Modeling the cost effectiveness and budgetary impact of Polypills for secondary prevention of cardiovascular disease in the United States

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Background There is underutilization of appropriate medications for secondary prevention of cardiovascular disease (CVD).

Methods Usual care (UC) was compared to polypill-based care with 3 versions using a validated micro-simulation model in the NHANES population with prior CVD. UC included individual prescription of up to 4 drug classes (antiplatelet agents, beta-blockers, renin-angiotensin-aldosterone inhibitors and statins). The polypills modeled were aspirin 81 mg, atenolol 50 mg, ramipril 5 mg, and either simvastatin 40 mg (Polypill I), atorvastatin 80 mg (Polypill II), or rosuvastatin 40 mg (Polypill III). Baseline medication use and adherence came from United Healthcare claims data.

Results When compared to UC, there were annual reductions of 130,000 to 178,000 myocardial infarctions and 54,000 to 74,000 strokes using Polypill I and II, respectively. From a health sector perspective, in incremental analysis the ICERs for Polypill I and II were $20,073/QALY and $21,818/QALY respectively; Polypill III was dominated but had a similar cost-effectiveness ratio to Polypill II when compared directly to usual care. From a societal perspective, Polypill II was cost-saving and dominated all strategies. Over a 5-year period, those taking Polypill I and II compared to UC saved approximately $12 and $6 per-patient-per-year alive, respectively. Polypill II was the preferred strategy in 98% of runs at a willingness to pay of $50,000 in the probability sensitivity analysis.

Conclusions Use of a polypill has a favorable cost profile for secondary CVD prevention in the United States. Reductions in CVD-related healthcare costs outweighed medication cost increases on a per-patient-per-year basis, suggesting that a polypill would be economically advantageous to both patients and payers. (Am Heart J 2019;214:77-87.)

Over half of heart attack and stroke survivors are not taking one or more indicated medications for secondary prevention, which includes up to one each of four medication classes for those with ischemic heart disease: anti-platelet agents, beta-blockers, angiotensin converting enzyme inhibitors (ACE-I) or angiotensin receptor blockers (ARB), and statins. Therefore, we face a challenge to improve both the initiation of and patient adherence to effective medications.

The "polypill" concept for secondary prevention, introduced as early as 2001,[1] suggests that combining the medications that reduce CVD risk into a single formulation would help the health sector prescribe and dispense drugs for CVD prevention while also improving patient adherence.[2,3] When taken in a fixed dose combination, these medications lead to similar reductions in the expected target risk factor (blood pressure, heart rate, LDL-cholesterol, or platelet reactivity) compared to when taken separately.[4,5] The UMPIRE,[5] FOCUS[6] and other trials[7,8] also found that those taking a fixed-dose combination medication are more adherent to their overall regimen compared to taking individual medications.

All of the polypill trials in people with established indications for the component medicines were focused

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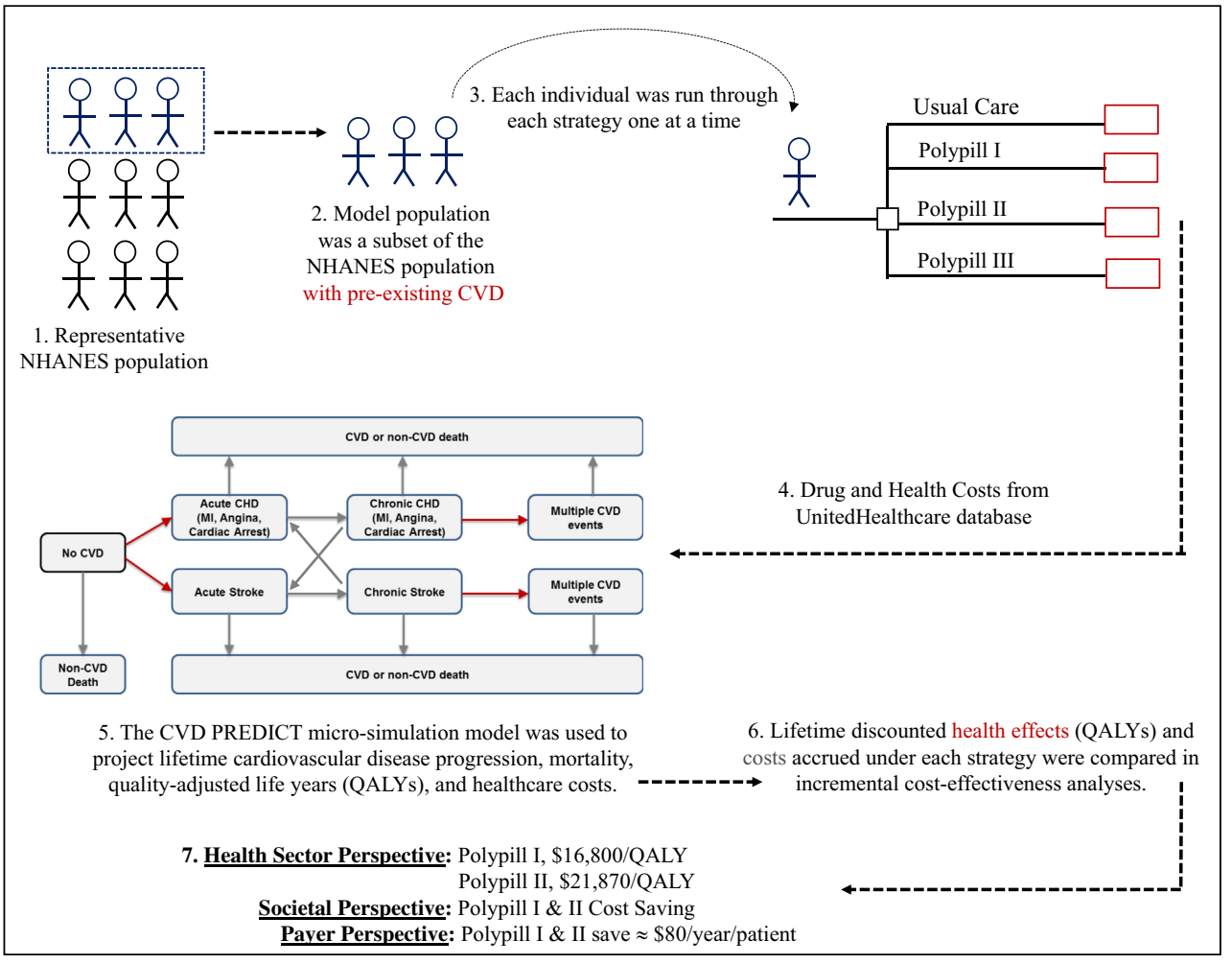
on whether adherence increased or whether expected intermediate outcomes such as blood pressure or LDL-cholesterol were affected—the trials were not designed to assess on cardiovascular events, and were too small and short-term to assess such effects. Further, the overall health benefits, the costs, and the cost-effectiveness of such an approach in secondary prevention in the United States are still unknown. In addition, private payers who insure over half of the US population who move in and out of plans due to employment transitions, have a shorter time horizon for decision making and thus need to understand the impact on a per-patient-per-year cost budget prior to supporting coverage. In this study, we compared three different polypill combinations and usual care strategies for secondary prevention to assess the health and financial impact in model-based incremental cost-effectiveness analyses and budgetary impact analyses, including a health care, societal and payer perspective.

Methods

Strategies compared

We compared usual care to three different versions of a polypill for secondary prevention for those with prior ischemic heart disease or stroke. We used a previously developed and validated computer-based micro-simulation model[9] using the NHANES population with prior CVD as depicted in Fig.1. The CVD PREDICT model was validated in 2017 to predict CVD events with current demographic trends, predicted risk of events based on the Framingham risk equations, current rates of medication and procedure usage as well as secular trends in CVD risk factors as well as in a commercial- and Medicare-aged population that reflects the Usual Care population for this model. We assume that the simulations for this Polypill analyses reflect the same trends with the exception of the higher used of the medications associated with higher medication use.

Figure 1



[Schematic of cost-effectiveness analyses options and model.]Source/Notes: SOURCE [Authors own depiction of model.]

Given the absence of such polypills in current use, validations of the model for these scenarios are not possible. Usual care included the individual prescription and their rate of use of up to four medications from recommended medication classes for secondary prevention. These include antiplatelet agents, beta-blockers, inhibitors of the renin-angiotensin aldosterone system (RAASs) and statins. For fixed dose combination therapies, there are many combinations and permutations of the individual agents within the four classes of medication that could potentially come to market. While many formulations are possible, a significant variation in combinations is in the choice of statin because they vary the in efficacy and/or price. Secondly, we evaluated combinations that had been used in prior trials. For simplicity, the polypill components we modeled are aspirin 81 mg, atenolol 50 mg, ramipril 5 mg, and either simvastatin 40 mg (Polypill I), atorvastatin 80 mg (Polypill II), or rosuvastatin 40 mg (Polypill III). For example, metoprolol in its extended release form could be substituted for atenolol at only $50 to $100 more per year with prices continuing to trend down; we tested its substitution in a sensitivity analysis; and lisinopril can be substituted for ramipril for $20 per year lower costs.

Perspectives

We evaluated the different polypill options in three different perspectives. We assessed the intervention from the Health Care Perspective first, accounting for the health effects of the intervention and all direct health care related expenses. Second, as recommended by the Second Panel on Cost-Effectiveness in Health and Medicine,[10] we evaluated the intervention from the Societal Perspective based on the methodology used by Kim et al. adding additional costs related to patient time lost, travel-related costs, productivity gains and consumption expenses.[11] Further, the decision to provide a medication as a benefit or place it on a payer's formulary is guided in part by its budget impact. Further, policy makers may be interested in the additional costs per patient not just aggregate costs accrued by all participants over their lifetime as they are totaled in the healthcare perspective. Thus, we also conducted a budget impact analysis evaluating the cost per-patient-per-year over a 5-year period (which is a time horizon used by payers to make decisions regarding changes in supporting new drug benefits).

Medication usage and adherence

For the Usual Care base-case we estimated baseline medication initiation rates from claims data of 4 million individuals with a prior diagnosis of ischemic heart disease, stroke, or peripheral vascular disease from United Healthcare (UHC); these are the same criteria used in the UMPIRE trial. Within this population, we then evaluated the proportion of patients who had pharmacy claims for either a beta-blocker; an angiotensin converting enzyme inhibitor or an angiotensin receptor blocker; or a statin (HMG coA reductase inhibitor). Because claims databases underestimate the use of aspirin (often bought over the counter), we estimated aspirin use from national data including NHANES aspirin use questions, showing its proportion used by those with the prior eligible CVD conditions.[12-14] We further assumed that aspirin initiation was independent of adherence to the other three classes of medications. For the Usual Care strategy, we then determined the proportion of people that were taking no medications, taking only one of the four individual drug classes, taking all drug classes, or taking one of the 10 possible combinations of the four drug classes: a) six possibilities for taking two of the four drug classes; b) four possibilities for taking three of the four drug classes. The results of this distribution are described in Figure II below. For the Polypill strategies, we assumed that all eligible patients start out on the medication.

However, because adherence also declines over time we modeled average declines in adherence over time based on the mean of prior observations in studies with longer follow-up. Baseline adherence rates over time for secondary prevention of individual drug classes are listed in the Appendix in eTable 5, which includes baseline rates for Usual Care arm and the increase in adherence in the polypill arms, as well as rates of decline for both arms through the first 3 years, which then remains constant after the end of the third year.[15] We modeled the polypill's impact on health, based on results from the UMPIRE trial, which showed a 26% increase in medication adherence compared to an average adherence of the individual drug classes in Usual Care. A recent Cochrane review[8] on fixed-dose combination therapies (including the polypill formulation used in the UMPIRE trial) estimated the increase in adherence could be 44% with a range from 26% to 65% for those with CVD. We chose the lower estimate to be conservative.

Individual medicine effectiveness data

We assume a class effect for the reduction in CVD based on previous meta-analyses on reductions in stroke- and ischemic heart disease-related deaths, for each medication included in the polypill.[16-19] For aspirin, beta-blockers, and RAAS-inhibition, we use the published results reported in the Appendix (eTable 3)[15] for both those in the Usual Care and the Polypills if they were adherent to the medications. The relative risk reduction for simvastatin is also listed in the Appendix (eTable 3).[15] LDL cholesterol reductions for atorvastatin and rosuvastatin at high intensity doses are similar (with rosuvastatin lowering LDL about 4% more) and both significantly greater than simvastatin at its maximum recommended dose of 40 mg. If a patient was taking atorvastatin (80 mg) or rosuvastatin (40 mg), we increased the risk-reduction in proportion to the additional 20% LDL reduction assumed from taking high doses of these medications

compared to simvastatin.[11,20,21] The relative risk reduction was then based on the overall consistency in the meta-analysis of a linear function of relative risk reduction and LDL which is consistent per mmol/L reduction regardless of agent used.[16] Given trial evidence indicating lack of interaction, the relative risk reductions from each of the four drug classes were independent.[22-27] This estimation, which is used in other modeling studies,[28-30] is based on the fact that the major trials used in the meta-analyses show the effect of each class of medications on the background of the other 3 medication classes in regular use.[16,17,31]

Cardiovascular disease micro-simulation model

We used the CVD-PREDICT model[9] – a previously developed and validated cardiovascular disease micro-simulation model – to project the lifetime health outcomes (cardiovascular disease progression and events, life expectancy, and quality-adjusted life years [QALYs]) and cardiovascular disease-related costs of adults (starting age 40-75 years) in the United States. Further details of the model are described in the Appendix.[15] The model was populated with individuals with a history of CVD from the 2005-2012 waves of the nationally representative National Health and Nutrition Examination Surveys (NHANES).[32] Appendix (eTable 2)[15] lists the base-case model inputs regarding risk reductions from the different medications.

Model outputs

The CVD PREDICT model keeps track of every CVD event for every individual run through the model, including deaths, average life expectancy, and yearly prevalence of every disease state. For cost-effectiveness analyses, the model outputs average lifetime per-person discounted costs and quality-adjusted life years (QALYs). The Appendix contains more details on the inputs specific to cost-effectiveness analyses including adverse costs associated with statin use (Appendix eTable 6) and utility values (Appendix eTable 9).[15]

Health sector costs

CVD event costs were age-based, with costs based on commercial insurance paid claims applied to patients under 65 years of age and costs based on Medicare claims for patients aged 65 years and older. Hospitalization costs for incident CVD events were based on the UHC database with prices for each event type listed in Table I for either commercial or Medicare claims. Paid claims were used to reflect actual payments made for the budget impact analysis. Annual chronic costs excluding incident CVD events are also listed in the Appendix.[15]

Medication costs

The annual cost per prescription of the four components of the medications are listed in Table I using the cost for generic medications paid for by United Health; aspirin was based on the average wholesale rates published in the Red Book. A typical individual taking all four of the individual components would spend up to $430 per year using generic medications. Costs for the polypills include the cost of the individual components plus a 10% increase to reflect the production cost of combining the medications into one pill and regulatory approval. Individuals taking either Polypill I, II, or III

Table I. Mean costs; United Healthcare Population

	Commercial ($)	Medicare ($)	Total Annual ($)*
Acute Events			
MI	43,222	28,004	-
Angina	26,624	21,395	-
CVA	44,069	27,900	-
Repeat MI	28,404	13,186	-
Repeat CVA	29,605	13,437	-
CABG procedure	76,889	42,433	-
PCI procedure	36,222	18,691	-
Annual Chronic Care Costs†			
IHD	13,699-16,941‡	11,843-15,085‡	-
CVA	22,555-25,797‡	15,959-19,201‡	-
Drug Formulation			
Usual Care Medications§	-	-	433.20
Polypill I	-	-	501.60
Polypill II	-	-	642.05
Polypill III	-	-	793.45

† Excludes acute events and includes follow-up testing, rehabilitation, non CVD events, and outpatient care.
‡ Includes all annual non-CVD costs; lower end of range indicates no recent event in prior 3 years, upper range indicates event within prior 3 years.
§ Generic prices for current use patterns of individually prescribed medications.
MI: myocardial infarction; CVA: cerebrovascular accident; CABG: coronary artery bypass grafting; PCI: percutaneous coronary intervention; IHD: Ischemic heart disease (angina, MI, or cardiac arrest).
* Includes dispensing and/or manufacturing costs; assumes 100% medication compliance.

would spend annually $500, $640, or $793 respectively. Slight reductions due to the reduced number of dispensing fees were estimated but they are relatively insignificant, averaging only a $1-2 per year difference assuming monthly (or 90-day) prescription rates. In the base case we assumed pricing at 2018 levels for all drugs. A summary of the annual drug costs for full compliance with each strategy are listed in Table I.

Societal perspective costs

In addition to health sector costs, we incorporated patient costs for time spent transporting to and receiving care, labor market earnings gained, and future consumption unrelated to health. Cost of patient time and travel costs and tables with the workforce participation rate, average wages, and consumption by age that were used in the model are listed in the Appendix.[15]

Cost-effectiveness and budgetary impact analyses

We used incremental cost-effectiveness analysis from the healthcare system perspective to compare each of the three polypill formulations individually to usual care. In doing so, we assumed that only one polypill formulation would be available in practice. It is possible that a decision-maker could choose among many polypill formulations, however, so we also performed a conventional incremental cost-effectiveness analysis to compare all four strategies (three polypill formulations and usual care) assuming they were mutually exclusive options. In budgetary impact analyses, we focused on the healthcare cost differences for scenarios with and without the polypill using a 5-year time horizon, and reported our results on a per-patient-per-year basis, a relevant metric for private healthcare payers in the United States. Costs for the budget impact analysis were undiscounted costs. Costs for the societal and healthcare system perspective were discounted at an annual rate of 3%.

Sensitivity analyses

We focused sensitivity analyses on the cost and effectiveness inputs directly related to the polypill strategies, such as effects on medication adherence. Overall model uncertainty was assessed in a probabilistic sensitivity analysis (PSA). In the PSA, 1000 random values for key model parameters from pre-specified probability distributions (Appendix eTable 10) for all inputs.

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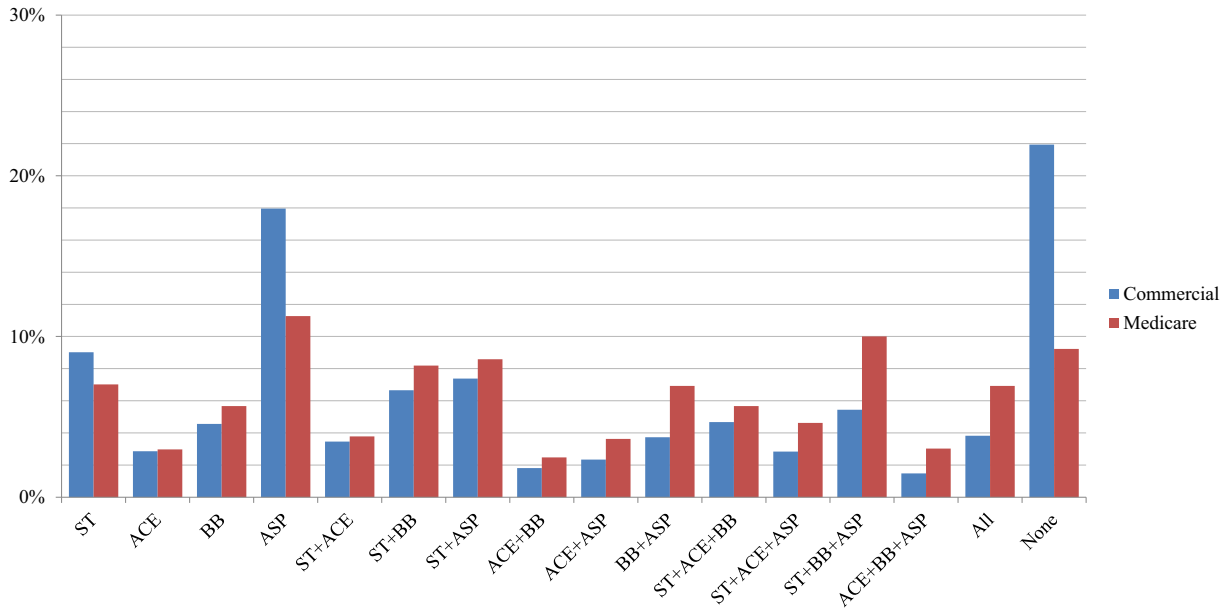
Results

Baseline population characteristics

The mean age (64.9 years), sex distribution (45.7% female), total cholesterol (185 mg/dl), systolic blood pressure (128.7 mmHg), smoking rate (21.7%), diabetes prevalence (31.8%), and prior MI (42.3%), angina (15.8%) and stroke (41.9%) prevalence were typical of the US adult population with CVD. Weighted baseline characteristics for the NHANES 2005-2012 population, are reported in the Appendix.[15]

Figure 2



[Medication distribution.] Source/Notes: SOURCE [Data from United Health Care] NOTES [ST: statin; ACE: angiotensin-converting enzyme; BB: beta blocker; ASP: aspirin.].

Table II. Cardiovascular disease and other health effects

	Usual Care	Polypill I Simvastatin	Polypill II* Atorvastatin
One-Year for US Adult Population			
MI Events	717,740	588,660	540,040
CVA Events	516,940	463,180	442,620
Statin-Induced Diabetes	3040	9800	9800
Lifetime for US Adult Population			
MI Events	10,185,040	9,557,340	9,310,000
CVA Events	7,488,040	7,088,420	6,992,320
Statin-Induced Diabetes	29,880	88,580	89,040
Life Expectancy (y)	78.37	78.78	78.93

MI: myocardial infarction; CVA: cerebrovascular accident.
*Polypill III similar results not shown.

The medication usage rates for Usual Care are based on the rates of usage derived from UHC data Fig.2. Over 20% of patients with private insurance and 10% of Medicare participants are taking none of the recommended medications, while less than 5% and 10% respectively are taking all four of the medications. The majority of patients were taking either one or two medications only with aspirin being the most commonly used single agent and ACE-Inhibitors the least used.

Morbidity, mortality, and life expectancy gains

When compared to Usual Care on an annual basis, there were reductions of nearly 6450 (18%) or 8815 (24.8%) myocardial infarctions per million population for those taking Polypill I (simvastatin) or Polypill II (atorvastatin), respectively. Additionally, there were reductions of 2700 (10.4%) or 3700 (14.4%) strokes compared to usual care for the Polypill I and II respectively. On a national level, these reductions were 130,000 to 178,000 fewer myocardial infarctions and 54,000 to 74,000 fewer strokes per year with the adult population with pre-existing CVD using Polypill I and II, respectively (Appendix eTable 11).[15] Reductions with Polypill III (rosuvastatin) were similar to those evaluated with atorvastatin.

The model predicted that there would be 627,700 to 875,000 fewer myocardial infarctions and 400-500,000 fewer strokes using Polypill I, II, or III (Table II)[15] over a lifetime horizon for a cohort of current adults in the United States. Polypill I had the lower health benefit while Polypill II or III both had greater benefits. Over the course of a lifetime, the modeled life expectancy of those taking Polypill I (simvastatin), or either Polypill II (atorvastatin) or III (rosuvastatin), was extended by approximately 4 and 6 months respectively when compared to Usual Care (Table II).[15]

Over the course of a lifetime, patients in the Usual Care strategy had $186,493 in allowed (actual amounts paid to providers and suppliers) discounted costs related to acute events, chronic care and medications (Table III). The majority of these costs are related to chronic outpatient costs and testing costs ($171,528; 91%) with lesser amounts being attributed to acute hospitalizations ($14,264; 8%) and the smallest proportion being additional spend on medications ($701; 1%). Compared to Usual Care, Polypills I, II, and III increased claims discounted costs over a lifetime by $3750, $5380, and $6173 respectively. However, the net increase in Polypill I was a result of decline in acute care costs of $921, an increase in drug costs of $1630, and an increase in chronic care costs by about $3041. The increase in chronic care costs, however, was primarily driven by the increased number of people alive in the Polypill strategy not because the chronic costs per patient increased. Similar findings were present for Polypill II and III, when compared with Usual Care, where drug costs increased (most for Polypill III by $3181 over the lifetime) and acute care costs per person declined and chronic costs overall increased but driven by the larger number alive each year.

Cost-effectiveness results

Health sector perspective. On a population-level, the polypill strategies increased costs and QALYs compared to Usual Care. The incremental cost-effectiveness ratio for Polypill I compared to Usual Care was $20,073 per quality-adjusted life-year (QALY) (Table III). Polypill II had an incremental cost-effectiveness ratio of $21,818/QALY compared to Polypill I. Polypill II dominated Polypill III (i.e., produced similar QALYs but lower costs). If the

Table III. Cost-effectiveness results: health sector perspective.

CEA	Discounted Cost	Incremental Cost	Discounted QALY	Incremental QALY	ICER
Polypills Compared to Previous Strategy					
Usual Care	$186,493	—	8.12	—	—
Polypill I	$190,243	$3750	8.31	0.19	$20,073
Polypill II	$191,873	$1630	8.38	0.07	$21,818
Polypill III	$192,666	$793	8.38	0	Dominated
Each Polypill Compared to Usual Care					
Usual Care	$186,493	—	8.12	—	—
Polypill I	$190,243	$3750	8.31	0.19	$20,073
Polypill II	$191,873	$5380	8.38	0.26	$20,571
Polypill III	$192,666	$6173	8.38	0.26	$23,603

QALY: quality adjusted life year; ICER: incremental cost-effectiveness ratio.

Table IV. Cost-effectiveness results: societal perspective.

CEA	Discounted Cost	Incremental Cost	Discounted QALY	Incremental QALY	ICER
Each Polypill Compared to Usual Care					
Usual Care	-$229,653	—	8.12	—	—
Polypill I	-$232,680	-$3027	8.31	0.19	Cost-saving
Polypill II	-$233,578	-$3925	8.38	0.26	Cost-saving
Polypill III	-$232,785	-$3132	8.38	0.26	Cost-saving
Polypills Compared to Previous Strategy					
Usual Care	-$229,653		8.12	—	—
Polypill II	-$233,578	-$3925	8.38	0.26	Cost-Saving

QALY: quality adjusted life year; ICER: incremental cost-effectiveness ratio.

Polypill versions were not regarded as competing, mutually exclusive options, but rather as alternative scenarios of a potential type of polypill, then each would be compared to Usual Care in separate incremental cost-effectiveness analyses, resulting in incremental cost-effectiveness ratios of $20,571/QALY and $23,603/QALY compared to Usual Care for Polypill II and Polypill III, respectively (Table III).

Societal perspective

After accounting for health and non-health care costs and benefits related to productivity, the total societal costs of all strategies were cost saving, reflecting that productivity gains outweigh healthcare related costs (Table IV). After inclusion of patient costs, non-health care consumption, and productivity gains, net discounted savings are over $400,000 for a lifetime compared to discounted life-time CVD health care costs of over $180,000. When all strategies are compared with each other, Polypill II is cost-saving and dominates all other strategies. When comparing one at a time with Usual Care, Polypill I and II are both cost-saving interventions compared to Usual Care with discounted savings of $3027 and $3925 respectively over a life-time. Polypill III was also cost-saving compared to Usual Care if generic pricing is assumed but not cost-saving at brand name pricing, though would have an ICER below the willingness to pay threshold of $24,364/QALY gained.

Expenditures and budgetary impact analysis results

In the lifetime analysis, costs increased primarily due to increases in chronic costs accrued by patients living longer. To assess whether per-year costs were also greater, we reviewed the results on a cost per-patient-per-year alive. When we evaluated costs per-patient-per-year alive, overall costs decline when comparing either Polypill I or Polypill II to Usual Care. Over a 5-year period, those taking the Polypill II compared to Usual care saved net approximately $6 per individual per patient year (Table V). Results for 1 and 10 years were similar. This savings was achieved through a reduction in acute care costs by nearly $200 per patient year and reductions in chronic costs of $83 annually, offset by an increase in annual medication costs of $272. Overall net savings were similar for Polypill I at $12 per patient year, but with smaller savings in acute costs offset by smaller increases in medication costs. Polypill III was similar to Polypill II except that drug costs where higher. If rosuvastatin is purchased at prices similar to atorvastatin from the beginning, then the two options are similar. Also, the benefits were more significant in terms of cost reductions for those under 65 and in Commercial Plans because their claims costs per acute admission to hospital were greater.

Sensitivity analyses

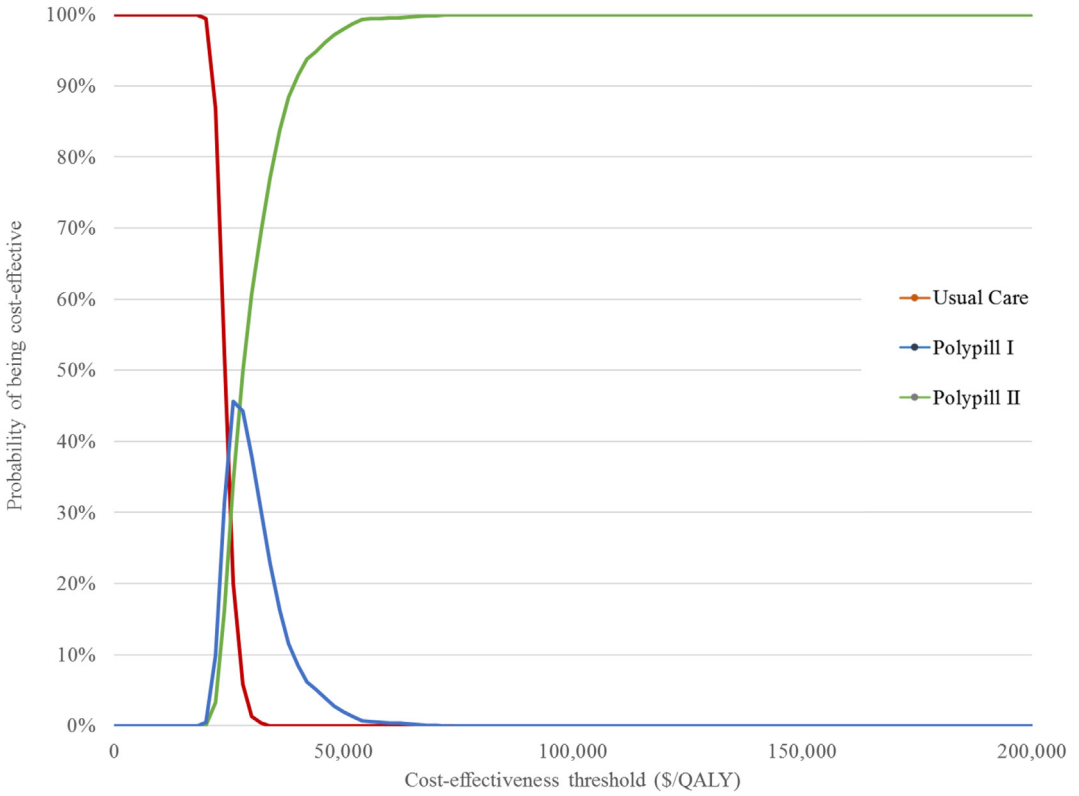
We tested whether the results were affected by a series of adjustments to our baseline assumptions and found

Table V. Cost results per patient year — 5-year model

Average undiscounted cost per patient year ($)		ALL AGES				UNDER 65				OVER 65			
		Total Cost*	acute only	chronic only	drug only	**Total Cost***	acute only	chronic only	drug only	**Total Cost***	acute only	chronic only	drug only
Usual Care		**17,973**	1427	16,460	86	**20,062**	1892	18,100	70	**16,006**	995	14,910	101
		Difference from Usual Care				**Difference from Usual Care**				**Difference from Usual Care**			
Polypill I	simvastatin	**–12**	–145	–63	195	**–54**	–199	–58	203	**45**	–92	–51	188
Polypill II	atorvastatin	**–6**	–196	–83	272	**–63**	–266	–75	278	**73**	–126	–68	267
Polypill III	rosuvastatin	**77**	–196	–83	355	**17**	–266	–75	358	**158**	–126	–68	352

*Total Cost is sum of acute, chronic, and drug costs.

Figure 3



[Cost-effectiveness Acceptability Curve for the Probabilistic Sensitivity Analysis.] Source/Notes: SOURCE [Authors' analysis of data from Harvard Predict Model]

that the results were minimally affected by changing the level of baseline adherence relatively by 25%. Further, when we tested the adherence boost of the Polypill by an additional 15% (from 26% to 41%), the impact was relatively small. Increasing or decreasing the cost of the polypill by 30% to 50%, such as for example substituting metoprolol for atenolol, had a larger impact on the cost-effectiveness ratio, increasing it or decreasing it by 15% to 33% respectively. Changes in the dispensing fee had minimal impact. All one-way sensitivity analyses are reported in the Appendix (eTable 11).[15] In a probabilistic sensitivity analysis (Fig.3) Polypill II was optimal at 98% of the strategies at a willingness to pay of $50,000/QALY and nearly 100% at $150,000/QALY.

Conclusions

Our model-based cost-effectiveness and budgetary impact analyses suggest that use of the polypill would have a favorable economic profile for secondary CVD prevention in the United States. Incremental cost-effectiveness ratios from the health sector perspective for different formulations of the polypill fell well below conventional benchmarks for the United States (<$50,000-$150,000/QALY)[33] for population-level results with a lifetime horizon. From a societal perspective when assuming generic pricing, all three polypills were cost-saving compared to Usual Care due to increases in productivity gains. Whereas Polypill III (using brand name prices) was no longer cost-saving but remained highly cost-effective using ACC/AHA recommended cost-effectiveness thresholds.[33] Furthermore, reductions in CVD-related healthcare costs outweighed medication costs increases on a per-patient-per-year alive basis, which suggests that a polypill made up of generic medications would be economically advantageous to payers that retain their members even in the short term as well as over the long term.

Results from our analyses show that use of any of the three hypothetical polypills we modeled would lead to significant reductions in both morbidity and premature mortality. These actions would go a long way to achieving goals set by the Million Hearts program initiated by the US Department of Health and Human Services, as well as meet many of the HEDIS measures (such as use of beta-blockers and statins for those with CVD history). On an annual basis, between 130,000 and 180,000 myocardial infarctions and between 55,0000 and 75,000 strokes

could be prevented if any one of the polypills were used in the whole US adult population eligible for secondary prevention with a prior history of coronary heart disease or stroke. Given that nearly half of all out-of-hospital myocardial infarctions are fatal, significant reductions in premature mortality would be gained by use of any of the polypills. For any individual, life expectancy could be increased by an additional 6 months by using any of the proposed formulations. Formulations with either atorvastatin or rosuvastatin would yield the greatest improvements in health compared to the polypill with simvastatin, but all three would perform better than Usual Care. Considering that in the last 35 years in the US, all health-related interventions combined—both medical and behavioral—have resulted in improvements per year, on average, of less than 2 months gained in life-expectancy, the expected gains of 6 months of life expectancy from using a polypill is quite impressive.[34]

Differences in costs for interventions depend on perspective as well as category. On an annual basis, acute CVD event-related costs were lower for all of the Polypills compared to Usual Care due to reduced numbers of acute events. Medication costs were higher for the Polypills, both because they include the cost of four medications, compared to a range from zero to four medications used in the Usual Care strategy, and because of increased refills owing to improved adherence and extended life expectancy. Lifetime discounted costs on a population level were higher for the Polypill strategies compared to Usual Care, driven primarily by longer life expectancies due to CVD mortality reductions.

However, in the budget impact analysis, from the perspective of a payer that is also receiving premiums, the cost per-patient-per-year is equally, if not more, important for financial planning. The Polypills were cost-saving in terms of cost per-patient-per-year alive. That is, the cost per-patient-year alive was lower for those receiving the Polypill compared to those getting Usual Care. This result was driven by lower chronic care costs for patients alive in addition to reductions in acute hospitalizations. Given that private payers or self-insured employers do not hold onto to members indefinitely, the change in per-patient-per-year cost is more relevant over a short horizon of 5 or 10 years. The knowledge, for payers or employers, that the polypill will reduce per-patient-per-year costs, in addition to improving quality of life for members, may encourage its introduction differently from knowing only that patients will live longer over a time period beyond when they may be an insured member or employee. This could also encourage payers to provide the medication for free to patients in order to reduce total medical expense.

Our results are consistent with other economic evaluation studies on polypills in other countries. Investigators in the U.K. found the use of a three-drug polypill (aspirin 100 mg, atorvastatin 20 mg, ramipril 2.5-10 mg) in those with a prior myocardial infarction had a cost-effectiveness of £8200/QALY gained compared to multiple monotherapy.[30] Another modeling study done in the UK population[35] showed that in order for a polypill to be cost-effective, the cost of the pill would need to be less than €302 or €410 per year which is very similar to our $500 -$642 per annum. Studies in low- and middle-income countries have also found the polypill to be cost-saving in Argentina,[36] other Latin American countries ($35/QALY),[37] and other regions of the world.[28]

Only one other published study has evaluated the polypill for secondary prevention in the United States.[38] That study was conducted before the results of the UMPIRE[5] study on adherence, before the new cholesterol guidelines were published recommending high dose statins for those with prior CVD, and before atorvastatin was available generically. The investigators, who used an estimate of increased adherence of only 10% attributed to the polypill, found that its use resulted in an ICER of $130,000/QALY. This value is larger than ours but still acceptable in current willingness to pay guidelines suggested by the ACC/AHA statement on cost/value methodology in clinical practice guidelines and performance measures.[33] There are two major differences between that analysis and ours. First, their analysis did not include stroke, which would also be reduced with polypill use and thus underestimates both QALYs gained and reductions in costs. Second, the dose of statin in our polypill II is 80 mg of atorvastatin compared to 40 mg of lovastatin used in their analysis, which can lead to nearly a doubling in LDL cholesterol reduction.[39]

Analyses for Polypill III assumed rosuvastatin at the current generic price that was available for the costs of drugs in 2019. Since, rosuvastatin has come off patent its prices have dropped considerably for its generic formulation. However, the cost is still nearly $150 per-year more than atorvastatin. Given the cholesterol lowering levels are similar, the atorvastatin strategy is still preferred. If rosuvastatin price became equal to or lower than atorvastatin, then it could be an equal or preferential choice in a polypill. We did not compare different RAS medications or beta-blockers as they are seen to have similar class effects[40,41] and have not been compared in a head-to-head fashion, but we would assume price and biocompatibility in the formulations to be a larger factor in choosing medications from those classes in a polypill. One additional limitation includes how we handled the increase in adherence. We chose to have the relative increase in adherence for the Polypill arms as a constant increase in comparison to the Usual Care, regardless of number of medications at baseline. Paradoxically, the increase in adherence for those taking the fewest medications at baseline may be the greatest. In fact, the greatest increase in adherence in the UMPIRE trial was for those taking the fewest number of agents at baseline, where adherence increased from 23% to 77% or a 3-fold increase and those prescribed the most medications at baseline had the fewest

gains in adherence with the fixed dose combination pill. Perhaps one could speculate that if a patient being prescribed zero to two of potentially four indicated medications they were perhaps more likely to be non-adherent compared to those already taking four and hence prescribed fewer due to prior history of non-adherence. However, given the lack of available data on adherence rates by the number of the different possible permutations of taking medicines from the four classes we calculated a mean value and then applied the mean increase in adherence from the UMPIRE trial. If, in fact, those who are taking fewer medications actually have larger increases in medication adherence, against our intuition, then we may have underestimated the cost-effectiveness of the Polypill.

Overall, the underutilization of both highly effective and inexpensive medications in millions of Americans with very high CVD risk is a national travesty. Large numbers of premature deaths and significant disability could be preventive with improved adherence to these medications. Medicines are prescribed with high rates at discharge from hospitalization from acute CVD,[42] but their continuation in the outpatient setting is more limited with reduced adherence in the long term[43,44] with less than 10% of patients on all four-medication classes. Early trials suggest that a polypill could lead to increased adherence, reduced CVD risk factors and possibly reduced cardiovascular events. Our study shows that polypills could be cost-effective compared to usual care, with a potentially cost-saving budgetary impact profile in the United States.

Appendix. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ahj.2019.04.020.

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