**−$251 (−$308 to −$194)**	**$780**	**$1349**	**−$569 (−$766 to −$372)**
Study drug (CES) costs	$522	$0	$522	$1089	$0	1089	$611	$0	$611
Total costs	**$775**	**$429**	**$346 ($294–$398)**	**$1452**	**$614**	**$838 ($781–$895)**	**$1391**	**$1349**	**$42 (−$155 to $239)**
Total costs (Discounted)	$646	$357	$289 ($246–332)	$1212	$511	$701 ($653–$749)	$1161	$1123	$38 (−$140 to $216)
Life -years	8.19	8.12	0.07 (0.04–0.10)	8.19	8.12	0.07 (0.04–0.10)	8.19	8.12	0.07 (0.04–0.10)
Utility score	0.86	0.86	0	0.86	0.86	0	0.86	0.86	0
QALYs	7.04	6.98	0.06 (0.04–0.08)	7.04	6.98	0.06 (0.04–0.08)	7.04	6.98	0.06 (0.04–0.08)
QALYs (Discounted)	5.86	5.81	0.05 (0.03–0.07)	5.86	5.81	0.05 (0.03–0.07)	5.86	5.81	0.05 (0.03–0.07)
ICER	$5767 ($5735–$5799)			$13,967 ($13,893–$14,041)			$700 (Cost-Neutral) ($662–$738)		
ICER (Discounted)	$5780 ($5748–$5812)			$14,020 ($13,946–$14,094)			$760 ($719–$801)		

FDC, Fixed Dose Combination.

Table 2: **Mean study and non-study drug costs per participant (2020 USD).**

Results

In LMIC the use of a CES-FDC pill reduced the mean cost of events and procedures (mean difference (MD): −$141; 95% CI: −$192 to −$90) as well as concomitant non-study medication (MD: −$35; 95% CI: −$40 to −$30) (Table 2). The total non-study drug cost per participant was $253 for the FDC pill and $429 for control (MD: −$176; 95% CI: −$228 to −$124). The CES FDC pill in LMIC was composed of atorvastatin 20 mg, lisinopril 20 mg, atenolol 100 mg and hydrochlorothiazide (HCT) 25 mg as these drugs were the cheapest equivalent substitutes. The daily cost for this CES-FDC pill plus aspirin is $0.35 per day. Based on our adherence estimates this would result in a mean study drug cost per participant of $522 (Table 2). Total costs in the CES-FDC pill group were $775 compared to $429 for control (MD: $346; 95% CI: $294–$398) (Fig. 1a).

Total savings from events, procedures and concomitant non-study medication were slightly more in UMIC ($251; 95% CI: −$308 to −$194). The CES-FDC pill used in our analysis for UMIC was assumed to contain simvastatin 40 mg, enalapril 20 mg, atenolol 100 mg and HCT 25 mg as these drugs were the cheapest equivalent substitutes in the UMIC. They had a daily cost of $0.73 with the addition of aspirin. This CES-FDC pill was also the most expensive of the three CES-FDC pills used in our analysis and resulted in a total mean cost per participant in the CES-FDC pill group of $1452 compared to $614 for control (MD: $838; 95% CI: $781–$895) (Fig. 1b).

In HIC, the CES-FDC pill significantly reduced event and procedure costs ($534 (95% CI: −$731 to −$337)). Total mean non-study medication savings were $569 (95% CI: −$766 to −$372) in HIC. The CES-FDC pill for these countries consisted of atorvastatin 20 mg, ramipril 10 mg, metoprolol 100 mg and HCT 25 mg with a daily cost of $0.41 with aspirin. The cost of this CES-FDC pill during the meta-analysis was $611 and resulted in a total mean cost per participant of $1391 for the FDC pill group compared to $1349 for control. This is a mean difference of $42 (95% CI: −$155 to $239) (Fig. 1c). Based on our prespecified definition, the bounds of cost neutrality in the present analysis are ±$67 (5% of $1349), thus the overall mean difference is cost neutral.

Cost-effectiveness analysis

Since the mean incremental costs in LMIC and UMIC were not cost-neutral or cost-saving, based on our criteria, we calculated the ICER for each income group. Participants in the FDC pill group experienced 2988 life-days (8.19 life-years) compared to 2965 life-days (8.12 life years) in the control group; a difference of 23 days (0.07 life-years; 95% CI: 0.04–0.10) over the trial period. The QoL results measured were equal between both groups at baseline (0.87) and at the final/penultimate visit (0.84). The average between both time points was 0.86 for both groups. Thus, the QALYs for each group were 7.04 and 6.98 for the CES-FDC pill and control group respectively. The incremental QALY was 0.06 (95% CI: 0.04–0.08) gained for the FDC pill group; for LMIC this results in an ICER of $5767/QALY, $13967/QALY for the UMIC group and $700/QALY for HIC.

Sensitivity and subgroup analyses

In our sensitivity analysis, varying the cost of the CES-FDC pill by ±50% in each income group had limited impact on the incremental costs. As did using a discounting rate of 3.5% for both cost and effect (Table 3, Supplementary Figure S1). The daily cost of a CES-FDC pill necessary to achieve no difference in total

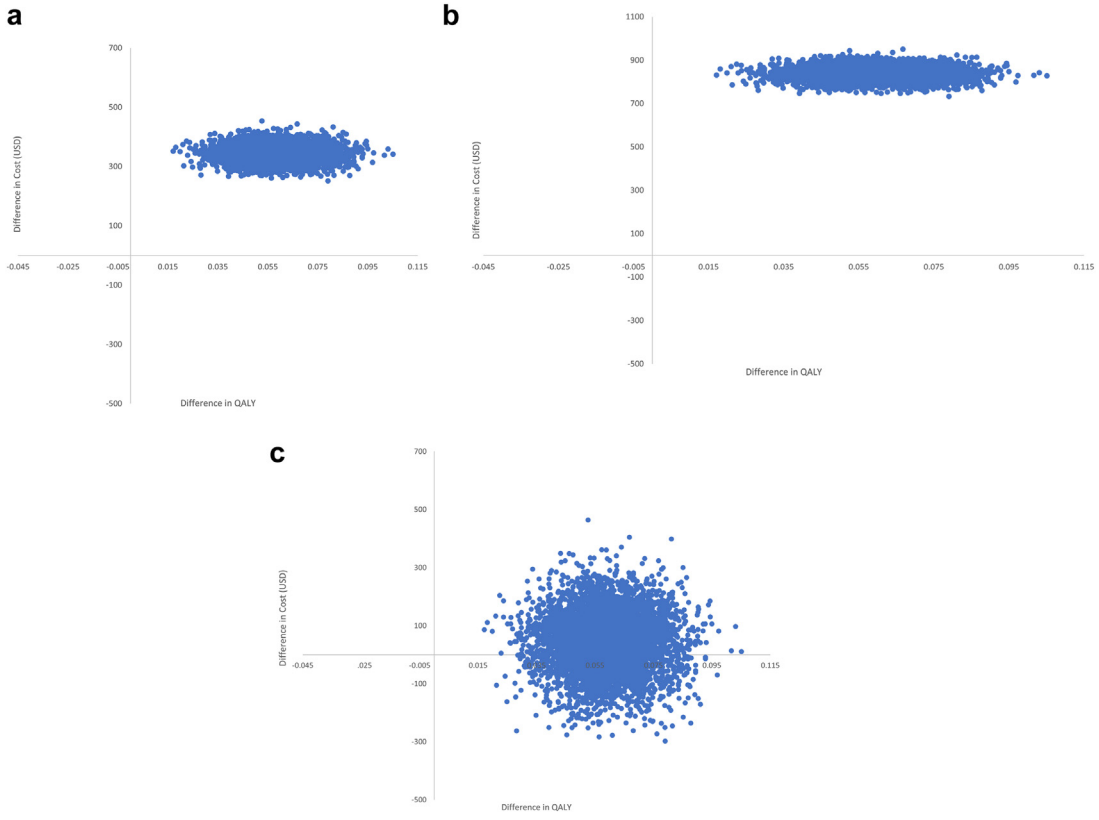

Fig. 1: **a–c: Base case bootstrap results on cost-effectiveness plane for a) lower middle income b) upper middle income and c) high income countries**. USD, United States Dollars; QALY, Quality Adjust Life Years.

mean incremental cost (i.e., mean difference = $0) in LMIC, UMIC and HIC is $0.12, $0.17 and $0.38 respectively.

In our analysis of the clinical subgroups, we found similar patterns across all regions with the estimated CVD risk greater than 22% having the lowest total incremental costs of all subgroups (Fig. 2a–c). The estimated CVD risk at 10 years is derived from many individual risk factors that were also included in our subgroup analyses. Therefore we decided to re-calculate the incremental QALYs for the estimated CVD risk at 10 years. The incremental QALYs were 0.01 (95% CI: −0.03 to 0.06), 0.04 (95% CI: 0.001–0.07), and 0.09 (95% CI: 0.04–0.14) for the lowest to highest risk tertiles respectively. The changes seen in QALYs reflect a difference in survival according to the estimated CVD risk. In all income groups, incremental costs for the highest risk tertile were lower than the base case results while the middle and low risk tertiles were associated with higher costs (Table 4). This resulted, in the highest risk tertile, better ICERs ($2033/QALY) in LMIC, ($7322/QALY) in UMIC to a cost saving situation (−$6000/QALY) in HI countries. On the other hand,

	LMIC			UMIC			HIC		
	FDC pill	Control	Difference FDC pill- placebo (95% CI)	FDC pill	Control	Difference FDC pill- Placebo (95% CI)	FDC pill	Control	Difference FDC pill- placebo (95% CI)
Base case	$775	$429	$346 ($294–$398)	$1452	$614	$838 ($781–$895)	$1391	$1349	$42 (−$155 to $239)
FDC pill −50% Cost	$514	$429	$85 ($33–$137)	$908	$614	$294 ($237–$351)	$1086	$1349	−$263 (−$460 to −$66)
FDC pill +50% Cost	$1036	$429	$607 ($555–$659)	$1997	$614	$1383 ($1326–$1440)	$1697	$1349	$348 ($151–$545)
Costs (Discounted 3.5%)	$530	$293	$237 ($201–273)	$994	$419	$575 ($536–$614)	$952	$921	$31 (−$114 to $176)
QALYs (Discounted 3.5%)	4.81	4.77	0.04 (0.02–0.06)	4.81	4.77	0.04 (0.02–0.06)	4.81	4.77	0.04 (0.02–0.06)
ICER (Discounted 3.5%)			$5925 ($5892–$5958)			$14,375 ($14,299–$14,451)			$775 ($733–$817)

Table 3: **Sensitivity analyses of Fixed Dose Combination (FDC) pill pricing on mean total costs per participant (2020 USD).**

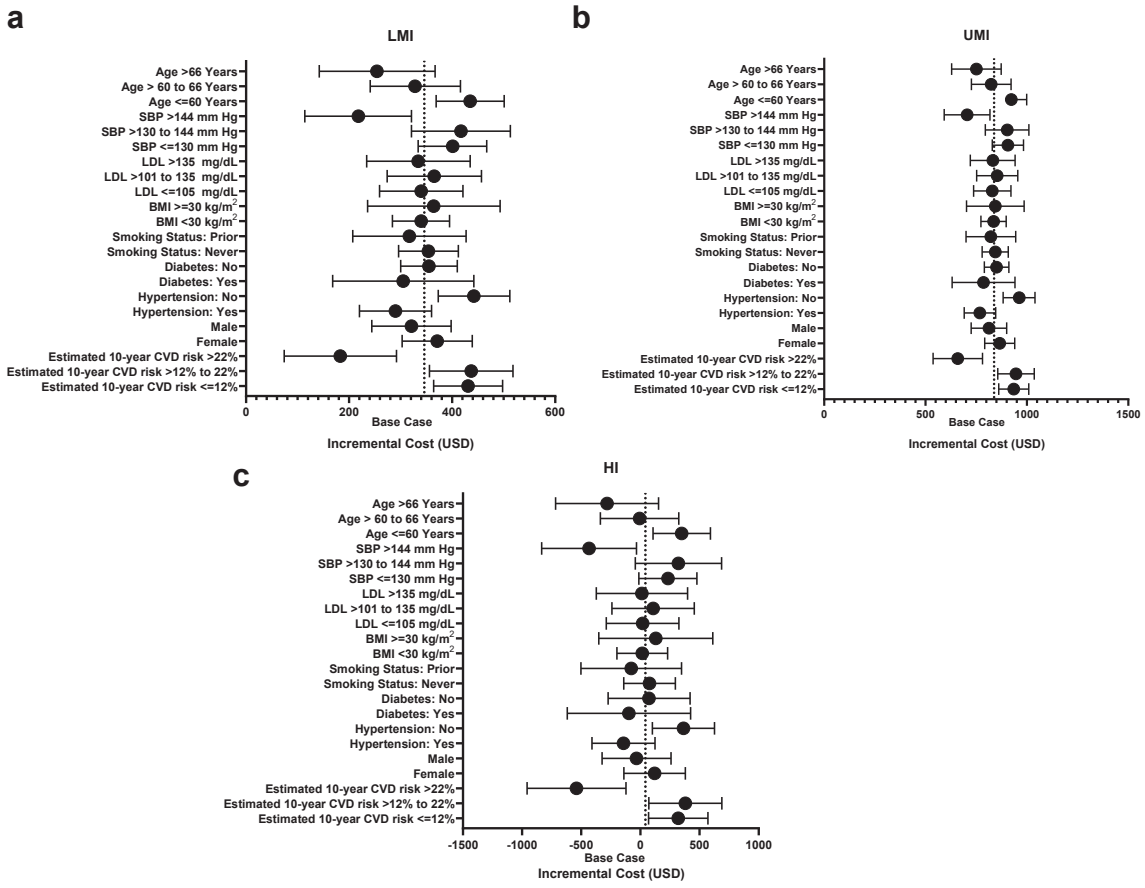

Fig. 2: **a–c: Forest Plot of Results of Subgroup Analyses for a) Lower Middle Income b) Upper Middle Income and c) High Income Countries (2020 USD)**. Data presented as Mean Cost with 95% CI. LMI, Lower Middle Income; UMI, Upper Middle Income; HI, High Income; USD, United States Dollars; SBP, Systolic Blood Pressure; LDL, Low-Density Lipoprotein; BMI, Body Mass Index; CVD, Cardiovascular Disease; LMIC, Lower Middle Income Countries; UMIC, Upper Middle Income Countries; HIC, High Income Countries; SBP, Systolic Blood Pressure; LDL, Low-Density Lipoprotein; BMI, Body Mass Index; CVD, Cardiovascular Disease.

results in lowest and middle tertiles are worse than the base case in all income groups. This interaction is the result of high-risk patients having more events and resources consumed and benefiting the most from the protective effect of the CES-FDC pill against placebo.

Discussion

In this in-trial economic analysis based on the meta-analysis of 3 large, long term, randomized trials, we demonstrate that a CES-fixed dose combination (FDC) pill (a statin, ACE-inhibitor or angiotensin receptor blocker, beta blocker and hydrochlorothiazide with aspirin) may

	LMIC			UMIC			HIC		
	Difference polypill-placebo (95% CI)	Incremental QALYs	ICER	Difference polypill-placebo (95% CI)	Incremental QALYs	ICER	Difference polypill-Placebo (95% CI)	Incremental QALYs	ICER
Base case	$346 ($294–$398)	0.06	$5767	$838 ($781–$895)	0.06	$13,967	$42 (−$155 to $239)	0.06	$700
Estimated 10-year CVD risk ≤12%	$431 ($364–$498)	0.01 (−0.03 to 0.06)	$43,100	$935 ($861–$1009)	0.01 (−0.03 to 0.06)	$93,500	$320 ($69–$571)	0.01 (−0.03 to 0.06)	$32,000
Estimated 10-year CVD risk >12%–22%	$437 ($356–$518)	0.04 (0.001–0.07)	$10,925	$946 ($856–$1036)	0.04 (0.001–0.07)	$23,650	$380 ($71–$689)	0.04 (0.001–0.07)	$9500
Estimated 10-year CVD risk >22%	$183 ($74–$292)	0.09 (0.04–0.14)	$2033	$659 ($537–$781)	0.09 (0.04–0.14)	$7322	−$540 (−$958 to −$122)	0.09 (0.04–0.14)	−$6000

Table 4: **Mean cost per participant (2020 USD) for estimated 10-year CVD risk subgroups.**

be a cost-effective strategy to prevent CVD according to each country's specific ICER threshold. This would be especially true for individuals at high risk of CVD where ICERs were consistently lower than our base case.

We used a deterministic approach combining results of the database of the FDC IPD meta-analysis with extensive data on costs for medication, events and procedures obtained from our previous economic analyses of HOPE-3 and TIPS-3.[17,18] The present study builds upon our earlier work on the cost-implications of HOPE-3 and TIPS-3 and pools these data with Poly-Iran's to give us access to the patient-data of over 18,000 participants that were included in the meta-analysis and more definitively addresses the cost implications and cost-effectiveness of the CES-FDC pill.

Our analysis focused on the FDC with or without aspirin versus control design as this was consist with the focus of the meta-analysis our current work is based on. In addition, any comparison of our present results with either the FDC + ASA or FDC-ASA subgroups would be difficult to juxtapose as the studies and the associated characteristics of the studies differ between all three comparisons.

As we had had access to patient-level data in the meta-analysis, we minimized assumptions used in our analysis. The ICER that we developed are reliable up to a mean of 5 years, but it is reasonable to extrapolate that, with a longer follow-up, the CES-FDC pill will be even more cost-effective as the rate of CVD events (Kaplan–Meier curves) experienced by the control group and the treatment group continue to diverge at the end of the follow-up.[7]

We used the cheapest equivalent substitute (CES) rather than using a specific FDC pill as no specific marketed polypills have been tested and the components of the polypill is different in each study included in the meta-analysis. We used the CES combination according to the lowest costs for each group of countries. This corresponds to a daily cost of $0.35, $0.73, and $0.41 in LMICS, UMICs and HICs respectively. The cost neutral results in the High Income Countries (HIC), are due to two factors: lower (relative to GDP and also in absolute terms) costs of medications in HIC than UMIC but also higher relative costs of events and procedures which were prevented by the FDC pill, providing further cost savings. The higher price of medication in the UMIC was unexpected. While the exact reasons for this probably differ between countries, it is a widespread situation as each individual component of the CES-FDC pill appears to be notably more expensive in UMIC than LMIC or HIC. A FDC pill at a lower price in UMIC would lead to significant savings and lower the incremental cost-effectiveness ratio.

It is expected that generic drug makers and distributors would be able to produce and distribute a FDC pill at a very lost cost through reductions derived from less packaging and distribution costs incurred of 1 pill rather than 4 or 5 components handled separately. The consolidation of these components would also result in increased adherence as has been demonstrated in trials such as SECURE.[26] However, we should recognize that drug manufacturers may charge a small premium for this benefit. The actual cost of any polypill manufactured and sold will have a significant impact on its cost-effectiveness and the impact of this can be explored with the equations of the lines of best fit we have provided for each income group. Unfortunately, commercially available polypills vary in formulation but mostly in price according to the country where the medication is produced and sold. Some countries produce cheaper FDC, below our threshold for cost-neutrality in LMI, UMI and HI countries. Governments and health leaders have a duty to provide an affordable FDC to their country, which could be achieved by selecting the most economical pharmaceutical producers or acquiring their products from other countries.

There have been few studies in the time frame we looked at that have evaluated the cost-effectiveness of a similar polypill in primary prevention.[27] Using a probabilistic approach, two studies in the United Kingdom (a HIC) reported a polypill was only cost-effective depending on price and population demographics.[28,29] Finding a common comparator across all studies is a challenge and may explain differences between our findings and other published literature. In addition, other possible explanations could be attributed to differences in treatment composition and costs across all studies. Our analysis used the cheapest equivalent substitute (CES) in each income group rather than a fixed composition FDC pill. As the availability of components differs between income groups, it may be more pragmatic to tailor the FDC pill for each income group. By using this CES approach, the FDC pill in our analysis represents the lowest priced option, based on the sum of all the individual components, in each income group while offering similar therapeutic outcomes.

Our analysis has limitations. First, our CES-FDC pill is not currently available in most countries but other formulations are available in some countries. Therefore, we estimated the incremental costs across a range of CES-FDC pill prices across multiple country income levels where a polypill would be considered cost-effective for primary CVD prevention strategy; setting a target for policy and drug makers. Secondly, only direct health care system costs were included in this analysis. Cost items that were not collected in our analysis include out of hospital patient costs, and nonmedical costs such as loss of productivity and the time provided by family and other caregivers. Such information would make the CES FDC pill even more economically attractive and these societal benefits should further incentivize investment of broad population polypill strategy.

While the National Institute for Health and Care Excellence (NICE) in the UK agrees than an ICER less

than £20,000/QALY should be considered cost-effective and in the US the ACC/AHA believes that an ICER below $50,000 is of high value,[30] these values are not likely to be appropriate for LMI and UMI countries and many of these countries do not have formal, published cost-effectiveness thresholds. In 2001 the Commission on Macroeconomics and Health suggested that an ICER below a country's GDP/capita was considered very cost-effective and an ICER between one and three times a country's GDP/capita was cost-effective.[31] Using this criterion, our findings would be cost-effective in all income groups. However, criticisms raised regarding the use of this approach as a definitive decision-making tool used independently of any other evidence[32,33] means that determination of an appropriate cost-effectiveness threshold for LMI and UMI countries is still a matter of contention among health economists. In 2016, estimates of cost-effectiveness thresholds for a number of countries using opportunity costs suggested that World Health Organization thresholds were too high and the threshold for many countries would be less than a country's GDP/capita.[34] It has more recently been proposed that a method of determining country-specific thresholds based on per capita health expenditures and life expectancy or healthy life expectancy could be used.[35] As neither of these methods has been widely adopted yet, some health agencies in LMI and UMI countries have recommended a threshold equal to the country's GDP per capita.[36–39] Overall, there is no widely accepted approach to determine country-specific threshold for all countries, but each country and their local decision makers should establish their own threshold (if not already done) according to their economic status and for their health priorities addressed.

In conclusion the FDC pill produced at CES costs is cost-neutral in HIC. Governments of LMI and UMI countries should assess these results based on the ICER threshold accepted in their own country and own specific health care priorities but should give serious consideration to adopting this strategy for patients with high CVD risk as a first step.

Contributors

All authors have read and approved the final version of the manuscript. AL, WT, PJ and PG have verified the underlying data.

AL designed and conducted the analysis as well as reviewed and assisted with the creation of the manuscript.

WT assisted with design of the study, conducted the analysis, and assisted with the creation of the manuscript.

PJ reviewed the manuscript and provided valuable feedback as the principal investigator of the FDC meta-analysis.

PG was responsible for data curation of the FDC database and reviewed the manuscript.

MH reviewed the manuscript and provided significant feedback which aided in its development.

GR helped with data collection and curation of the PolyIran database and reviewed the manuscript.

RZ helped with data collection and curation of the PolyIran database and reviewed the manuscript.

PL-J reviewed the revised manuscript and provided feedback which aided in its development.

PP reviewed the revised manuscript and provided feedback which aided in its development.

DX reviewed the revised manuscript and provided feedback which aided in its development.

AA reviewed the revised manuscript and provided feedback which aided in its development.

AD reviewed the revised manuscript and provided feedback which aided in its development.

HG reviewed the revised manuscript and provided feedback which aided in its development.

SY assisted with the design of the study and assisted with creation of the manuscript.

Data sharing statement

Individual participant data will not be made available. Other requests for data will be considered upon receipt by the corresponding author.

Declaration of interests

AL, WT, PJ, PG, RM, GR, PL-J, PP, AA, AD and HG have no conflicts to declare.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2024.102651.

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