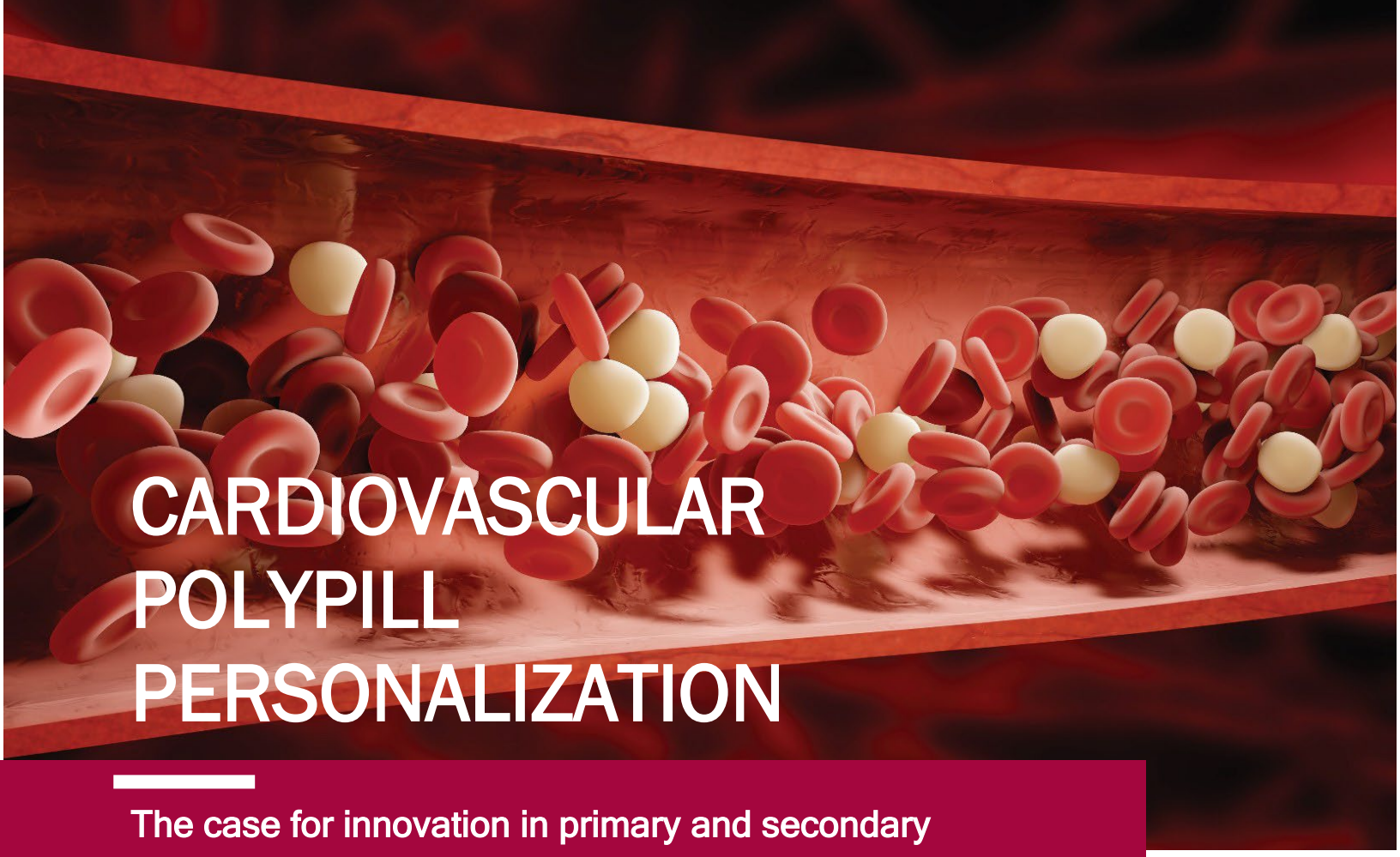

CARDIOVASCULAR POLYPILL PERSONALIZATION

The case for innovation in primary and secondary prevention by combining economic testing, personalized formulation, and on-demand precision manufacture in a patient-friendly forms that enhance adherence and reduce adverse side medication effects

Oneful Health Inc

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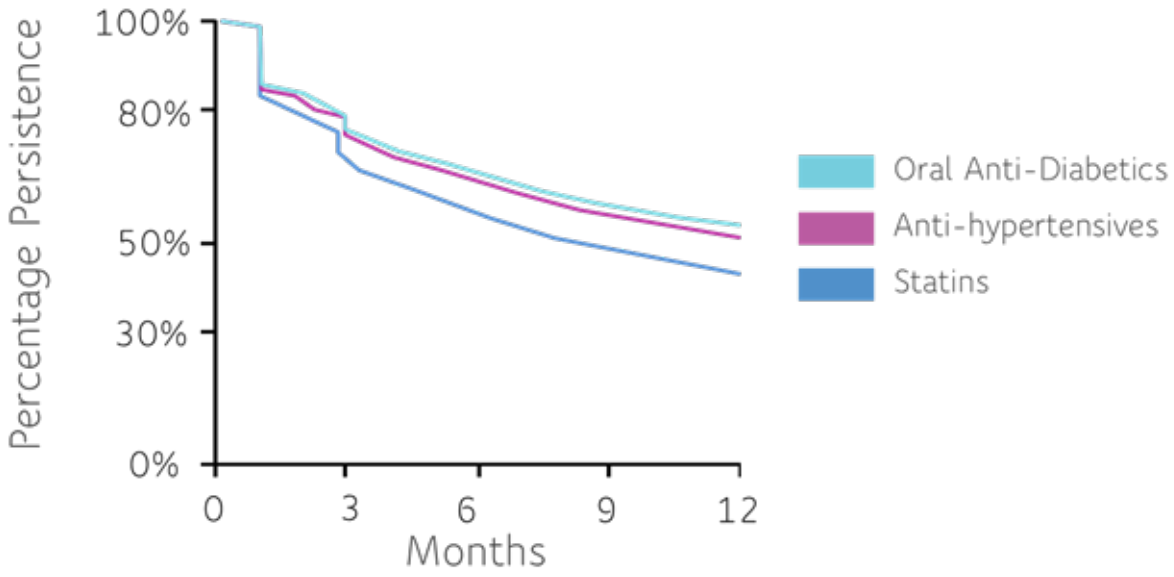
OneFul

Summary Points

- OneFul Health's company mission is to provide personalized multi-drug therapies in forms that improve medication adherence, formulated to improve drug effectiveness and minimize adverse side effects.

- Non-adherence due to polypharmacy and adverse drug reactions continues to be a major healthcare problem, increasing costs of care and resulting in many unnecessary deaths each year. Cardiometabolic treatments that are known to be very effective are prone to low adherence in a high percentage of secondary cases. It is estimated that non-adherence and adverse effects to prescribed treatments cause 100,000 preventable deaths and result in $100B in preventable medical costs per year.



*Adapted from - Adherence Behavior Across Treatment Classes (Yeaw et al.)

- Using approved and known safe generic Active Pharmaceutical Ingredients('APIs'), multi-drug prescriptions are combined to meet a physician's prescription for an individual patient.

- This method is allowed under industry regulations following guidelines under 503A, and as permitted under 503B guidelines (See 503A/503B).

- The Company's initial and most significant multi-drug products, or "polypills", are modeled on the formulation of existing fixed-dosed polypills, for both primary cardiovascular disease prevention, and chronic therapy for post-event or diagnosis

of heart attacks, stroke, by-pass graft surgery, stent placement, angina, or heart failure. (See One Pill for Them All: Polypill Therapy).

- There exist several fixed-dose/ fixed-combination cardiovascular polypills available in international markets, though none have been approved for use in the USA. Oneful's systems are designed to allow for variable combinations of APIs that are safe in combination, at variable doses to meet individual treatment as determined by their licensed physicians.

- This approach satisfies the major objections to fixed-dose polypills noted by the FDA's review of the polypill data (2014), that some patients would receive drugs they should not take or that interact with other drugs in their regimen, some are sub-clinically treated while others overdosed for their medical needs.

- As most of the polypill formulations have3 or more API ingredients, it is considered highly unlikely that any set of fixed-dose combinations for cardiovascular disease would be approved by the FDA, as only two(2) fixed-dose combinations with 4 ingredients have been approved in recent decades. Despite overwhelming clinical and aftermarket evidence of the benefits of cardiovascular polypills to patient outcomes, economic and regulatory barriers have prevented the approval of broad-spectrum cardiovascular combination products.

- While compounding pharmacies using physician prescriptions have broad regulatory authority to make safe combination polypills and equivalents, the industry needs technical and regulatory upgrades to scale to meet the potentially large demand for a personalized cardiovascular polypill. Compounding pharmacies are typically small firms using high-skill pharmacists to manually prepare individualized prescriptions. The current model cannot generally be scaled while also maintaining high levels of quality, accuracy, and drug safety.

- The economics of personalized polypills made using verified generic drugs and automated compounding robotics is excellent. Many of the combinations of commonly prescribed cardiovascular medications can be made and sold for as little as $1/day. For example, the fixed-dosed polypill used in the recently reported SECURE study can be sold at the $1 / day price point while generating 80% gross margins on the Oneful system. At this price point, a recent study by Vanderbilt University showed that such a product can support underserved and poorly insured populations resulting in substantially better outcomes.

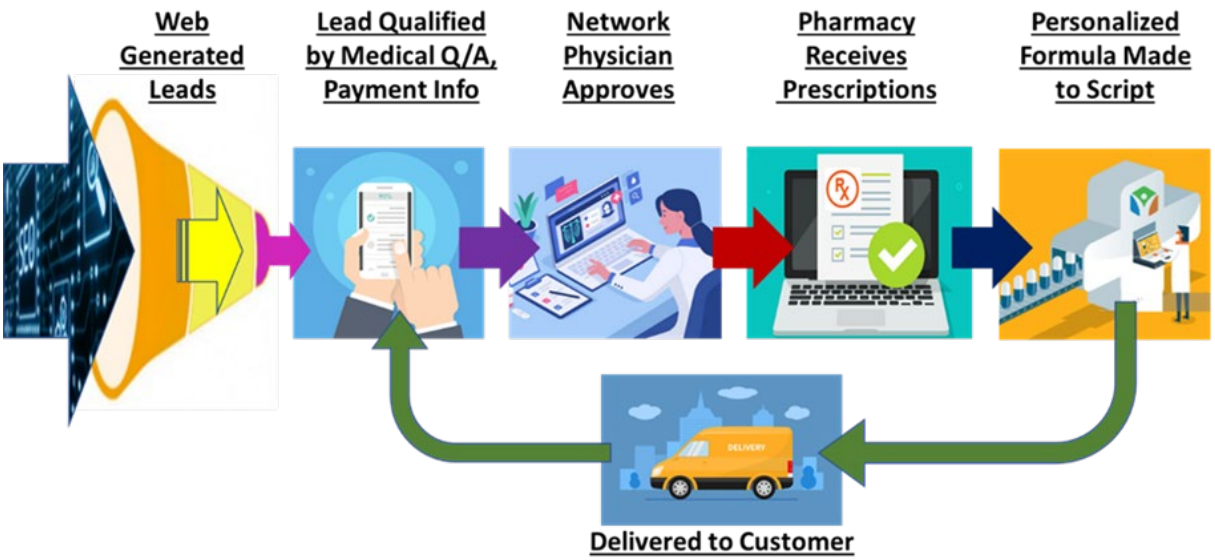
SCALABLE PLATFORMS SUPPORTING PERSONALIZATION

- The technology enables personalized polypills but requires a regulatory or path-to-market that engages the oversight and forward-thinking of the medical community. During the COVID pandemic, the growth of robust physician networks employing telemedicine concepts is an equally profound enabler of innovations in personalized medicine such as the polypill. Telemedicine has given rise to large telemedicine physician networks for specific health conditions, raising large sums of capital to ensure a place in the healthcare industry, examples such as RO ($876M), Carbon Health ($523M), Hims&Hers ($232M), Thirty Madison ($210M), Capsule ($570), Lemonaid Health ($58M).

- Specialized cardiology platforms such as HeartBeat Health, Ventricle Health, and others can provide consultations that ensure that any patient receiving a polypill has been screened and professionally advised. General practitioners including Physician 360 and private concierge group MDVIP have also become more telemedicine friendly and have welcomed the personalized polypill product as being a differentiator for their customer bases and so have agreed to work with Oneful on an ad-hoc basis.

- Oneful's wholly-owned compounding facility, Triangle Compounding Pharmacy, has operated as a 503A accredited facility since 2008 and operated as an FDA Outsourcing Facility under 503B cGMP guidelines for sterile and non-sterile products. Oneful uniquely includes a team of automation engineers that have designed, built, and commissioned robotic automation that ensures cGMP manufacturing under "quality by design". Oneful's operational management is led by a veteran PharmD, guided by a science team including drug developer and contract drug manufacturing, and advised by a former FDA regulator. The company has been granted 13 patents in personalized medicine and drug delivery forms, with additional IP pending that enables a large range of individualized combination treatments, initially focused on cardiovascular disease, with cardiometabolic combinations in development.

- Discussions with a network of nationally licensed compounding pharmacies have indicated that embedding the Oneful technical solution into regionally based partner pharmacies, and connecting the prescribing by telemedicine through the existing Sure Scripts systems is a technically and economically attractive path to national coverage of personalized polypill products.
- Direct-to-Consumer has become a viable go-to-market model for marketing that is highly scalable.



SUPPORTING CARDIOVASCULAR POLYPILL EVIDENCE

- Over 10 clinical research studies, highlighted in the following pages, conducted for over 10 years by academia and healthcare systems provide significant evidence for cardiovascular polypills as an effective means for improving outcomes and reducing the year-over-year risks of life-threatening coronary events. Fixed-dose combination polypills have shown clear evidence of markedly improved adherence as a major factor, with efficacy equal to multi-pill protocols, and safety.

	Drug MoA	Coagulation		Beta Blocker		ACE Inhibitor			ARB		Calcium Blocker	Diuretic	Statins		
PolyPill Clinical Research	Subjects in Study	aspirin	clopidogrel	Atenolol	metoprolol	lisinopril	ramipril	Enalapril	losartan	Candesartan	amlodipine	HCTZ	atorvastatin	pravastatin	simvastatin
TIPS1 (2009)	2,053	X		X			X					X			X
Redheart Pill 1 (2010)	2,000			X		X						X			
UMPIRE (2012)	378	X		X		X						X			
Wald et al (2012)	86								X		X	X			
TIPS2 (2012)	518	X		X			X					X			X
HOPE 3 (2019)	12,705									X		X			
Poly-Iran (2019	6,838	X						X				X	X		
TIPS-3 (2020)	5,713	X		X			X					X			X
Munoz (Vanderbilt -2019)	303								X		X	X	X		
SECURE (2022)	2,499	X					X						X		
FHG CABG (2018)	NA	X	X		X		X							X	
Total N =	**33,093**														

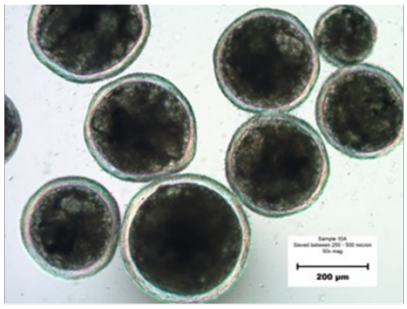
- In addition to these clinical trials, sixteen (16) commercial fixed-dosed polypills have been used clinically in international markets, using a broad range of commonly prescribed generic APIs[1]. The combined pharmacopeia of these clinical trials and approved commercial fixed combinations are the baseline for Oneful's personalized offerings. Oneful will provide certificates of analysis by certified laboratories of all APIs being used, assuring the purity, potency, and absence of contaminants for all combined drugs.

Name	Composition	Pharmaceutical company
Atamra CV kit	Atorvastatin, ramipril, and clopidogrel	Amra Remedies
CV-Pill kit	Ramipril, metoprolol, atorvastatin, and aspirin	Torrent Pharmaceuticals
GSK3074477[a]	Amlodipine and rosuvastatin	GlaxoSmithKline
Heart Pill	Ramipril, atorvastatin, and aspirin	Excella Pharma
Livalo fixed-combination drug[a]	Pitavastatin and valsartan	JW Pharmaceutical
Polycap	Simvastatin, atenolol, hydrochlorothiazide, ramipril ± aspirin	Cadila Pharmaceuticals
Polypill-E	Aspirin, atorvastatin, hydrochlorothiazide, and enalapril	Alborz Darou Pharmaceuticals
Polypill-V	Aspirin, atorvastatin, hydrochlorothiazide, and valsartan	Alborz Darou Pharmaceuticals
Ramitorva	Aspirin, ramipril, and atorvastatin	Zydus Cadila Healthcare
RIL-AA	Ramipril, atorvastatin, and aspirin	East West Pharma
Starpill	Aspirin, losartan, atenolol, and atorvastatin	Cipla
Trinomia	Atorvastatin or simvastatin, ramipril, and aspirin	Ferrer
Triveram	Perindopril, amlodipine, and atorvastatin	Servier
Unnamed[a]	Irbesartan and atorvastatin	Sanofi
Unnamed[a]	Valsartan and rosuvastatin	EMS
ZYCAD-4 kit	Ramipril, metoprolol, atorvastatin, and aspirin	Zydus Cadila Healthcare

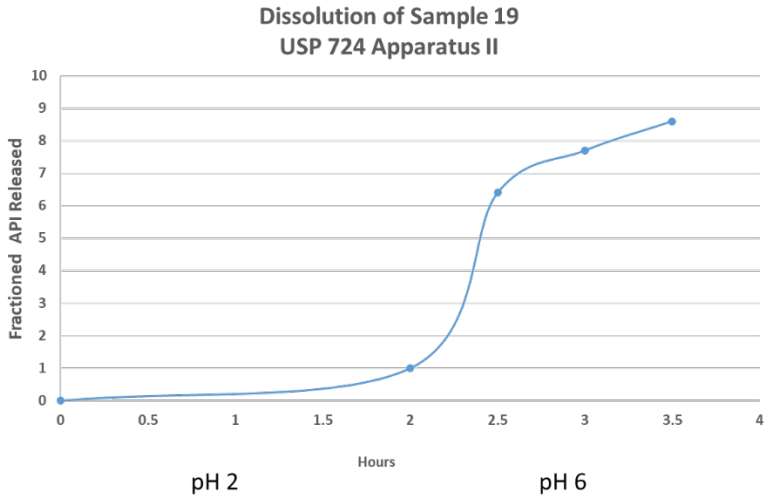
[a]These drugs have not yet received marketing approval.

Fixed-dose combination therapy to reduce the growing burden of cardiovascular disease in low- and middle-income countries: feasibility and challenges - Nansseu - 2018 - The Journal of Clinical Hypertension -

- As the Oneful pharmacopeia is expanded to include new APIs, Oneful will conduct the appropriate dissolution and bioequivalence studies to ensure that the combination forms release drugs at the desired rate and potency. Oneful has patented methods that will also support the timed release of individual drugs where medically beneficial or to match the release rate of approved sustained-release versions. This medical data will be made available to physicians to give them confidence in the quality and efficacy of the polypill products.



Patent Pending "Suspensions Of Encapsulated Pharmaceuticals And Methods Of Making And Using The Same", (US Patent Application 62/567,779)

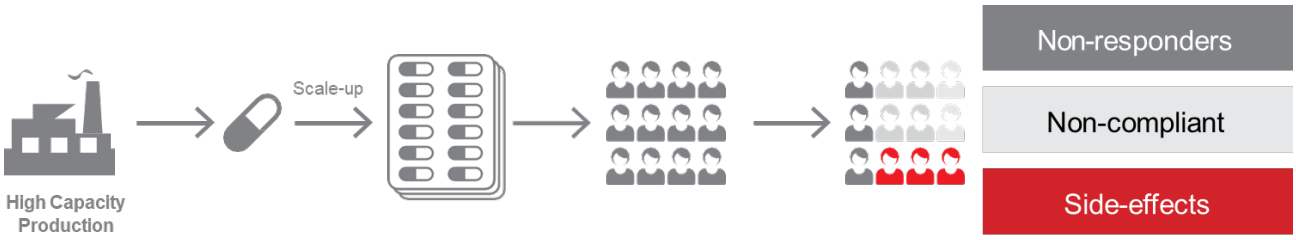


pH 2 pH 6

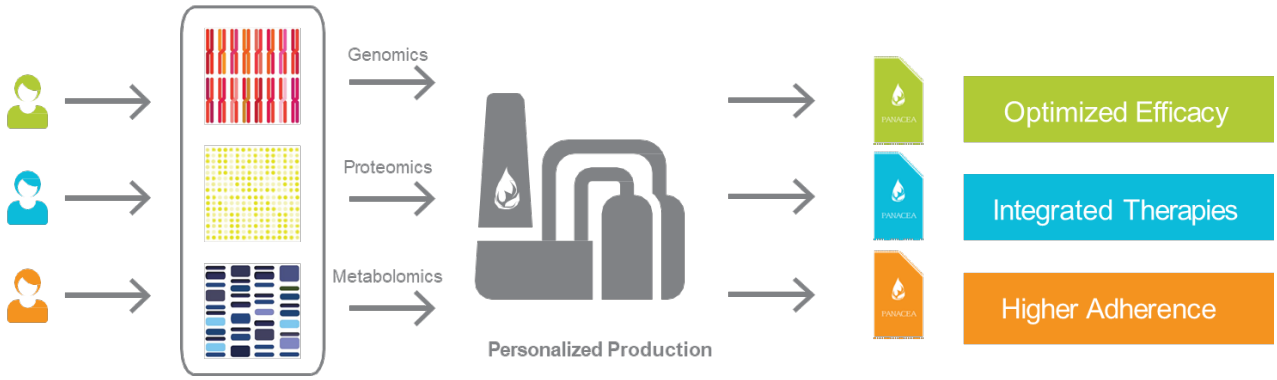
FUTURE DIRECTIONS - PERSONALIZED FORMULATION

- Oneful's technology enables the use of a growing body of evidence to adjust the formulation of cardiovascular and metabolic treatments using biomarkers that are becoming readily available and economic to use. The "on-demand" nature of the technology enables the accurate titration of individual drugs, compacting them into single-serving drug delivery forms with each drug individually dosed to meet the metabolic profile of the patient.

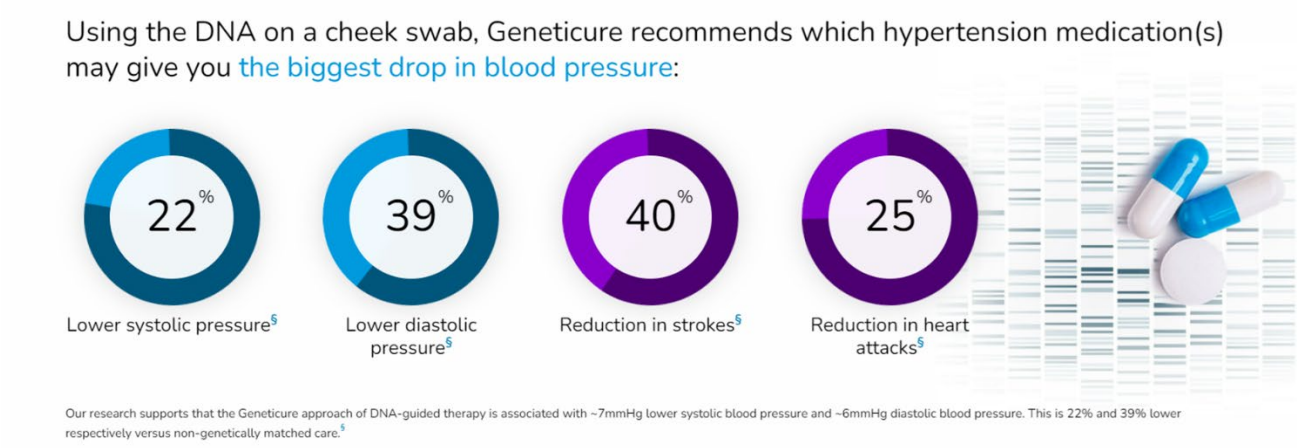
Established Drug Development Model



Oneful Health's Personalized Formulation Model



- Pharmacogenomics has become better understood as a method to improve efficacy and reduce adverse effects for individual patients. Studies at Mayo Clinic conducted in conjunction with Geneticure have focused on cardiovascular disease and the genetic relationships to the drugs that are part of the Oneful cardiovascular pharmacopeia. Oneful's patients will have the opportunity to generate a report for their cardiologist that may lead to better effectiveness.



- Technology developments including low-cost whole genome sequencing, home-based testing, and consumer wearable health sensors underpin the long-term expansion of demand for personalized medicine. OneFul can be the first to market integration of these developments in products that go beyond just producing patient-specific data. Oneful intends to work with hospital and physician groups to provide such near real-time titration and reformulation processes in the next five years to create “precision generics” as a value-added service.

OneFul

Recent Polypill Press

The New York Times

How to Get Heart Patients to Take Their Pills? Give Them Just One.

Patients given a combination "polypill" after a heart attack were more likely to stick to their regimens, researchers reported.

Give this article

People who were given a three-in-one polypill within six months of a heart attack were more likely to stick to their drug regimens and had fewer cardiovascular events than those receiving the usual assortment of pills. Georgia Kirkos/McMaster University, via Associated Press

Here are a few of the links to the recent polypill news :

[How to Get Heart Patients to Take Their Pills? Give Them Just One. - The New York Times (nytimes.com)]

[Combination 'polypill' lowers the risk of major cardiovascular events, study finds - CNN]

[Combination 'polypill' cuts heart disease deaths, study finds (nbcnews.com)]

[‘Polypill’ Reduces Risk of Repeat Heart Attacks | Everyday Health]

['Polypill' reduces cardiovascular mortality by 33% in patients treated after a heart attack (medicalxpress.com)]

[What Is a 'Polypill'? How a Single-Dose Treatment Can Help Lower the Risk of Major Cardiovascular Events (health.com)]

KEY PAPERS

ORIGINAL ARTICLE

Polypill Strategy in Secondary Cardiovascular Prevention

J.M. Castellano, S.J. Pocock, D.L. Bhatt, A.J. Quesada, R. Owen, A. Fernandez-Ortiz, P.L. Sanchez, F. Marin Ortuño, J.M. Vazquez Rodriguez, A. Domingo-Fernández, I. Lozano, M.C. Roncaglioni, M. Baviera, A. Foresta, L. Ojeda-Fernandez, F. Colivicchi, S.A. Di Fusco, W. Doehner, A. Meyer, F. Schiele, F. Ecarnot, A. Linhart, J.-C. Lubanda, G. Barczi, B. Merkely, P. Ponikowski, M. Kasprzak, J.M. Fernandez Alvira, V. Andres, H. Bueno, T. Collier, F. Van de Werf, P. Perel, M. Rodriguez-Manero, A. Alonso Garcia, M. Proietti, M.M. Schoos, T. Simon, J. Fernandez Ferro, N. Lopez, E. Beghi, Y. Bejot, D. Vivas, A. Cordero, B. Ibañez, and V. Fuster, for the SECURE Investigators*

ABSTRACT

BACKGROUND

A polypill that includes key medications associated with improved outcomes (aspirin, angiotensin-converting–enzyme [ACE] inhibitor, and statin) has been proposed as a simple approach to the secondary prevention of cardiovascular death and complications after myocardial infarction.

METHODS

In this phase 3, randomized, controlled clinical trial, we assigned patients with myocardial infarction within the previous 6 months to a polypill-based strategy or usual care. The polypill treatment consisted of aspirin (100 mg), ramipril (2.5, 5, or 10 mg), and atorvastatin (20 or 40 mg). The primary composite outcome was cardiovascular death, nonfatal type 1 myocardial infarction, nonfatal ischemic stroke, or urgent revascularization. The key secondary end point was a composite of cardiovascular death, nonfatal type 1 myocardial infarction, or nonfatal ischemic stroke.

RESULTS

A total of 2499 patients underwent randomization and were followed for a median of 36 months. A primary-outcome event occurred in 118 of 1237 patients (9.5%) in the polypill group and in 156 of 1229 (12.7%) in the usual-care group (hazard ratio, 0.76; 95% confidence interval [CI], 0.60 to 0.96; P=0.02). A key secondary-outcome event occurred in 101 patients (8.2%) in the polypill group and in 144 (11.7%) in the usual-care group (hazard ratio, 0.70; 95% CI, 0.54 to 0.90; P=0.005). The results were consistent across prespecified subgroups. Medication adherence as reported by the patients was higher in the polypill group than in the usual-care group. Adverse events were similar between groups.

CONCLUSIONS

Treatment with a polypill containing aspirin, ramipril, and atorvastatin within 6 months after myocardial infarction resulted in a significantly lower risk of major adverse cardiovascular events than usual care. (Funded by the European Union Horizon 2020; SECURE ClinicalTrials.gov number, NCT02596126; EudraCT number, 2015-002868-17.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Dr. Fuster can be contacted at vfuster@cnic.es or at Centro Nacional de Investigaciones Cardiovasculares, Melchor Fernández Almagro 3, Madrid 28029, Spain.

*A list of the SECURE investigators is provided in the Supplementary Appendix, available at NEJM.org.

This article was published on August 26, 2022, at NEJM.org.

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Cardiovascular disease is the leading cause of death and complications worldwide.[1-3] Despite effective pharmacotherapy for secondary prevention, the incidence of recurrent ischemic events is still high.[4,5] Patient adherence to secondary prevention medications has been estimated to be approximately 50%,[6,7] a lack of adherence that has been associated with poorer outcomes.[8]

Barriers to adherence include factors related to the characteristics of patients, their prescribers, and their health care systems.[9] Certain features regarding the period after myocardial infarction — treatment complexity, polypharmacy, treatment of asymptomatic conditions, coexisting illness, and age — frequently preclude adequate secondary prevention.[10] An increased frequency of dosing and treatment complexity have repeatedly been shown to decrease adherence.[11] The aging of the population and the improved survival of patients with coronary artery disease have resulted in more patients who are eligible for secondary prevention.[12-14]

A polypill strategy has been shown to improve medication adherence by virtue of treatment simplification.[7,15-17] A recent meta-analysis of three randomized, controlled trials showed a lower occurrence of cardiovascular events among patients who were assigned to receive a polypill than among control patients in primary prevention.[18]

In the phase 3, randomized, controlled, multinational Secondary Prevention of Cardiovascular Disease in the Elderly (SECURE) trial, we assessed the efficacy of a polypill-based strategy, as compared with usual care, with respect to major cardiovascular outcomes in older patients with recent myocardial infarction.

Methods

Trial Design and Oversight

The trial was conducted at 113 centers in Spain, Italy, France, Germany, Poland, the Czech Republic, and Hungary (Table S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org). The trial was designed by the members of the steering committee, who oversaw the trial conduct, the collection and analysis of the data, and the interpretation of results, along with staff members at Centro Nacional de Investigaciones Cardiovasculares.

The trial was funded by the European Union Horizon 2020. Ferrer International provided the polypill that was used in the trial; the company had no other role in the trial. Appropriate approvals were provided by the ethics committee at each trial site. All the patients provided written informed consent.

The first author wrote the first draft of the manuscript, and all the authors made the decision to submit the manuscript for publication. Members of the steering committee vouch for the completeness and accuracy of data and for the fidelity of the trial to the protocol, available at NEJM.org.

Patients

Eligible patients had a history of type 1 myocardial infarction (i.e., attributable to acute coronary atherothrombotic injury resulting from plaque rupture or erosion and thrombosis with or without ST-segment elevation)[19] within the previous 6 months. All the patients were either older than 75 years of age or at least 65 years of age with at least one of the following risk factors: diabetes mellitus, mild or moderate kidney dysfunction (creatinine clearance, 30 to 60 ml per minute per 1.73 m^2 of body-surface area), previous myocardial infarction (defined as infarction occurring before the index event), previous coronary revascularization (including percutaneous coronary intervention [PCI]) or coronary-artery bypass grafting [CABG]), or previous stroke. Details regarding the eligibility criteria are provided in Table S2. Patients were excluded from the trial if they were receiving oral anticoagulation. Patients who had been scheduled for PCI or CABG did not undergo randomization until after the procedure had been performed.

Trial Treatments and Procedures

Patients were randomly assigned to a polypill strategy or usual care (with a care program determined on the basis of current European Society of Cardiology guidelines) by means of a centralized online system. Randomization was stratified according to trial center. The polypill contained any of three formulations of Polypill AAR40 — a single pill containing aspirin (100 mg), ramipril (2.5, 5, or 10 mg), and atorvastatin (40 mg). If the investigator decided to reduce the atorvastatin dose on the basis of the patient's history or the results of blood tests, the patient could be switched to Polypill AAR20 (same as AAR40 but with a reduced dose of atorvastatin [20 mg]). Among the

patients who had not received ramipril, treatment was started at a dose of 2.5 mg; among those who were already taking an angiotensin-converting–enzyme (ACE) inhibitor, treatment was started at a bioequivalent dose of ramipril. The dose was increased to a goal of 10 mg (if the patient had no unacceptable side effects) at 3-week intervals. Details regarding the two treatment groups are provided in the protocol, available at NEJM.org.

Follow-up visits occurred at months 6, 12, and 24, with additional telephone follow-up at 18, 36, and 48 months. Blood pressure was recorded and fasting blood samples were obtained at every visit. At 6-month and 24-month intervals, adherence was measured with the use of the eight-item Morisky Medication Adherence Scale, which ranges from 0 to 8, with higher scores indicating better adherence.[20] Treatment satisfaction was measured at baseline and at 24 months with the use of the Treatment Satisfaction Questionnaire for Medication.

EFFICACY AND SAFETY OUTCOMES

The primary outcome was a composite of cardiovascular death, nonfatal type 1 myocardial infarction, nonfatal ischemic stroke, or urgent coronary revascularization. The key secondary outcome was a composite of cardiovascular death, nonfatal type 1 myocardial infarction, or nonfatal ischemic stroke. Other secondary outcomes included individual components of the primary outcome, treatment adherence at 2 years, a change in risk-factor control at 2 years (with measurement of the low-density lipoprotein [LDL] cholesterol level and systolic and diastolic blood pressure), and treatment satisfaction. All cardiovascular events were adjudicated by an independent clinical-events committee whose members were unaware of treatment assignments.

Secondary safety outcomes included death from any cause and adverse events (including bleeding, kidney failure, drug allergic reaction, and drug discontinuation). A complete list of efficacy and safety outcomes is provided in the trial protocol.

STATISTICAL ANALYSIS

The primary composite outcome was evaluated for noninferiority, which was defined as an upper boundary of the one-sided 97.5% confidence interval of less than 1.373 for the hazard ratio. Once the criterion for noninferiority had been met, a test for superiority with respect to the primary outcome was performed. A test for superiority for the key secondary outcome would be performed only if superiority for the primary outcome was confirmed. All other secondary outcomes were considered to be exploratory.

For the primary composite outcome, an annual event rate of 7.2% was expected in the usual-care group.[8] We determined that a sample size of 3206 patients with a minimum 2 years of follow-up would provide 90% power to reject a finding of noninferiority and 80% power to detect a 21% relative risk reduction in the polypill group, with a two-sided alpha level of 0.05, assuming 5% loss to follow-up. The projected annual event rate in the usual-care group was later revised to 7.7% on the basis of 3 years of recruitment and a minimum of 2 years of follow-up so that a sample size of 2514 patients would have 78% power to detect superiority.

Analyses were performed according to the intention-to-treat principle. Per-protocol analyses were performed for the primary outcome and key secondary outcome after the exclusion of patients with a major protocol deviation. A P value of less than 0.05 was considered to indicate statistical signifiance.

We performed Kaplan–Meier analyses and log-rank tests to calculate time-to-event values. Proportional-hazards models were stratified according to country and were used to estimate hazard ratios with 95% confidence intervals. Missing outcome data were not imputed for analysis of the primary outcome or key secondary outcome. Sensitivity analyses of the primary outcome and key secondary outcome were performed after adjustment for age (<75 years or ≥75 years) and for the presence or absence of diabetes, mild or moderate kidney dysfunction, and previous cardiovascular events (myocardial infarction, stroke, or revascularization). Sensitivity analyses were also performed to consider noncardiovascular death as a competing risk for the primary outcome and key secondary outcome.

For secondary outcomes aside from the key secondary outcome, the 95% confidence intervals were not adjusted for multiple testing and should not be used to infer definitive treatment effects. Ordinal logistic regression was used to calculate common odds ratios comparing adherence categories. Mean differences in scores for treatment satisfaction and changes in risk factors from baseline were compared with the use of two-sample

Table 1. Demographic Characteristics of the Patients at Baseline.*

Characteristic	Polypill Group (N=1237)	Usual-Care Group (N=1229)
Age		
Mean — yr	75.8±6.7	76.1±6.5
Distribution — no. (%)		
<75 yr	516 (41.7)	482 (39.2)
≥75 yr	721 (58.3)	747 (60.8)
Sex — no. (%)		
Male	853 (69.0)	848 (69.0)
Female	384 (31.0)	381 (31.0)
Country — no. (%)		
Czech Republic	85 (6.9)	87 (7.1)
France	74 (6.0)	70 (5.7)
Germany	182 (14.7)	184 (15.0)
Hungary	45 (3.6)	45 (3.7)
Italy	366 (29.6)	365 (29.7)
Poland	63 (5.1)	60 (4.9)
Spain	422 (34.1)	418 (34.0)
Race — no. (%)†		
White	1221 (98.7)	1211 (98.5)
Black	3 (0.2)	0
Other	7 (0.6)	10 (0.8)
Missing data	6 (0.5)	8 (0.7)
Education level — no. (%)		
Less than high school	580 (46.9)	576 (46.9)
Some high school	415 (33.5)	424 (34.5)
More than high school	179 (14.5)	162 (13.2)
Missing data	63 (5.1)	67 (5.5)
Employment — no. (%)		
Full time	37 (3.0)	27 (2.2)
Part time	17 (1.4)	13 (1.1)
Not working	39 (3.2)	34 (2.8)
Retired	1117 (90.3)	1132 (92.1)
Missing data	27 (2.2)	23 (1.9)

* Plus–minus values are means ±SD. Details regarding the patients' vital signs and medical history at baseline are provided in Tables S4 and S5.
† Race was reported by the patients.

t-tests and analysis of covariance, respectively. The numbers of safety outcomes were summarized according to treatment group and compared with the use of chi-square tests. All analyses were performed with the use of Stata software, version 17.0 (StataCorp).

RESULTS

PATIENTS

From August 2016 through December 2019, a total of 4003 patients underwent screening; of these patients, 1504 (37%) were either not eligi-

ble or declined to participate in the trial. A total of 2499 patients underwent randomization (1258 to the polypill group and 1241 to the usual-care group). The median time between the index myocardial infarction and randomization was 8 days (interquartile range [IQR], 3 to 37). Follow-up data were missing for 21 patients in the polypill group and 12 in the usual-care group, so the intention-to-treat population consisted of 2466 patients (1237 in the polypill group and 1229 in the usual-care group) (Fig. S1). Of these patients, withdrawal during follow-up was reported in 174 patients in the polypill group and 166 in the usual-care group; data for these patients were censored at time of withdrawal (Table S3).

The demographic and medical characteristics and vital signs of the patients at baseline are shown in Tables 1, S4, and S5. The mean age was 76.0±6.6 years, 31.0% of the patients were women, 77.9% had hypertension, 57.4% had diabetes, and 51.3% had a history of smoking. The mean systolic blood pressure was 129.1±17.7 mm Hg, and the mean LDL cholesterol level was 89.2±37.2 mg per deciliter.

TREATMENT EFFECTS

Most patients in the polypill group (91.7%) received the 40-mg formulation of atorvastatin (Table S6), whereas 40.4% of the patients in the usual-care group were treated with a high-potency statin drug (Table S7). The use of ACE inhibitors in the usual-care group is shown in Table S8. A total of 98.7% of the patients in the usual-care group received aspirin, and the percentage of patients who received an additional antiplatelet agent was 94.0% in the polypill group and 95.1% in the usual-care group (Table S9). Total numbers of cardiovascular therapies are shown in Table S10.

At 6 months, high levels of adherence were seen in 70.6% of the patients in the polypill group and in 62.7% of those in the usual-care group (risk ratio, 1.13; 95% confidence interval [CI], 1.06 to 1.20) (Table 2). At 24 months, high levels of adherence were seen in 74.1% of the patients in the polypill group and in 63.2% of those in the usual-care group (risk ratio, 1.17; 95% CI, 1.10 to 1.25).

The mean systolic and diastolic blood pressure levels at 24 months were 135.2 mm Hg and 74.8 mm Hg, respectively, in the polypill group and 135.5 mm Hg and 74.9 mm Hg, respectively,

Table 2. Treatment Adherence at 6 Months and 24 Months.*

Treatment Adherence	Polypill Group				Usual-Care Group				Risk Ratio (95% CI)†
	No. of Patients	Low	Medium	High	No. of Patients	Low	Medium	High	
		number of patients (percent)				*number of patients (percent)*			
At 6 mo	1077	59 (5.5)	258 (24.0)	760 (70.6)	1057	100 (9.5)	294 (27.8)	663 (62.7)	1.13 (1.06–1.20)
At 24 mo	881	37 (4.2)	191 (21.7)	653 (74.1)	851	59 (6.9)	254 (29.8)	538 (63.2)	1.17 (1.10–1.25)

* Treatment adherence was measured with the use of the eight-item Morisky Medication Adherence Scale, which ranges from 0 to 8, as follows: low adherence, <6; medium adherence, 6 to <8; and high adherence, 8.
† The risk ratio was calculated as the probability of high treatment adherence as compared with low or medium adherence in the polypill group as compared with the usual-care group. The 95% confidence intervals were not adjusted for multiple testing and should not be used to infer definitive treatment effects.

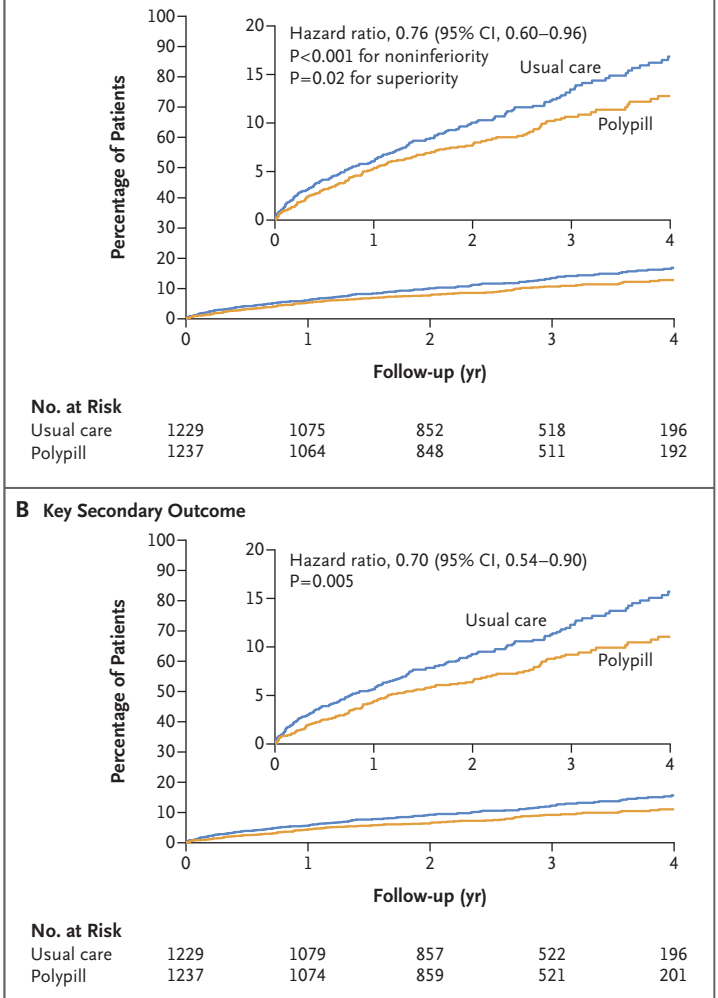

Figure 1. Primary and Key Secondary Outcome at a Median of 36 Months.

Panel A shows the cumulative incidence of a primary-outcome event (death from cardiovascular causes, nonfatal type 1 myocardial infarction, nonfatal ischemic stroke, or urgent revascularization) in the polypill group and the usual-care group. Panel B shows the cumulative incidence of a key secondary-outcome event (cardiovascular death, nonfatal type 1 myocardial infarction, or nonfatal ischemic stroke). The insets show the same data on an expanded y axis.

in the usual-care group (Table S11). No substantial differences were found in LDL cholesterol levels over time between the groups, with a mean value at 24 months of 67.7 mg per deciliter in the polypill group and 67.2 mg per deciliter in the usual-care group. The distribution of LDL cholesterol levels and systolic and diastolic blood pressures among patients in the two groups at each follow-up visit is provided in Figure S2.

At 6 months, results from the treatment satisfaction questionnaire for medication revealed a mean (±SD) global satisfaction score of 71.5±18.1 for 847 patients in the polypill group and 67.7±18.5 for 818 patients in the usual-care group (Table S12). At 24 months, the global satisfaction score was 74.4±17.5 and 67.8±17.9, respectively.

PRIMARY OUTCOME

The median follow-up duration was 3.0 years (IQR, 2.0 to 3.9). A primary-outcome event (cardiovascular death, nonfatal type 1 myocardial infarction, nonfatal ischemic stroke, or urgent revascularization) occurred in 118 of 1237 patients (9.5%) in the polypill group and in 156 of 1229 (12.7%) in the usual-care group (hazard ratio, 0.76; 95% CI, 0.60 to 0.96; P<0.001 for noninferiority; P=0.02 for superiority) (Fig. 1A and Table 3). A key secondary-outcome event (a composite of cardiovascular death, type 1 myocardial infarction, or ischemic stroke) occurred in 101 patients (8.2%) in the polypill group and in 144 (11.7%) in the usual-care group (hazard ratio, 0.70; 95% CI, 0.54 to 0.90; P=0.005) (Fig. 1B).

All components of the primary outcome contributed to the observed treatment effect (Fig. S3). Cardiovascular death occurred in 48 patients (3.9%) in the polypill group and in 71 (5.8%) in the usual-care group (hazard ratio, 0.67; 95% CI, 0.47 to 0.97). The frequency of death from any cause was similar in the two groups (hazard ratio, 0.97; 95% CI, 0.75 to 1.25) (Table S13). Treatment effects with respect to the primary outcome in prespecified subgroups (according to country, age, sex, and the presence or absence of diabetes, chronic kidney disease, and previous vascular event) are shown in Figure 2. Results of the per-protocol analyses were consistent with those of the primary analyses (Table S14). Sensitivity analyses with respect to the primary and secondary outcomes after adjustment for sex, age (<75 years or ≥75 years), and the presence or absence of diabetes, chronic kidney disease, and previous vascular events also remained consistent (Table S15). Analyses that were stratified according to trial center are shown in Table S16. The results of sensitivity analyses were consistent with those of the primary analysis; in these analyses, death from noncardiovascular causes was considered as a competing risk for the primary outcome, for the key secondary outcome, and for cardiovascular death; death from any cause was considered as a competing risk for

Table 3. Primary and Secondary Outcomes.

Outcome	Polypill (N=1237)	Usual Care (N=1229)	Hazard Ratio (95% CI)*	P Value
	number of patients (percent)			
Primary outcome†	118 (9.5)	156 (12.7)	0.76 (0.60–0.96)	<0.001 for noninferiority; 0.02 for superiority
Key secondary outcome				
Composite of cardiovascular death, nonfatal type 1 myocardial infarction, or nonfatal ischemic stroke	101 (8.2)	144 (11.7)	0.70 (0.54–0.90)	0.005
Components of primary outcome				
Cardiovascular death	48 (3.9)	71 (5.8)	0.67 (0.47–0.97)	
Nonfatal type 1 myocardial infarction	44 (3.6)	62 (5.0)	0.71 (0.48–1.05)	
Nonfatal ischemic stroke	19 (1.5)	27 (2.2)	0.70 (0.39–1.26)	
Urgent revascularization	27 (2.2)	28 (2.3)	0.96 (0.57–1.63)	
Safety				
Death from any cause	115 (9.3)	117 (9.5)	0.97 (0.75–1.25)	
Death from noncardiovascular cause	67 (5.4)	46 (3.7)	1.42 (0.97–2.07)	

* The 95% confidence intervals were not adjusted for multiple testing and should not be used to infer definitive treatment effects.
† The primary outcome was a composite of death from cardiovascular causes, nonfatal type 1 myocardial infarction, nonfatal ischemic stroke, or urgent revascularization.

type 1 myocardial infarction, ischemic stroke, and urgent revascularization (Table S17).

ADVERSE EVENTS

Adverse events were reported in 404 of 1237 patients (32.7%) in the polypill group and in 388 of 1229 (31.6%) in the usual-care group. Nonfatal serious adverse events occurred in 237 patients (19.2%) in the polypill group and in 224 (18.2%) in the usual-care group. Other specific safety outcomes in the two groups are provided in Table S18.

DISCUSSION

In the SECURE trial, a treatment strategy for secondary prevention with a polypill containing aspirin, ramipril, and atorvastatin in older patients with recent myocardial infarction resulted in a lower risk of major adverse cardiovascular events than a usual-care strategy of administration of medications on the basis of current European Society of Cardiology guidelines. The results were consistent regardless of country, age, sex, or the presence or absence of diabetes, chronic kidney disease, or previous revascularization. The trial results are broadly applicable to the general population, especially considering that the average age at the time of a first myocardial infarction is now 65.6 years for men and 72.0 years for women,[21] along with the high prevalence of diabetes mellitus, chronic kidney disease, and previous coronary artery disease in these patients.[13,21] Table S19 provides detailed information on the representativeness of the patients who were included in the trial.

The risk reductions that were observed in the polypill group may be explained partly by increased adherence.[22] In a trial involving patients with recent myocardial infarction, investigators assessed pharmacy claims to investigate the relationship between adherence to the prescribed drugs and the risk of major adverse cardiovascular events. They found that cardiovascular risk was 27% lower among the patients with a high degree of adherence than among those with a low degree of adherence.[8] In another similar

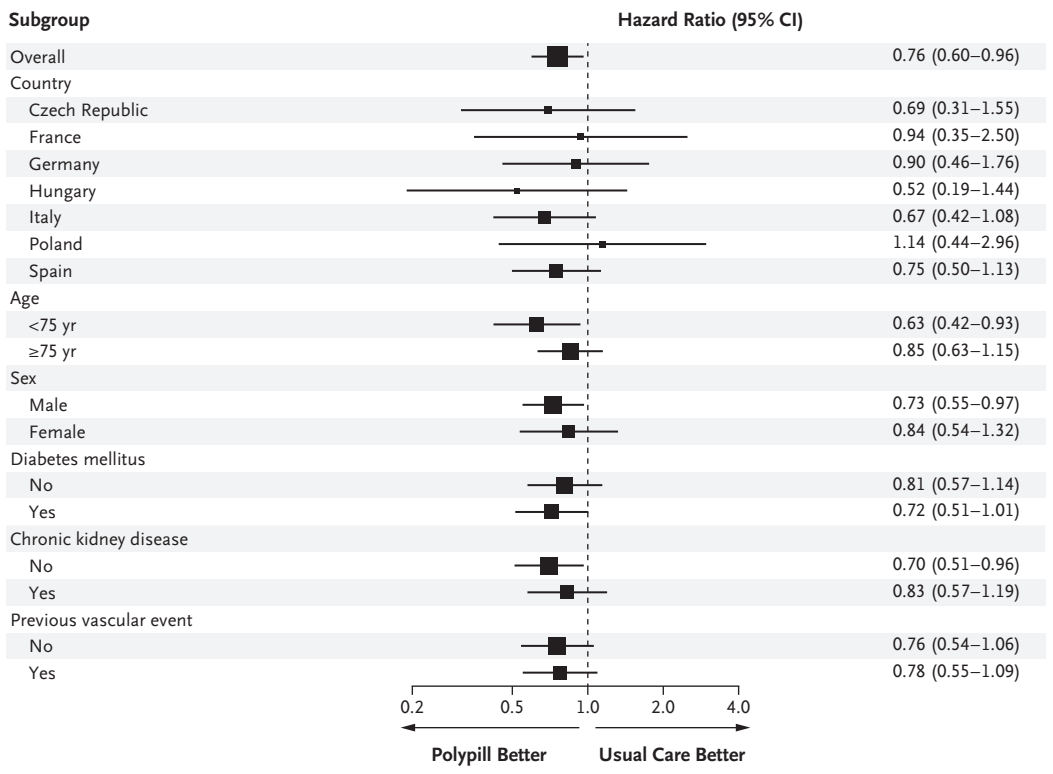

Figure 2. Primary Composite Outcome, According to Subgroup.

Shown is the risk of a primary-outcome event (death from cardiovascular causes, nonfatal type 1 myocardial infarction, nonfatal ischemic stroke, or urgent revascularization) in prespecified subgroups of patients who were receiving either polypill treatment or usual care.

trial with a 2-year follow-up, investigators found that patients who received a polypill containing aspirin, ramipril, and atorvastatin for secondary prevention had a 27% lower frequency of recurrent cardiovascular events than those who received other treatments for lowering lipid levels and blood pressure.[23] These results are consistent with those of our trial and support the hypothesis that the use of a polypill strategy as secondary prevention in older patients reduces the risk of recurrent cardiovascular events, at least partly through increased adherence.

The lack of a between-group difference in blood pressure and LDL cholesterol levels during follow-up may be due partly to the relatively low mean levels for these measures at baseline and partly to the open trial design, which could have resulted in potential differences in health behaviors. The lower risk of cardiovascular events in the absence of substantial differences in blood pressure and LDL cholesterol levels may be further explained by pleiotropic effects of statins and ACE inhibitors beyond the effects on LDL levels and blood pressure levels, respectively.[24,25] Furthermore, trials in which antiplatelet therapy was compared with placebo have shown a relative risk reduction of 20% or more in similar populations, so the greater adherence to the aspirin component of the polypill may add to this benefit.[26]

Among the components of the primary outcome, the frequency of cardiovascular death was 3.9% in the polypill group and 5.8% in the usual-care group. However, because this is an exploratory analysis, no formal inference can be drawn from these values.

The incidence of death from any cause was similar in the two groups. Although there was no substantial between-group difference in the incidence of death from noncardiovascular causes, more cases were observed in the polypill group than in the usual-care group, driven mainly by cancer deaths (21 in the polypill group vs. 11 in

the usual-care group). This finding may be explained by competing risks between cardiovascular and cancer mortality[27] — in other words, fewer cardiovascular deaths in the polypill group left more patients vulnerable to die from noncardiovascular causes (e.g., cancer), particularly in consideration of the average age of the patients and the fact that 55% were current or previous smokers. Adverse events were similar in the two groups.

This trial has some limitations. Although the trial was not performed in a blinded manner, the event adjudicators were unaware of trial-group assignments, and the outcome assessments were unbiased. No adjustment was made for multiple comparisons of secondary outcomes, so any between-group difference in the incidence of cardiovascular death should be viewed as hypothesis-generating. Withdrawal and loss to follow-up may potentially bias comparisons between groups, although the frequency of withdrawal was similar in the two groups. All the patients were enrolled by the end of 2019 before the start of the pandemic. Given the high-risk nature of the patients, it is reasonable to infer that the pandemic precluded some patients from completing trial visits, owing to site closures, travel restrictions, and stay-at-home requirements, especially during the year 2020.[28]

In the current trial involving older patients with recent myocardial infarction, a treatment strategy that was based on the receipt of a polypill containing aspirin, ramipril, and atorvastatin for secondary prevention led to a lower frequency of cardiovascular events than a usual-care strategy. The use of a cardiovascular polypill as a substitute for several separate cardiovascular drugs could be an integral part of an effective secondary prevention strategy. By simplifying treatment complexity and improving availability, the use of a polypill is a widely applicable strategy to improve accessibility and adherence to treatment, thus decreasing the risk of recurrent disease and cardiovascular death.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

APPENDIX

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ORIGINAL ARTICLE

Polypill for Cardiovascular Disease Prevention in an Underserved Population

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ABSTRACT

BACKGROUND

Persons with low socioeconomic status and nonwhite persons in the United States have high rates of cardiovascular disease. The use of combination pills (also called "polypills") containing low doses of medications with proven benefits for the prevention of cardiovascular disease may be beneficial in such persons. However, few data are available regarding the use of polypill therapy in underserved communities in the United States, in which adherence to guideline-based care is generally low.

METHODS

We conducted a randomized, controlled trial involving adults without cardiovascular disease. Participants were assigned to the polypill group or the usual-care group at a federally qualified community health center in Alabama. Components of the polypill were atorvastatin (at a dose of 10 mg), amlodipine (2.5 mg), losartan (25 mg), and hydrochlorothiazide (12.5 mg). The two primary outcomes were the changes from baseline in systolic blood pressure and low-density lipoprotein (LDL) cholesterol level at 12 months.

RESULTS

The trial enrolled 303 adults, of whom 96% were black. Three quarters of the participants had an annual income below $15,000. The mean estimated 10-year cardiovascular risk was 12.7%, the baseline blood pressure was 140/83 mm Hg, and the baseline LDL cholesterol level was 113 mg per deciliter. The monthly cost of the polypill was $26. At 12 months, adherence to the polypill regimen, as assessed on the basis of pill counts, was 86%. The mean systolic blood pressure decreased by 9 mm Hg in the polypill group, as compared with 2 mm Hg in the usual-care group (difference, –7 mm Hg; 95% confidence interval [CI], –12 to –2; P=0.003). The mean LDL cholesterol level decreased by 15 mg per deciliter in the polypill group, as compared with 4 mg per deciliter in the usual-care group (difference, –11 mg per deciliter; 95% CI, –18 to –5; P<0.001).

CONCLUSIONS

A polypill-based strategy led to greater reductions in systolic blood pressure and LDL cholesterol level than were observed with usual care in a socioeconomically vulnerable minority population. (Funded by the American Heart Association Strategically Focused Prevention Research Network and the National Institutes of Health; ClinicalTrials.gov number, NCT02278471.)

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Cardiovascular disease remains the leading cause of death and disability in the United States.[1] Persons with low socioeconomic status and nonwhite persons are particularly vulnerable and have high cardiovascular mortality.[2] There is wide geographic variation, with disproportionate disease burden in the southeastern United States and rural areas.[3]

Two leading risk factors for cardiovascular disease are elevated blood pressure and an elevated low-density lipoprotein (LDL) cholesterol level. Nearly two thirds of adults in the United States have high blood pressure as defined by the 2017 American College of Cardiology (ACC)–American Heart Association (AHA) guidelines regarding hypertension.[4] Nonetheless, fewer than half the adults with hypertension are treated and have their hypertension controlled.[5] Similarly, approximately one third of adults in the United States are eligible for statin therapy according to the 2013 ACC–AHA cholesterol guidelines, but only a minority receive therapy.[6,7] Hypertension and hypercholesterolemia are particularly common in groups with low socioeconomic status, in which treatment rates are strikingly low.[8-11]

Although pharmacologic measures are frequently used to manage cardiovascular risk factors, there are differing opinions regarding implementation. The traditional strategy identifies high-risk persons on the basis of clinical prediction algorithms, an approach that is endorsed in major guidelines. In contrast, a population-based strategy focuses on shifting the entire risk distribution by means of broadly applied, low-cost interventions that involve relatively few side effects.[12] A consideration that favors the population-based approach is the recognition that many persons who have a cardiovascular event would be classified by conventional algorithms as being at low or intermediate risk.[13,14] There are additional challenges with a risk-based approach in resource-limited settings. It is unclear whether traditional prediction algorithms are applicable to persons with low socioeconomic status. Furthermore, a risk-based strategy may be difficult to implement owing to the need for frequent testing and follow-up visits and complex medication regimens.

The "polypill" is a fixed-dose combination of medications with proven benefits for the prevention of cardiovascular disease.[15] In population-based strategies for the prevention of cardiovascular disease, the polypill offers potential advantages over conventional pharmacotherapy. First, the simplicity of using a daily pill may improve adherence to therapy. Second, the elimination of requirements for dose adjustment may be useful in settings in which frequent follow-up visits are impractical. Third, for blood-pressure control, the combination of multiple low-dose medications rather than the use of one or two higher-dose medications may improve the safety profile, given that side effects are typically dose-dependent.[16]

Although there have been previous trials of polypills for the prevention of cardiovascular disease,[17-25] this approach has not been extensively studied in underserved minority populations. Therefore, we undertook a randomized, clinical trial to assess the effectiveness of a polypill-based strategy in an underserved population of persons with low socioeconomic status.

A Quick Take is available at NEJM.org

Methods

Clinical Trial Design

We designed a two-group, open-label, randomized, controlled, clinical trial comparing polypill therapy with usual care. The trial protocol, which is available with the full text of this article at NEJM.org, was approved by the Vanderbilt University institutional review board, the Oversight Advisory Committee of the AHA Strategically Focused Prevention Research Network, and two committees of the Southern Community Cohort Study (SCCS). The trial was monitored by an independent data and safety monitoring board and by the Food and Drug Administration under a noncommercial Investigational New Drug application. The authors vouch for the completeness and accuracy of the data and for the fidelity of the trial to the protocol.

Setting and Recruitment

The SCCS was initiated in 2001 to examine root causes of health disparities in cancer.[26] The study enrolled 85,000 participants, predominantly from minority populations, across a network of community health centers in the southeastern United States; enrollment was completed in 2009. Potentially eligible participants for the polypill trial were identified among previously enrolled SCCS participants living within 50 miles of the Franklin Primary Health Center in Mobile, Alabama, or among current non-SCCS patients or residents near the center.

Eligibility criteria and screening examinations were identical for both the SCCS and non-SCCS participants. Potentially eligible persons 45 to 75 years of age who had no reported history of coronary heart disease, stroke, cancer, liver disease, or insulin-dependent diabetes were sent a prescreening questionnaire. Respondents who were taking no more than two antihypertensive medications were invited to the Franklin Primary Health Center for a clinical examination, which included blood pressure, fasting lipid, and blood chemical measurements. Eligible participants met each of the following criteria: a systolic blood pressure between 120 and 160 mm Hg, an LDL cholesterol level of less than 190 mg per deciliter (4.90 mmol per liter), an estimated glomerular filtration rate of at least 60 ml per minute per 1.73 m^2 of body-surface area, normal potassium levels, hepatic aminotransferase levels of less than three times the upper limit of the normal range, no contraindications to any polypill component, status of not being pregnant, and current use of no more than two antihypertensive medications. In June 2016, the criterion for the upper boundary of systolic blood pressure (160 mm Hg) was removed after consultation with the institutional review board and the data and safety monitoring board. Eligible participants who provided written informed consent were randomly assigned to receive either the polypill or usual care.

TREATMENTS

Participants who were assigned to the polypill group received 90-day refillable supplies of daily trial medication prepared by the Vanderbilt Investigational Drug Service. The polypill consisted of four low-dose medications: atorvastatin (10 mg), amlodipine (2.5 mg), losartan (25 mg), and hydrochlorothiazide (12.5 mg). Generic versions were placed securely in sealed gelatin capsules and bottled in 90-day supplies. The trial pills were produced at a cost to the investigators of $26 per month per participant. The initial dispensation of the polypill supply was shipped overnight to the individual participants, with subsequent refills shipped to the Franklin Primary Health Center pharmacy for distribution to participants.

Participants who were assigned to the usual-care group were offered routine care at the Franklin Primary Health Center, in conjunction with any ongoing care that they were receiving from a primary care physician. For participants in either group, our trial team engaged in consistent communication with each participant's primary care physician, including a standard letter conveying clinical data and the reminder that the physician was free to implement any additional therapies that were deemed to be appropriate.

FOLLOW-UP VISITS

All participants were scheduled for follow-up visits at 2 months and 12 months after randomization. A clinical examination was conducted, blood pressure measured, and a fasting blood sample obtained. Adherence to the polypill regimen was assessed by means of pill counts performed by the trial coordinator at each trial-related visit. Participants received $50 remuneration for each clinic visit that was completed.

OUTCOME MEASURES

The two primary outcomes were the changes in systolic blood pressure and LDL cholesterol level from baseline to 12 months. Blood-pressure data were obtained by calculating the mean of two resting, manual, in-clinic measurements of blood pressure by a trial nurse. An appropriately sized blood-pressure cuff was selected on the basis of the size of the patient. Lipid profiles were obtained by a trained phlebotomist and sent to a single, local laboratory facility. The Martin–Hopkins equation was used to calculate the LDL cholesterol level, with a direct measurement of the LDL cholesterol level when the triglyceride level exceeded 400 mg per deciliter (4.52 mmol per liter). In the polypill group, adherence to therapy was assessed by means of pill count and participant report. Secondary outcomes included changes from baseline to 12 months in the diastolic blood pressure, total cholesterol level, high-density lipoprotein cholesterol level, triglyceride level, and predicted 10-year risk of cardiovascular disease. The 2013 ACC–AHA risk estimator was used to predict the 10-year risk of cardiovascular disease on the basis of the pooled cohort equations; the risk score indicates the likelihood of a person having an atherosclerotic cardiovascular event in the next 10 years.[27,28] Safety outcomes, including serious adverse events, were assessed in both trial groups. Specific side effects were assessed, including the incidence of myalgias, hypotension, and light-headedness.

STATISTICAL ANALYSIS

We estimated the power for our trial on the basis of assumptions about the degree of correlation between the baseline and 12-month values for both systolic blood pressure and LDL cholesterol level. Estimates of baseline variability were based on data from the SCCS and the Jackson Heart Study.[29,30] Assuming a correlation (r) of 0.7 between the two measurements for the two primary outcomes, we calculated that the enrollment of 150 participants in each group would provide the trial with 80% power to detect a between-group difference of 5.3 mm Hg for the systolic blood pressure and 9.8 mg per deciliter (0.25 mmol per liter) for the LDL cholesterol level. Details are provided in the trial protocol.

For the primary analyses, we evaluated changes in systolic blood pressure and LDL cholesterol level from baseline to 12 months. Similar analyses were conducted for changes from baseline to 2 months. Crude differences were calculated and tested for significance with the use of Student's t-test, followed by multivariable regression models with the difference as the dependent variable and treatment group as the primary exposure variable; additional covariates were age, sex, body-mass index, presence or absence of diabetes, presence or absence of hypertension of stage 2 or higher (baseline systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg), and cardiovascular risk score.[28] In sensitivity analyses, we used multiple imputation to account for outcome data that were missing because of death or discontinuation. Two-sided P values of less than 0.05 were considered to indicate statistical significance for the two primary outcomes.

For secondary outcomes, between-group differences and 95% confidence intervals are reported. The 95% confidence intervals were not adjusted for multiplicity, and therefore inferences drawn from these intervals may not be reproducible. To assess adherence to the polypill regimen, we completed pill counts at each refill and computed the percentage of participants reporting at the 2-month and 12-month visits that they had taken the polypill the day before. Prespecified analyses of subgroups according to sex, hypertension of stage 2 or higher (yes or no),

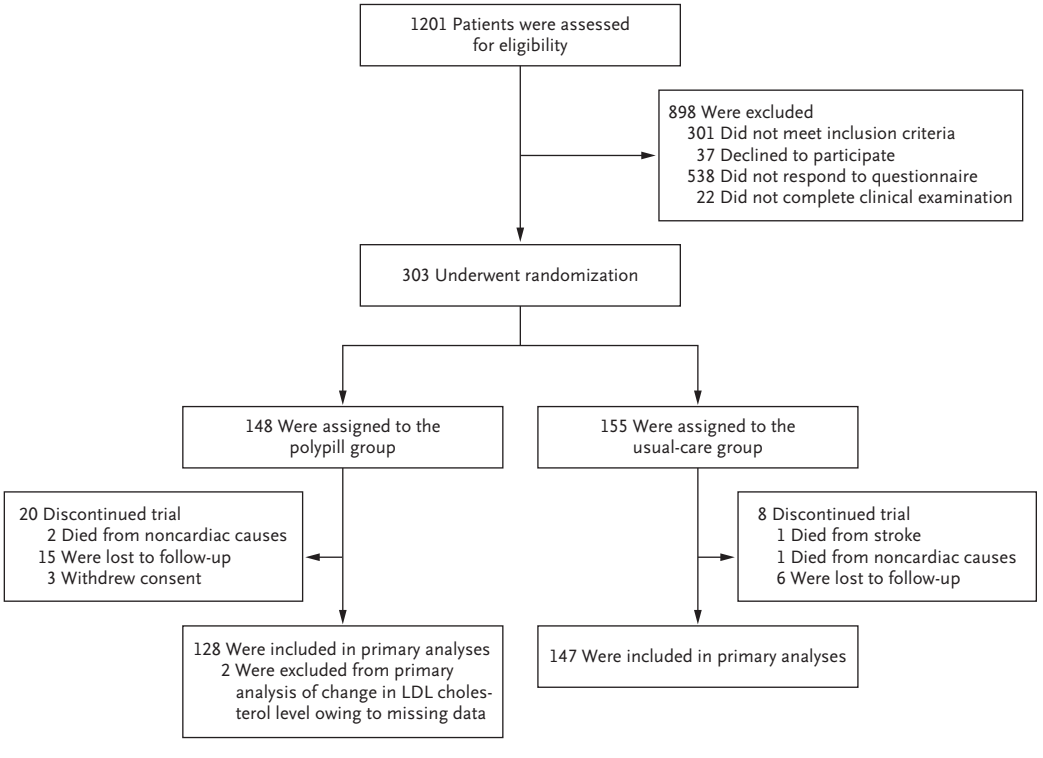

Figure 1. Randomization and Treatment of the Participants.
LDL denotes low-density lipoprotein.

Table 1. Characteristics of the Participants at Baseline.*

Characteristic	Polypill Group (N=148)	Usual-Care Group (N=155)
Age — yr	56±6	56±6
Male sex — no. (%)	65 (44)	56 (36)
Black race — no. (%)†	141 (95)	151 (97)
Body-mass index‡	31.3±8.5	30.4±8.4
Hypertension of stage ≥2 — no. (%)	62 (42)	67 (43)
Diabetes mellitus — no. (%)	17 (11)	22 (14)
Predicted 10-yr risk of cardiovascular disease — %§	12.4±8.9	13.0±10.1
Current smoking — no. (%)	65 (44)	80 (52)
Current medication use — no. (%)		
Any antihypertensive drug	78 (53)	84 (54)
Statin	26 (18)	27 (17)
Amlodipine	31 (21)	35 (23)
Losartan	6 (4)	14 (9)
Hydrochlorothiazide	27 (18)	26 (17)
Blood pressure — mm Hg		
Systolic	140±18	140±17
Diastolic	83±8	83±8
Cholesterol — mg/dl		
LDL	114±32	112±37
HDL	61±21	64±23
Triglycerides — mg/dl	116±86	110±74
Annual household income — no. (%)¶		
<$15,000	107 (72)	120 (77)
$15,000 to <$25,000	28 (19)	21 (14)
$25,000 to <$50,000	7 (5)	11 (7)
$50,000 to <$100,000	6 (4)	3 (2)

* Plus–minus values are means ±SD. There were no significant between-group differences (P<0.05) in the baseline characteristics of the participants. To convert the values for cholesterol to millimoles per liter, multiply by 0.02586. To convert the values for triglycerides to millimoles per liter, multiply by 0.01129. CI denotes confidence interval, HDL high-density lipoprotein, and LDL low-density lipoprotein.
† Race was reported by the participant.
‡ The body-mass index is the weight in kilograms divided by the square of the height in meters.
§ The predicted 10-year risk of cardiovascular disease was calculated by the 2013 American College of Cardiology–American Heart Association risk estimator on the basis of the pooled cohort equations.[27,28]
¶ Annual household income was reported by the participant.

baseline prescription antihypertensive therapy (yes or no), baseline LDL cholesterol level (<130 or ≥130 mg per deciliter [<3.5 or ≥3.5 mmol per liter]), and baseline statin therapy (yes or no) were performed.

RESULTS

CHARACTERISTICS OF THE PARTICIPANTS

From December 2015 through July 2017, a total of 977 SCCS participants met the age criteria for trial eligibility, and 439 returned prescreening questionnaires. A total of 279 potentially eligible SCCS participants underwent screening examinations, and 150 (54%) were enrolled. In addition, 224 Franklin Primary Health Center patients or residents of the surrounding community underwent screening examinations; from this group, 176 persons were found to be eligible, and 153 (68%) were enrolled. Thus, a total of 303 participants were enrolled and underwent randomization, 148 to the polypill group and 155 to the usual-care group (Fig. 1).

A total of 60% of the participants were women. The mean age of the participants was 56 years, and the trial population was predominantly black (96%) (Table 1). Approximately three quarters of the participants reported having an annual household income below $15,000. Obesity was common; the mean body-mass index (the weight in kilograms divided by the square of the height in meters) of the participants exceeded 30, and 43% of the participants had hypertension of stage 2 or higher. The mean estimated 10-year cardiovascular risk was 12.7% overall (12.4% in the polypill group and 13.0% in the usual-care group). Overall, the baseline blood pressure was 140/83 mm Hg, and the baseline LDL cholesterol level was 113 mg per deciliter (2.90 mmol per liter). None of the baseline characteristics differed significantly (P<0.05) between the groups.

MEDICATION USE

At the final visit, 80% of the participants who had received a prescription for polypills reported having taken the pill the day before. On the basis of counts of unused pills that were conducted at each refill visit, the median adherence to the polypill regimen was 86% (interquartile range, 79 to 93).

In the polypill group, clinicians reduced doses of other antihypertensive or lipid-lowering medications or discontinued their use in 44% of the patients. A total of 2% of the participants in the

Table 2. Primary and Secondary Outcomes.*

Outcome	Polypill Group		Usual-Care Group		Difference (95% CI)†	P Value
	Baseline	At 12 Mo	Baseline	At 12 Mo		
Primary outcomes						
Systolic blood pressure (mm Hg)	140±19	131±21	140±17	138±23	−7 (−12 to −2)	0.003
LDL cholesterol (mg/dl)	113±33	98±35	113±37	109±32	−11 (−18 to −5)	<0.001
Secondary outcomes						
Diastolic blood pressure (mm Hg)	83±8	78±9	83±8	81±10	−3 (−5 to −1)	—
Total cholesterol (mg/dl)	198±37	183±47	199±42	194±37	−11 (−19 to −3)	—
HDL cholesterol (mg/dl)	62±21	60±21	64±23	63±21	−1 (−4 to 2)	—
Triglycerides (mg/dl)	116±88	118±104	110±76	115±71	−2 (−20 to 15)	—
Predicted 10-yr risk of cardiovascular disease (%)	12.0±8.8	9.4±8.0	12.8±9.9	13.3±11.5	−3.1 (−4.6 to −1.6)	—

* Plus–minus values are means ±SD. Data on systolic blood pressure (at both baseline and 12 months) were available for 128 participants in the polypill group and for 147 in the usual-care group; and data on the LDL cholesterol level (at both baseline and 12 months) were available for 126 and 147, respectively. A total of 20 participants in the polypill group and 8 in the usual-care group discontinued trial participation and did not have data at 12 months. Two participants in the polypill group had missing baseline data on the LDL cholesterol level, owing to an insufficient blood sample (in 1) and missing direct measurement of LDL cholesterol (in 1). One participant in the polypill group had data on the triglyceride level censored because the value was greater than 1000 mg per deciliter (11.30 mmol per liter).

† The 95% confidence intervals were not adjusted for multiplicity, and therefore inferences drawn from these intervals may not be reproducible. For cardiovascular disease risk, the between-group difference is shown in percentage points.

polypill group had an escalation in therapy. In the usual-care group, none of the participants had a deescalation of therapy and 10% had an escalation of therapy.

OUTCOMES

A total of 275 participants (91%) completed the 12-month trial visit. Data for the two primary outcomes are shown in Table 2 and Figure 2. The mean systolic blood pressure decreased by 9 mm Hg in the polypill group, as compared with 2 mm Hg in the usual-care group (difference, −7 mm Hg; 95% confidence interval [CI], −12 to −2; P=0.003). The mean LDL cholesterol level decreased by 15 mg per deciliter (0.40 mmol per liter) in the polypill group, as compared with 4 mg per deciliter (0.10 mmol per liter) in the usual-care group (difference, −11 mg per deciliter; 95% CI, −18 to −5 [−0.30 mmol per liter; 95% CI, −0.45 to −0.10]; P<0.001).

To account for patients with missing data on the systolic blood pressure or LDL cholesterol level at 12 months, we performed a sensitivity analysis using multiple imputation. The multivariable-adjusted differences in the changes from baseline to 12 months remained significant for both systolic blood pressure (between-group difference, −7 mm Hg; 95% CI, −11 to −2; P=0.002) and LDL cholesterol level (between-group difference, −11 mg per deciliter; 95% CI, −17 to −5 [−0.30 mmol per liter; 95% CI, −0.45 to −0.10]; P<0.001).

Data for the secondary outcomes are shown in Table 2. At 12 months, the net difference in the diastolic blood pressure between the polypill group and the usual-care group was −3 mm Hg (95% CI, −5 to −1), and the net difference in the total cholesterol level was −11 mg per deciliter (95% CI, −19 to −3 [−0.30 mmol per liter; 95% CI, −0.50 to −0.10]). Changes in the systolic blood pressure and LDL cholesterol level in the two treatment groups, according to prespecified subgroups, are shown in Table 3. We also examined systolic blood pressure and LDL cholesterol level at the 2-month visit, with data available for 291 participants (96%). At the 2-month visit, the net between-group difference in the systolic blood pressure was −5 mm Hg (95% CI, −9 to −2), and the net between-group difference in the LDL cholesterol level was −18 mg per deciliter (95% CI, −24 to −12 [−0.45 mmol per liter; 95% CI, −0.60 to −0.30]).

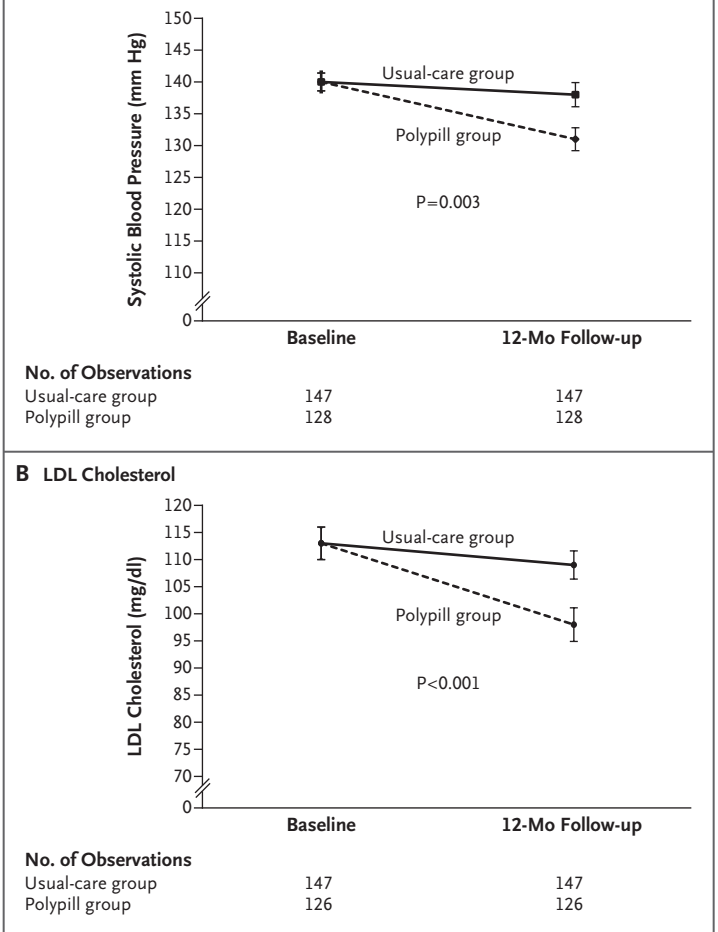

Figure 2. Changes in Systolic Blood Pressure and LDL Cholesterol Level at 12 Months.

I bars indicate the standard error. To convert the values for cholesterol to millimoles per liter, multiply by 0.02586. Two participants in the polypill group were excluded from the analysis of the LDL cholesterol level owing to missing baseline data (an insufficient blood sample in one participant and a missing direct measurement of LDL cholesterol in one).

SAFETY

During the trial, there were five serious adverse events: three noncardiac deaths (one death due to complications after urologic surgery and one death due to acute alcohol intoxication in the polypill group and one death due to a motor vehicle accident in the usual-care group), one death from stroke (in the usual-care group), and one case of coronary-artery bypass surgery (in the usual-care group). None of the events were judged by the data and safety monitoring board to be related to the trial. In the polypill group, the reported incidence of myalgias was 1% and the incidence of hypotension or light-headedness was 1%. No participants in the polypill group had abnormal results on liver-function tests.

DISCUSSION

In this randomized trial, the use of a polypill yielded greater reductions from baseline in systolic blood pressure and LDL cholesterol level than were observed with usual care in a socioeconomically vulnerable, minority population. There are several distinctive aspects of this trial. First, the trial showed the feasibility and effectiveness of a polypill-based strategy in a real-world clinical setting in which most patients reported an annual household income of less than $15,000. Second, there are limited data on the use of a dedicated polypill in the United States, especially in black patients, in whom patterns of cardiovascular risk factors may differ from those in white patients. Third, the trial was conducted entirely at a federally qualified community health center. These centers provide an important safety net in medically underserved communities, but these populations of patients are poorly represented in clinical trials.

The observed reductions in systolic blood pressure and LDL cholesterol level were statistically and clinically significant. On the basis of meta-analyses of cardiovascular-outcomes trials in primary prevention,[31-37] we estimate that such changes, if sustained, would lead to an approximate 25% reduction in the incidence of cardiovascular events. This figure is consistent with the 25% relative reduction in the estimated cardiovascular risk that was observed among the participants who had been randomly assigned to receive the polypill, as compared with those assigned to receive usual care (Table 2).

Retention in the trial was high, with 91% of participants completing the final trial visit. Notwithstanding the limitations of participant reports and pill counts, adherence in the polypill group appeared to be high, a finding that is noteworthy given that approximately half the patients in the United States stop their prescribed cardiovascular medications within 1 year.[5] The simplicity of taking a single daily pill may be an important contributor to adherence.

Participants in the trial were free to continue

Table 3. Changes in Systolic Blood Pressure and LDL Cholesterol Level, According to Prespecified Subgroups.*

Outcome and Subgroup	No. of Participants	Polypill Group		Usual-Care Group		P Value for Interaction
		Baseline	At 12 Mo	Baseline	At 12 Mo	
Systolic blood pressure (mm Hg)						
Sex						0.15
Male	103	144±20	136±23	140±16	135±20	
Female	172	138±17	128±19	140±18	139±25	
Hypertension of stage ≥2						0.21
Yes	119	157±16	141±21	156±14	151±25	
No	156	127±6	123±16	128±6	129±17	
Baseline therapy†						0.82
Yes	146	139±17	131±19	142±18	142±25	
No	129	142±20	132±22	137±16	133±20	
LDL cholesterol (mg/dl)						
Sex						0.84
Male	102	105±36	93±35	101±38	100±34	
Female	171	118±30	101±35	119±35	114±29	
LDL cholesterol level						0.55
≥130 mg/dl	81	151±17	122±33	157±19	137±26	
<130 mg/dl	192	98±23	88±30	94±24	97±26	
Statin use at baseline						0.53
Yes	43	108±33	101±31	102±30	102±25	
No	230	114±33	98±35	115±38	110±33	

* Plus–minus values are means ±SD. A total of 20 participants in the polypill group and 8 in the usual-care group discontinued trial participation and did not have data at 12 months. Two participants in the polypill group had missing baseline data on the LDL cholesterol level, owing to an insufficient blood sample (in 1) and a missing direct measurement of LDL cholesterol (in 1).

† Baseline therapy was defined as the use of any prescription antihypertensive therapy before enrollment.

or discontinue their nontrial medications. One potential concern is undertreatment if patients substitute the polypill for more potent regimens. It is reassuring, then, that the subgroup of participants who had been taking statins or antihypertensive medications before trial enrollment still had reductions in blood pressure and LDL cholesterol level with the polypill.

Several limitations of the trial warrant comment. We used an open-label design to preserve clinician flexibility to adjust medications in either trial group and to assess the real-world effectiveness of the polypill approach. We cannot rule out the possibility that the treatment of participants in one or both groups was influenced by trial involvement or trial-group assignment. We also acknowledge that the trial was conducted in a single community health center and therefore may not be generalizable to other settings.

The primary outcomes could be ascertained only in participants who completed the 12-month visit. Thus, between-group differences in loss to follow-up could have influenced the results. However, the results were similar in sensitivity analyses in which multiple imputation was used for missing outcome data. In addition, even if the results for each participant in the polypill group who did not complete the 12-month visit did not differ from those for patients who received usual care, the overall mean reductions in systolic blood pressure and LDL cholesterol level

would be attenuated only slightly (to between-group differences of –6 mm Hg and –10 mg per deciliter [–0.25 mmol per liter], respectively).

Participants in the polypill group were not charged for the trial medication, which introduced the possibility that reduced drug cost contributed to the results. However, our trial site had a 340B pharmacy program that provided medications free of charge or nearly free of charge to all uninsured patients. The only expense would have been a copayment of $3 or less for a 90-day supply of medication. Thus, drug cost was probably not a substantial barrier in the usual-care group.

We recognize that a "one size fits all" approach to cardiovascular disease prevention runs counter to current trends in precision medicine, in which clinical, genomic, and lifestyle factors are used for the development of individualized treatment strategies.[38,39] Although the precision approach has clear virtues, a broader approach may benefit patients who face barriers to accessing the full advantages of precision medicine. Challenges in implementing cardiovascular disease prevention that are due to lack of income, underinsurance, and multiple visits for testing and drug-dose adjustment may be especially problematic in populations with low socioeconomic status. Thus, the simplicity and low cost of the polypill regimen make this approach attractive when such barriers are common. It is important to emphasize that use of the polypill does not preclude individualized, add-on therapies for residual elevations in blood-pressure or cholesterol levels, as judged by a patient's physician.

In conclusion, in this randomized trial in a low-income, minority population, a polypill-based strategy led to reductions from baseline in systolic blood pressure and LDL cholesterol level that were significantly greater than those observed with usual care.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

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CLINICAL TRIAL REGISTRATION

The *Journal* requires investigators to register their clinical trials in a public trials registry. The members of the International Committee of Medical Journal Editors (ICMJE) will consider most reports of clinical trials for publication only if the trials have been registered. Current information on requirements and appropriate registries is available at www.icmje.org/about-icmje/faqs/.

Table 1: Polypill Studies Comparison[4-11]

Study/ Author	Design/Comparison	Patients	Demographics	Follow up	Inclusion Criteria	Exclusion Criteria	Formulation of Polypill	Primary Outcomes	Secondary Outcomes
TIPS-1 Yusuf, S et.al., 2009[4]	Randomized, Double Blinded Polypill vs. "Usual Care" Usual Care=8 Groups: ASA alone, Simvastatin alone, HCTZ alone, Three combinations of the two BP lowering meds, Three BP lowering meds alone, and the three BP lowering drugs + ASA	N=2053 N=412 to Polycap	43.9% Female Mean Age: 54 Population: 50 centers in India	16 weeks	Individuals without CVD with one risk factor	-Already receiving one of the study drugs -Taking two or more BP lowering drugs -Serum LDL-C≥4.5 mmol/L -Cr ≥2.0 mg/dL -K+ ≥5.5 mmol/L -Abnormal liver function -Asthma -Pregnant or lactating	-HCTZ 12.5 mg -Atenolol 50mg -Ramipril 5mg -Simvastatin 20mg -ASA100mg	LDL-C decrease 0.7% vs. 0.83% (simvastatin alone) Mean BP decrease 7.4 mm Hg vs. 6.9 mm hg in other groups with three BP lower agents HR decrease 7 bpm (95% CI 6–8) in both Polycap and groups with atenolol Reduction in Urinary 11-dehydrothromboxane B2 283.1 ng/mmol (95% CI 229.1–337.0) vs. 348.8 (277.6–419.9) ng/mmol in ASA alone and 350ng/mmol (294.6–404.0) in other group with ASA Rate of discontinuation for safety (major cardiovascular event or bleed) 14.8%	Total cholesterol decreases by 0.83% in polypill and simvastatin alone Overall side Effects for Polypill -Dizziness or hypotension (6.3%) -Cough (5.3%) -Gastritis/dyspepsia (1.2%) -Bradycardia (0.2%) -Cr increase by 50% (8.5%) -K+ ≥5.5 (2.9%)
PILL Rodgers, A et.al., 2011[9]	Randomized, Double Blinded Polypill vs. Placebo	N= 378 Polypill: N=189 Placebo: N=189	80% male 20% female Mean age 61.2 Population: Australia: 21 Brazil: 8 India: 109 Netherlands: 102 New Zealand: 12 UK:113 USA: 13	12 weeks	- Estimated 5-year risk of 7.5% or greater)*	Specific indication for any components in the polypill Contraindications to any of the components Diagnosis of Diabetes Mellitus GFR ≤30 mL/min	-ASA 75mg -Lisinopril 10mg -HCTZ 12.5mg -Simvastatin 20mg	Decrease in SBP by 9.9 mm hg (95% CI: 7.7 to 12.1) compared to placebo Decrease in LDL-C 0.8 mmol/L (95% CI: 0.6 to 0.9) compared to placebo	Discontinuation rate 23% vs. 18% Hypotension/Dizziness 30% vs. 11% Gastric irritation/bleeding tendency 17% vs. 6% There were no reported deaths, major vascular events, major bleeding events

Wald et al., 2012[5]	Randomized, Double-blind, Crossover (polypill x12 weeks, and placebo x 12 weeks) Polypill vs. Placebo	N=86 N=43 to each group and then switching after 12 weeks	74% male 26% female Mean Age 59 Population: Adults in London, UK	12 weeks	Age ≥50 AND no history of cardiovascular disease Recruited from group already taking simvastatin and BP lowering agents for a cardiovascular prevention program	No contraindications to polypill components	-Amlodipine 2.5mg -Losartan 25mg -HCTZ 12.5mg -Simvastatin 40mg	Decrease in Mean SBP of 17.9 mm Hg (95% CI, 15.7–20.1) Decrease in LDL-C by 1.4 mmol/dL (95% CI, 1.2–1.6)	Decrease in DBP by 9.8 mm Hg (95% CI, 8.1–11.5) Muscles aches: N=9 vs. N=1 100% adherence to polypill, 2 people stopped placebo
TIPS-2 Yusuf, S et.al., 2012[6]	Randomized, double blinded, 2x2 controlled 1. Single-dose polypill plus placebo 2.Two polypill capsules plus K+	N=518 1.Low dose (single polypill)- N= 261 2. High dose (two polypills) N=257	Group 1: 58% male Group 2: 59% male Mean age: 57 Population: 27 clinical centers in India	8 weeks	-Previous vascular disease OR high-risk diabetes mellitus -BP >130/80 or >120/80 on medications	-Intolerance to any medications in study -Clear indication to any specific medication in study -Cr ≥2 or GFR ≤45 -K+ ≥5	-HCTZ 12.5mg -Atenolol 50mg -Ramipril 5mg -Simvastatin 20mg -Aspirin 100mg	Changes in SBP --2.8 mm Hg more in Group 2(95% CI, –0.17 to –2.8 mm Hg) Changes in Heart Rate -No difference LDL-C (CI, –11.3 to –1.9; P=0.006) -increased by 16.6 mmol/L in Group 1 -increased by 10 mmol/L in Group 2	Changes in Potassium -4.3 mmol/L vs. 4.4 mmol/L (CI, –0.03 to 0.1; P=0.20) Changes in Cr -No difference Dyspepsia 1. 0.7% 2. 0.5% Dizziness 1. 1.8% 2. 1.1% Hypotension 1. 0.8% 2.0.9% Discontinuation 1. 6.9% 2. 7.8%
Muñoz D et al., 2019[7]	Randomized Controlled Polypill vs. Usual care (multiple pills)	N=303 N=148 to polypill (group 1) N=155 to usual care (group 2)	Group 1: 44% male Group 2: 36% male Mean Age 56 Population: Adults in Alabama, United States	12 months	-No hx of CAD, Stroke, Liver Disease, Insulin-dependent Diabetes Mellitus -SBP between 120 and 160	-LDL-C >190 -GFR <60 -Abnormal Potassium levels -Abnormal aminotransferase levels -Pregnancy -One more than two anti-hypertensive medications	-Atorvastatin 10mg -Amlodipine 2.5mg -Losartan 25mg -HCTZ 12.5mg	Change compared to Usual care -Mean SBP: -7 mm Hg -Mean LDL-C: 11 mmol/dL	Adherence 86% Change Compared to Placebo -DBP: -3 mm Hg -Total chol: -11 -HDL-C: -1 -TG: -2 -10 yr cardiovascular risk: -3.1%

			Black 96% Other minority populations 4%						Incidences in polypill group of -Myalgias 1% -hypotension or light headedness 1%
HOPE-3 Yusuf S et al.,2018[8]	Randomized controlled 2x2'' Group 1: Rosuvastatin 10 vs. Placebo Group 2: BP Polypill vs. Placebo Group 3: BP Polypill +Rosuvastatin vs. Placebo	N= 12,705 1.Rosuvastatin 10 (6,361) vs. placebo (6,344) 2.BP polypill (6,356) vs. Placebo (6,349) 3.BP polypill and rosuvastatin (3180) vs Placebo (3,168)	46% Female Mean age 65.8 Population: Chinese: 29% Hispanic:27% White 20% SouthAsian:15% Black: 2%	5.6 years	Men ≥5 Women ≥65 PLUS at least one of the following: -Elevated waist-to-hip ratio -Low HDL-C -Current or recent tobacco use -Dysglycemia -Family history of premature CAD -Mild renal dysfunction -Women with at least two of the above risk factors	Participants with CVD Indication for or contraindication to: -statins, -ACEi/ARBs -thiazide diuretics	Candesartan 16mg, HCTZ 12.5mg	Composite of CV Death/MI/Stroke Group 1 -3.7% vs. 4.8% Group 2. -4.1% vs.4.4% Group 3. -3.6% vs. 5.5%	Group 1 -MI 0.7% vs1.1% -CAD 1.7% vs. 2.2% -Hospitalizations for CAD 4.4% vs. 5.8% -Adherence 77.3% vs. 74.8% Group 2 -MI 0.8% vs. 1% -Stroke 1.2% vs. 1.5% -Hospitalizations for CAD 5% vs. 5.2% -Symptomatic hypotension 3.4% vs. 2% -Adherence: 76.8% vs. 75.7% Group 3 -CV death 2.4% vs. 2.9% -MI 0.7% vs. 1.2% -Hospitalizations for CAD 4.4% vs. 6% -Adherence 74.6% vs. 71.8%
Poly-Iran Roshandel G et al., 2019[10]	Randomized (1:1) cohort study; Clustered (assorted by villages) Polypill vs. Minimal Care(Lifestyle education)	N=6838 -N=3417 to minimal care -N=3421 to polypill	Polypill group: 5.15% women Minimal care group: 49.1% women Ages 50-75 yrs Population: Members of Golestan province in Iran	5 years	Participants from rural areas (Golestan province) >50yrs	-Hypersensitivity to any of the components of the polypill -Angioedema -Hx of GI bleed within 3 months -Hx of stroke -Pregnancy or Lactation	-HCTZ 25mg -ASA 81 mg -Atorvastatin 20mg -Enalapril 5mg	Major CV Events 5.9% vs. 8.8% Mortality 5.9% vs. 6.5%	Fatal Ischemic Heart Disease 3.7% vs. 4.9% Non-Fatal Ischemic Heart Disease 3.7% vs. 4.9% Non-CV related death 4.4% vs. 3.6% Heart Failure 0.4% vs. 0.5% Non-Fatal Stroke 0.5% vs. 1.1%

						-Hx of bleeding disorder (ex. hemophilia) -Alcohol consumption >3x/day -Advanced Liver disease -Uncontrolled seizures -Cr ≥2 or GFR ≤30 -Hgb ≤10 in women or ≤11 in men -SBP <90 and/or DBP<60			Fatal Stroke 0.2% vs. 0.6% Sudden Death 0.6% vs. 0.8% Intracranial Hemorrhage: N=10 vs. 11 GI Bleed: N= 13 vs. 9 Median Adherence 80.5%
Study[11]: TIPS-3 Authors Yusuf,S et al 2020	1:1 Randomized Controlled then 2x2 1. Polypill vs. Placebo 2. ASA vs. Placebo 3. Polypill + ASA vs. Placebo	N= 5,713 -N=2,861 to polypill -N=2,852 to placebo -Also randomized to ASA vs. placebo	53% Female 47% Male Mean Age 63.9 Population -India: 2739 -Philippines: 1676 -Colombia: 489 -Bangladesh: 295 -Canada: 131 -Malaysia: 119 -Indonesia: 118 -Tunisia: 107 -Tanzania: 39	4.6 years	-Men ≥50 y -women ≥55y AND INTERHEART Risk Score (IHRS) of ≥10 OR Men/women ≥65 years with an IHRS of ≥5	-Vascular disease -Contraindication to any of the drugs involved or aspirin or Vitamin D -SBP ≤120mm Hg -Symptomatic hypotension -Peptic ulcer dz/dyspepsia/bleeding	-Atenolol 10mg -Simvastatin 10mg -HCTZ 25mg -Ramipril 10mg	-CV death: 1. 2.9% vs. 3.5% 2. 3% vs. 3.5% 3. 3.6% vs. 5.3% -MI: 1. 0.6% vs. 0.9% 2. 0.8% vs. 0.7% 3. 3.6% vs. 5.3% -Stroke: 1. 0.9% vs. 1.3% 2. 0.8% vs. 1.4% 3. 0.7% vs. 1.6% -Arterial revascularization: 1. 0.4% vs. 0.9%	Mean difference in systolic BP: 1. 5.8 mm Hg Mean difference in LDL-C: 19 mg/dl All-cause mortality: 1. 5.2% vs. 5.7% 2. 5.1% vs. 5.9% 3. 5.2% vs. 6.5% Dizziness or hypotension: 1. 2.7% vs. 1.1% Major bleeding 2. 0.7% vs. 0.7% GI Bleed 2. 0.4% vs. 0.4% Adherence: 43% discontinued polypill by the end

*The risk score (Framingham) included age, sex, SBP, ratio of total to high-density lipoprotein cholesterol (HDL-C), diabetes, smoking, and a 5% adjustment for people from the Indian subcontinent(when applicable).

ACEi (Angiotensin Converting Enzyme Inhibitors), ARB (Angiotensin Receptor Blocker), ASA (aspirin), BP (Blood Pressure), BPM (beats per minute), CAD (coronary artery disease), CV (cardiovascular), CVD (cardiovascular disease), Cr (creatinine), DBP (Diastolic Blood Pressure), dL (deciliter), mL (milliliters), GFR (Glomerular Filtration Rate), HCTZ (Hydrochlorothiazide), Hgb (hemoglobin), Hx (history), K+ (Potassium), L (liter), LDL-C (Low Density Lipoprotein-cholesterol), mg (milligrams), MI (myocardial infarction), min (minute), mmol (millimoles), Polycap (Polypill Capsule), SBP (Systolic Blood pressure)

The International Polycap Study-3 (TIPS-3): Design, baseline characteristics and challenges in conduct

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Background It is hypothesized that in individuals without clinical cardiovascular disease (CVD), but at increased CVD risk, a 50% to 60% reduction in CVD risk could be achieved using fixed dose combination (FDC) therapy (usually comprised of multiple blood-pressure agents and a statin [with or without aspirin]) in a single "polypill". However, the impact of a polypill in preventing clinical CV events has not been evaluated in a large randomized controlled trial.

Methods TIPS-3 is a 2x2x2 factorial randomized controlled trial that will examine the effect of a FDC polypill on major CV outcomes in a primary prevention population. This study aims to determine whether the Polycap (comprised of atenolol, ramipril, hydrochlorothiazide, and a statin) reduces CV events in persons without a history of CVD, but who are at least at intermediate CVD risk. Additional interventions in the factorial design of the study will compare the effect of (1) aspirin versus placebo on CV events (and cancer), (2) vitamin D versus placebo on the risk of fractures, and (3) the combined effect of aspirin and the Polycap on CV events.

Results The study has randomized 5713 participants across 9 countries. Mean age of the study population is 63.9 years, and 53% are female. Mean INTERHEART risk score is 16.8, which is consistent with a study population at intermediate CVD risk.

Conclusion Results of the TIP-3 study will be key to determining the appropriateness of FDC therapy as a strategy in the global prevention of CVD. (Am Heart J 2018;206:72-9.)

Introduction and rationale of the TIPS-3

With 80% of cardiovascular disease (CVD) cases now occurring in low- and middle-income countries (LICs and MICs), there is a growing need to implement CVD preventive strategies that are highly impactful, low cost, and can be adopted across a range of health resource settings. An immediately impactful strategy is to modify major risk factors for CVD development using combinations of proven, safe, widely available and inexpensive drugs. This approach has been the basis for the development of fixed dose combination (FDC) therapy or "the polypill concept" for the prevention of CVD.

Studies comparing the effects of a FDC pill (usually containing two or three blood pressure agents and a statin) on risk factor levels have shown that significant reductions in blood pressure and cholesterol levels can be achieved, with better adherence compared to usual care.[1] Furthermore, the extent of blood pressure and cholesterol lowering achieved could translate to reductions in CVD risk ranging from 50–60%.[1] However, studies that directly examine clinical outcomes with a FDC pill are lacking, and even a meta-analysis of existing trials had too few events to provide a reliable estimate of the benefits of a polypill on CVD.[2] The Heart Outcomes Prevention Evaluation (HOPE)-3 placebo-controlled randomized controlled trial (RCT) tested a "strategy" of FDC blood pressure and cholesterol lowering therapy with

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ORIGINAL RESEARCH ARTICLE

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Preservation of Bioavailability of Ingredients and Lack of Drug-Drug Interactions in a Novel Five-Ingredient Polypill (Polycap™)

A Five-Arm Phase I Crossover Trial in Healthy Volunteers

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Abstract

Background: The Polycap™ (polypill; aspirin [acetylsalicylic acid], ramipril, simvastatin, atenolol, and hydrochlorothiazide) was found to be safe and effective for reducing multiple cardiovascular risk factors in The Indian Polycap™ Study (TIPS).

Objective: We evaluated the bioavailability of each ingredient of the Polycap™ and determined any drug-drug interactions relative to single component reference preparations.

Methods: The bioavailability of the ingredients of the Polycap™ (T; test) when formulated as a single capsule was compared with that of identical capsules with each of its ingredients administered separately (R; reference) in a five-arm, randomized, single-dose, two-period, two-treatment, two-sequence, crossover trial with at least a 2-week washout period in a total of 195 healthy volunteers. Plasma concentrations of each drug and, where applicable, its active metabolite were measured using validated liquid chromatography-tandem mass spectrometry and ultra-performance liquid chromatography. Mean pharmacokinetic parameters and their standard deviations were computed for each analyte.

Results: Comparative bioavailability was computed and no drug-drug interactions and no difference in comparative bioavailability were concluded for each ingredient based on point estimates of the T/R ratio of the geometric means falling within 80–125% for peak plasma concentration (C_{max}), area under the plasma concentration-time curve from time zero to the last measurable concentration (AUC_t), and AUC from time zero to infinity (AUC_∞). The T/R ratio for C_{max}, AUC_t and AUC_∞ was within 80–125% for atenolol, hydrochlorothiazide, ramipril, ramiprilat and dose-normalized salicylic acid. However, for simvastatin, the T/R point estimates for C_{max}, AUC_t and AUC_∞ for Ln-transformed data were significantly lower (~3–4%) than the lower bound of 80%. For its active metabolite, simvastatin acid, these estimates were significantly higher (~25–35%) than the higher bound of 125%. Thus, the increased bioavailability of active simvastatin acid appeared to compensate for the loss of bioavailability of simvastatin.

Conclusion: The Polycap™ was found to be effective and safe in the previously published TIPS trial. The present study in healthy volunteers establishes that Polycap™ is safe (no serious adverse events) and well tolerated, and that there is no indication of pharmacokinetic drug-drug interactions for any of the ingredients, with their bioavailabilities being well preserved.

Background

Administering multiple proven drugs in a single pill or capsule has been advocated for both secondary[1] and primary prevention[2] of cardiovascular disease, and has been postulated to reduce the morbidity/mortality associated with this disease by 75–80% by reducing risk factors. However, no study has examined whether several active ingredients recommended for a polypill for cardiovascular disease can be effectively and safely combined.[2] We therefore conducted a large phase II

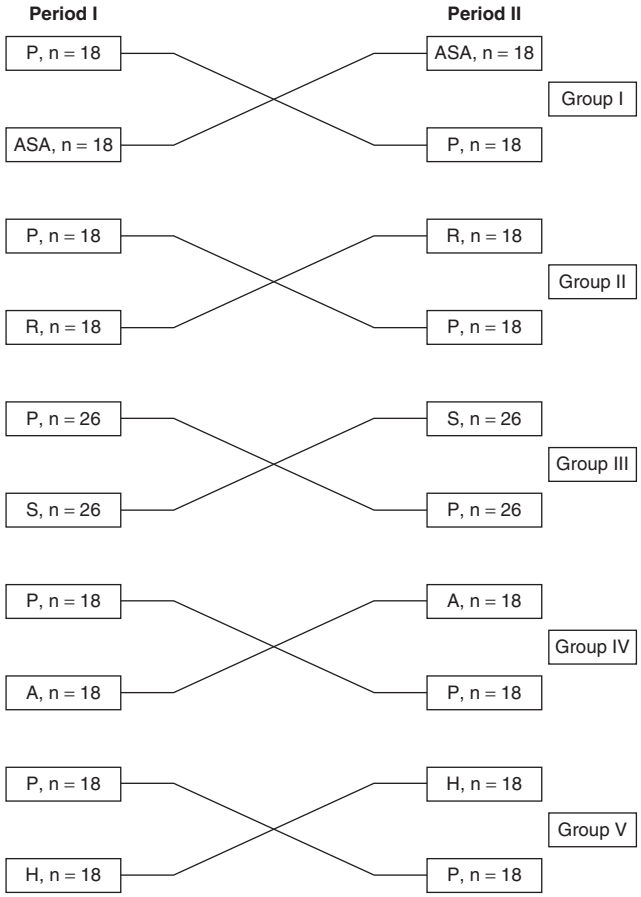

Fig. 1. Schematic representation of the trial design. **A** = atenolol; **ASA** = aspirin (acetylsalicylic acid); **H** = hydrochlorothiazide; **P** = Polycap™ capsules; **R** = ramipril; **S** = simvastatin.

randomized trial, The Indian Polycap™ Study (TIPS), in 2000 patients with at least one cardiovascular risk to evaluate whether the Polycap™ (Cadila Pharmaceuticals Ltd, Ahmedabad, Gujarat, India) [a polypill], containing enteric-coated aspirin (acetylsalicylic acid) [100 mg], ramipril (5 mg), simvastatin (20 mg), atenolol (50 mg), and hydrochlorothiazide (12.5 mg), would effectively and safely reduce selected cardiovascular risk factors.[3] The Polycap™ was found to significantly reduce multiple risk factors for cardiovascular diseases. The reductions in SBP, DBP, and HR observed in the study were 7.4 mmHg, 5.6 mmHg, and 7.0 beats/min, respectively; these effects were similar to the additive effects of its individual ingredients as assessed in a control group who received the components separately. The Polycap™ also significantly reduced low-density lipoprotein (LDL) cholesterol levels (by 0.70 mmol/L) and the urinary 11-dehydrothromboxane B2 level (by 283.1 ng/mmol of creatinine); these reductions were slightly less than those with simvastatin or aspirin alone. Although statistically noninferior to the reference drugs administered separately in TIPS, both the antidyslipidemic and BP-lowering effects of the Polycap™ were 20% smaller than those of the combined effects of the theoretical polypill proposed by Wald and Law.[2,3] The safety and tolerability of Polycap™ were similar to those of the single ingredients.[3]

When more than one drug is combined in a single pharmaceutical preparation, drug-drug and drug-metabolite interactions may occur which could result in altered bioavailability of some of its components. Such interactions can lead to toxic or suboptimal levels of one or more ingredients (and metabolites), which may lead to increased adverse effects or alternatively decreased efficacy. In either scenario, the causes may be pharmacokinetic (drug or metabolite concentrations may increase or decrease) or pharmacodynamic (individual biologic drug effects may change) or both. While the phase II clinical trial TIPS[3] was designed to test the efficacy (in terms of risk factor reductions) and clinical safety of the Polycap™, we studied the pharmacokinetics of the Polycap™ (bioavailability and

Table I. Baseline parameters (mean ± SD) of participants enrolled in the study

Group	No. of participants	Age (y)	Cholesterol level (mg/dL)	Platelet count ($\times 10^3/\mu L$)	Body mass index (kg/m^2)	Triglyceride level (mg/dL)	SBP at predose (mmHg)	DBP at predose (mmHg)
I (Polycap™ vs aspirin [acetylsalicylic acid])	36	32.94 ± 6.64	177.50 ± 33.44	295.11 ± 66.87	21.58 ± 2.14	138.22 ± 63.21	124.63 ± 5.29	81.89 ± 2.05
II (Polycap™ vs ramipril)	36	34.89 ± 8.77	175.58 ± 30.19	274.75 ± 60.68	21.16 ± 2.55	128.72 ± 57.59	124.89 ± 5.52	81.72 ± 2.44
III (Polycap™ vs simvastatin)	52	32.56 ± 7.30	170.04 ± 31.77	278.21 ± 60.58	20.83 ± 2.32	120.46 ± 66.71	118.85 ± 9.45	75.19 ± 5.45
IV (Polycap™ vs atenolol)	35	32.09 ± 8.69	166.86 ± 37.21	273.57 ± 72.58	20.28 ± 2.10	131.66 ± 70.19	126.51 ± 4.48	81.89 ± 2.11
V (Polycap™ vs hydrochlorothiazide)	36	32.81 ± 7.19	178.06 ± 36.49	256.86 ± 70.05	20.59 ± 2.14	128.61 ± 67.75	124.33 ± 4.50	81.33 ± 1.85

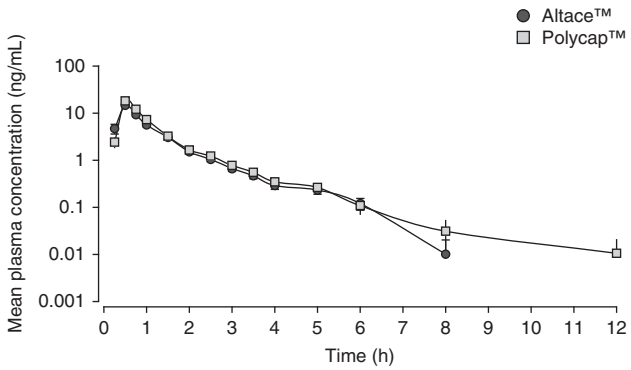

Fig. 2. Mean (±SE) plasma ramipril concentration-time profiles in 35 evaluable healthy volunteers following administration of a single dose of Polycap™ or Altace™ 5 mg capsules.

drug-drug interactions) in a parallel pharmacokinetic trial involving healthy volunteers. The latter study, presented in this article, was undertaken at about the same time as TIPS; results are reflected in light of both the studies.

Materials and Methods

Participants

One hundred and ninety-six healthy adult male volunteers from the central Gujarat area of India aged between 18 and 50 years (83 participants were aged between 36 and 50 years, representing a more vulnerable age group for cardiovascular morbidity) with a body mass index (BMI) of 18–25 kg/m^2 were selected from our database for this study. This database was generated from voluntary participation in different pharmacokinetic/pharmacodynamic studies over the preceding 5 years. All volunteers were assessed as healthy based on medical history, clinical examination, BP, 12-lead ECG, 2-D echocardiography, treadmill test, and laboratory investigations (hematology, serology, blood chemistry, urine analysis, and chest x-ray). Subjects were excluded if they had a history or evidence of cardiac, hepatic, renal, gastrointestinal, or hematological deviations; any acute/chronic disease; drug allergy; positive urinary screening test for drugs of abuse (amphetamines, barbiturates, benzodiazepines, cocaine, morphine, and marijuana); positive alcohol breath analyzer test; or coffee/tea/xanthine-containing food consumption within 48 hours prior to the study. Also excluded were subjects who participated in any other clinical investigation using an experimental drug or had bled more than 300 mL in the past 3 months.

Study Design and Interventions

In a five-arm, randomized, single-dose, two-period, two-treatment, two-sequence, crossover study (figure 1), we evaluated the bioavailability and pharmacokinetic interactions of the test Polycap™ (test; T), which contained five drugs (ramipril 5 mg, atenolol 50 mg, hydrochlorothiazide 12.5 mg, simvastatin 20 mg, and enteric-coated aspirin 100 mg) and reference market preparations (reference; R) of its individual ingredients (Altace™ [ramipril] 5 mg capsules, King Pharmaceuticals, Bristol, TN, USA; Tenormin™ [atenolol] 50 mg tablets, AstraZeneca Pharmaceuticals, Wilmington, DE, USA; Microzide™ [hydrochlorothiazide] 12.5 mg capsules, Watson Labs, CA, USA; Zocor™ [simvastatin] 20 mg tablets, Merck & AMP, NJ, USA; and enteric-coated low-dose Baby Aspirin™ [aspirin] 81 mg tablets, Bayer Inc., Morristown, NJ, USA). Formulations containing each of the ingredients were administered separately in identical conditions as those of the Polycap™ capsules. The studies of ramipril and simvastatin also included measurement of the pharmacokinetic parameters of their active metabolites (ramiprilat and simvastatin acid, respectively).

The study protocol and the informed consent forms were reviewed and approved by an independent ethics committee. The study was performed in accordance with the revised Declaration of Helsinki on biomedical research involving human subjects and the requirements for Good Clinical Practice. All participants gave written informed consent prior to initiation of the study.

Randomization

The eligible volunteers who fulfilled the inclusion and exclusion criteria were randomly assigned to one of five groups (figure 1). Groups I, II, IV, and V, with 36 volunteers in each,

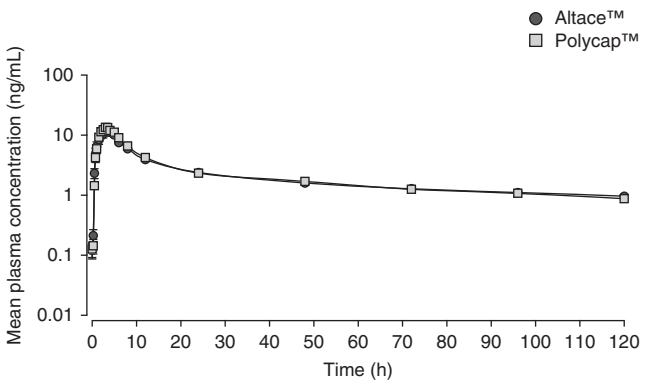

Fig. 3. Mean (±SE) plasma ramiprilat concentration-time profiles in 35 evaluable healthy volunteers following administration of a single dose of Polycap™ or Altace™ 5 mg capsules.

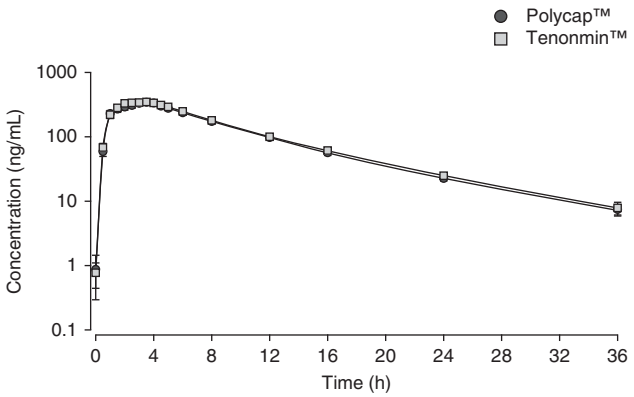

Fig. 4. Mean (±SE) plasma atenolol concentration-time profiles in 31 evaluable healthy volunteers following administration of a single dose of Polycap™ or Tenormin™ 50 mg tablets.

compared Polycap™ versus aspirin, ramipril, atenolol, and hydrochlorothiazide, respectively; group III had 52 volunteers and compared Polycap™ versus simvastatin.

These volunteers were also randomly assigned to one of the two possible sequences of administration (TR and RT) following a balanced randomized scheme. SAS statistical software version 9.1.3 (SAS Institute Inc., Cary, NC, USA) was used to generate the randomization schedule. The randomization codes were accessible to the study statistician only.

Dose Administration

The volunteers were admitted to the clinical facility and, after an overnight fast of at least 10 hours, received either a single dose of the R preparation (aspirin, ramipril, simvastatin, atenolol, or hydrochlorothiazide) or the T formulation (Polycap™) with 240 mL of drinking water. Standardized meals (lunch, dinner, and evening snacks) were provided to the volunteers 4, 9, and 13 hours after dosing. No other food was permitted during the first 24 hours after drug administration. Liquid consumption was permitted *ad libitum* 2 hours after dosing. However, xanthine-containing drinks such as tea, coffee, and cola were not permitted.

After a washout period of at least 2 weeks (in the aspirin, simvastatin, atenolol, and hydrochlorothiazide arms) or 20 days (in the ramipril arm), the study was repeated in the same manner to complete the crossover design. All studies were carried out between 9 September 2008 and 12 December 2008.

Sample Size

The sample size per arm was determined using the following formula (equation 1) in which the T/R ratio and intrasubject variability were obtained from previous bioavailability studies of the given analyte that we had conducted or based on the literature. Additional standby subjects were added in each sequence to account for dropouts (assumed to be about 10% in each arm).

$$N = [t_{\alpha,2n-2} + t_{\beta,2n-2}]^2 \, [CV/(V - \delta)]^2 \qquad \text{(Eq. 1)}$$

where N = the number of subjects per sequence; t = the appropriate value from the t-distribution; α = the significance level, taken as 5% on each tail; 1-β = power, taken as 80%; CV = intrasubject variability; V = no difference or non-interaction limit = ln (0.80) to ln (1.25); and δ = the T/R ratio.

Blood Sample Collection

For all groups, blood (5 mL) was sampled from the antecubital or cubital veins and collected into K_2EDTA (dipotassium ethylene diamine tetra-acetic acid) tubes. All blood samples were centrifuged at 3000 rpm for 10 minutes at 4°C. Plasma was separated and stored below −20°C until the analysis of drug (and/or metabolite) was performed.

Blood samples of all participants were collected at predose (0 hour), three to four sample points during the absorption phase, three to four sample points at the time of peak plasma concentration (C_{max}) [t_{max}] to determine C_{max} accurately, and four to five sample points during the elimination phase (up to 16, 120, 36, 36, and 60 hours after dosing for the aspirin, ramipril, simvastatin, atenolol, and hydrochlorothiazide groups, respectively), to achieve accurate area under the plasma concentration-time curve (AUC) data. The number of blood samples drawn from each subject was 20 (5 mL each) except for the atenolol arm (group IV), in which 17 (5 mL each) blood

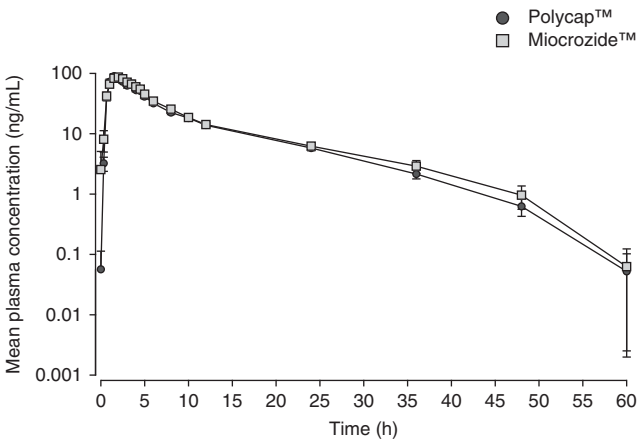

Fig. 5. Mean (±SE) plasma hydrochlorothiazide concentration-time profiles in 33 evaluable healthy volunteers following administration of a single dose of Polycap™ or Microzide™ 12.5 mg capsules.

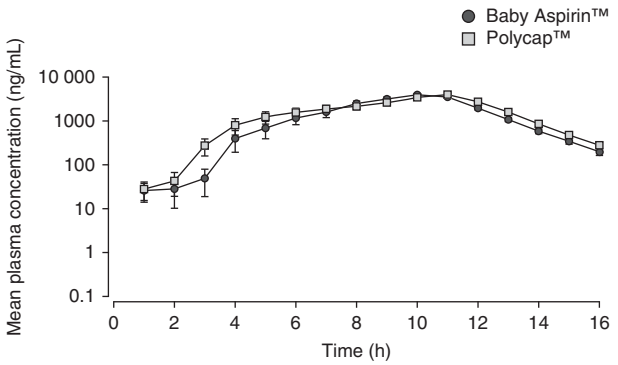

Fig. 6. Mean (±SE) plasma salicylic acid concentration-time profiles in 32 evaluable healthy volunteers following administration of a single dose of Polycap™ or Baby Aspirin™ 81 mg tablets. All salicylic acid concentrations from Polycap™, which contains 100 mg of aspirin (acetylsalicylic acid), were dose normalized for comparison with the 81 mg dose of the reference.

samples were collected because of the relatively lower variations anticipated in C_{max} values.

Bioanalytical Analysis

All drugs and metabolites, except aspirin, in the plasma samples from the volunteers were analyzed by four separate liquid chromatography-tandem mass spectrometry (LC-MS/MS) techniques. Each LC-MS/MS method was validated for accuracy, precision, sensitivity, specificity, recovery of analysis, and stability of samples. Aspirin was analyzed by ultra-performance liquid chromatography (UPLC). The working standard of all analytes and internal standards were obtained from Cadila Pharmaceuticals Ltd (Ahmedabad, Gujarat, India). Only high-performance liquid chromatography-grade chemicals and highly pure reagents were used throughout validation and clinical sample analyses.

Extraction of analytes from plasma was carried out using liquid-liquid, protein precipitation, or solid phase extraction techniques. The calibration curves were linear between the ranges of 52.0–6000.0 ng/mL for salicylic acid, 0.32–40.0 ng/mL for both ramipril and ramiprilat, 0.25–60.0 ng/mL for both simvastatin and simvastatin acid, 1.02–200.2 ng/mL for atenolol, and 1.5–500.2 ng/mL for hydrochlorothiazide. The intra-day and inter-day lack of precision for both LC-MS/MS and UPLC for all the analytes were between 0.97% and 9.7%. The inter-day and intra-day accuracy for both LC-MS/MS and UPLC for all the analytes was between 94.8% and 107.0%. A dilution method was used for values beyond the linear ranges of the calibration curves mentioned. During method validation, dilution integrity experiments at the one-fifth and one-tenth levels were also performed. To calculate the actual concentration of the diluted samples, an appropriate dilution factor was applied. All validated methods showed stability of samples over the entire period of analysis in storage conditions as well as continued stability during sample handling and concentration analysis.

Pharmacokinetic and Statistical Analysis

Plasma concentrations of each analyte generated by fully validated UPLC or LC-MS/MS systems were sent for pharmacokinetic and statistical analysis. Verified data for each subject and analyte were run in WinNonlin 5.0.1 (Pharsight, Mountain View, CA, USA) statistical software using a noncompartmental model to calculate pharmacokinetic parameters, namely C_{max}, AUC from time zero to the last measurable concentration (AUC_t), AUC from time zero to infinity (AUC_∞) derived from C_t/λ, where C_t is the last measurable concentration and λ is the terminal elimination rate, t_{max}, apparent first-order elimination rate constant, and apparent half-life.

Statistical analysis of bioavailability of the five parent drugs and two metabolites (ramiprilat and simvastatin acid) was carried out by comparing the geometric mean of each parameter for T with that of the individual R formulation using SAS statistical software version 9.1.3. Comparative bioavailability for each ingredient was computed and lack of drug-drug interaction and no difference in comparative bioavailability were concluded based on point estimates of the T/R ratio of the geometric means falling within 80–125% for C_{max}, AUC_t, and AUC_∞. For each T/R ratio of the geometric means, a 90% confidence interval (CI) was constructed for descriptive

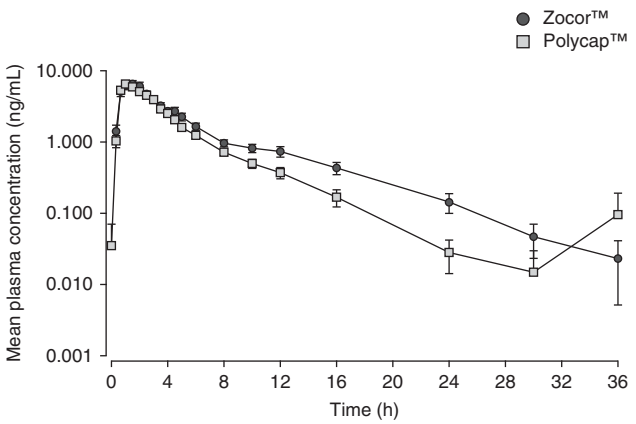

Fig. 7. Mean (±SE) plasma simvastatin concentration-time profiles in 49 evaluable healthy volunteers following administration of a single dose of Polycap™ or Zocor™ 20 mg tablets.

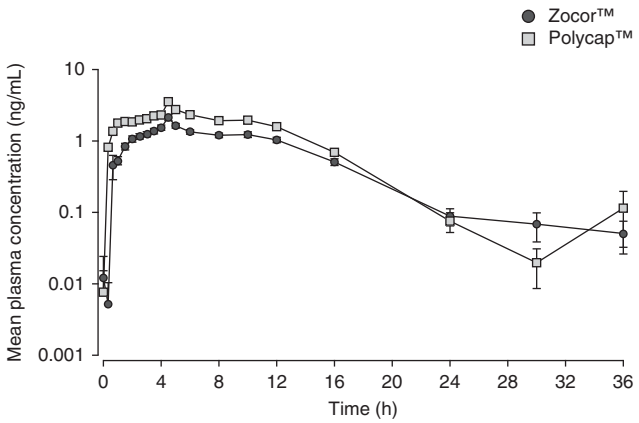

Fig. 8. Mean (±SE) plasma simvastatin acid concentration-time profiles in 49 evaluable healthy volunteers following administration of a single dose of Polycap™ or Zocor™ 20 mg tablets.

purposes only; it was not used for any conclusion regarding bioavailability or drug-drug interaction. The point estimates are expressed as a percentage relative to the least-square mean of the R treatments. The 90% CIs were calculated using the two one-sided t-tests for assessment of comparative bioavailability for the difference between treatments' least-square means for ln-transformed C_{max}, AUC_t, and AUC_∞.

In the case of aspirin, the plasma salicylic acid concentration was dose normalized for the calculations of comparative bioavailability, as the R single dose contained 81 mg of enteric-coated aspirin while the Polycap™ contained 100 mg of enteric-coated aspirin. For dose normalization, the concentration values obtained for 81 mg of aspirin at each timepoint for each volunteer was multiplied by 1.23 (T dose 100 mg/R dose 81 mg). All plasma concentrations were analyzed after log transformation. The point estimates were derived as the anti-log of the transformed least-square means.

Results

Of 196 subjects selected, 195 were enrolled in the study. One subject in the atenolol arm (group IV) was discontinued from the study because of high BP (160/104 mmHg) during physical examination just prior to entry to the clinic for period I. 180 participants completed the studies; pharmacokinetic data for these individuals are presented and interpreted in this article. Mean (±SD) values of all baseline variables (age, BMI, SBP, DBP, total cholesterol level, triglyceride level, and platelet count) are presented in table I. Among the 15 subjects who discontinued, four were withdrawn because of medical reasons (three had high serum potassium levels and one had the presence of respiratory rhonchi on clinical examination), two were withdrawn because of a positive breath analyzer test for alcohol prior to period II, seven did not show up for their respective period II, and two dropped out for personal reasons. Participants who dropped out for medical reasons did not do so because of the study drug interventions. Adverse events were documented before check-in of period II, which started after a washout period for 14 days; a single dose of the study drug interventions would be unlikely to cause high potassium levels or respiratory rhonchi in the previously screened healthy volunteers.

Figures 2–5 show mean plasma concentrations over time of ramipril, ramiprilat, atenolol, and hydrochlorothiazide, respectively, from the Polycap™ and each R formulation; the concentrations are superimposable. Figure 6 shows plasma concentrations of salicylic acid from the Polycap™ (containing 100 mg enteric-coated aspirin) following dose adjustment; these concentrations are also superimposable compared with those of the R preparation (81 mg of enteric-coated aspirin). As for simvastatin and its active metabolite, simvastatin acid, plasma concentrations from the Polycap™ and R preparation were not superimposable in the distribution and elimination phases of the pharmacokinetic profiles (figures 7 and 8, respectively).

The mean values for pharmacokinetic parameters and their standard deviations (for the number of participants completing each arm) are presented in table II. All parameters with the Polycap™ including t_{max} were similar to those with the individual R products.

Table III gives the point estimates of the T/R ratio of the geometric means of C_{max} and AUC_t, and the relative bioavailability of all analytes. The relative bioavailability values, based on the ratio of AUC_∞ (T)/AUC_∞ (R), of aspirin, ramipril, ramiprilat, atenolol, and hydrochlorothiazide were 95.5%, 109.1%, 105.9%, 96.9%, and 92.7%, respectively. The relative bioavailabilities of all these drugs were in the bioequivalence range of 80–125%.

From table III, it can also be seen that the estimate of relative bioavailability for simvastatin was 76.7% (90% CI 65.0, 90.4) and for simvastatin acid was 150.2% (90% CI 132.5, 170.3).

Adverse Events

There were no serious adverse events. Four adverse events were reported during the study. Two subjects had mild abdominal pain and diarrhea (aspirin group), which resolved within 3 hours following symptomatic treatment. The other two had vomiting and abdominal pain (one each in the ramipril and

hydrochlorothiazide arms); only one needed symptomatic treatment and symptoms resolved within 2 hours.

Discussion

Aspirin, ramipril, atenolol, and hydrochlorothiazide from the Polycap™ were absorbed with a similar rate and extent to those of the single-agent preparations. This resulted in comparable relative bioavailabilities. Furthermore, pharmacokinetic parameters for the ingredients of Polycap™ on average fell within the range of 80–125% for ln-transformed C_{max}, AUC_t, and AUC_∞ relative to the disposition of the single drugs. This clearly indicates that there was no pharmacokinetic drug-drug interaction *in vivo* and that the bioavailability of ramipril, atenolol, hydrochlorothiazide, and aspirin is preserved in the novel five-ingredient Polycap™. The pharmacokinetic parameters for the rate and extent of bioavailability of these agents from the Polycap™, namely C_{max}, AUC_t, and AUC_∞ (with 90% CIs), in this study are comparable to those reported in the literature for all five drugs.[4-8]

These pharmacokinetic findings are in concordance with recently published data on pharmacodynamic parameters of Polycap™, which have also shown that Polycap™ is noninferior to its individual ingredients in reducing BP and HR.[3] The reduction in BP observed in the TIPS with Polycap™ was less than the projections made by Wald and Law.[2] Based on the findings of the present study, the smaller reductions in BP would not be due to differences in the bioavailability of the BP-lowering drugs in the Polycap™ compared with the individual preparations. Instead, it is likely that the actual decrease in BP

Table II. Pharmacokinetic parameters (mean ± SD) of the different analytes (simvastatin, simvastatin acid, ramipril, ramiprilat, hydrochlorothiazide, atenolol, and salicylic acid) as calculated from the plasma concentration data of evaluable participants (N) receiving either the individual reference preparation or the test formulation (Polycap™)

Analyte (N)	C_{max} (ng/mL)	AUC_t (ng • h/mL)	AUC_∞ (ng • h/mL)	t_{max} (h)	K_{el} (L/h)	$t_{½}$ (h)
Salicylic acid						
Salicylic acid from Polycap™ capsule (32)	5041.2 ± 1688.8	27 191.2 ± 0571.8	28 304.8 ± 11 335.2	5.0 ± 1.6	0.3 ± 0.1	2.3 ± 0.7
Salicylic acid from low-dose Baby Aspirin™ tablet (32)	6204.0 ± 1344.1	27 773.0 ± 7404.0	28 840.4 ± 8442.2	4.3 ± 1.2	0.3 ± 0.1	2.3 ± 0.7
Ramipril						
Ramipril from Polycap™ capsule (35)	19.2 ± 9.1	14.8 ± 6.0	15.6 ± 6.2	0.6 ± 0.2	0.7 ± 0.3	1.3 ± 1.1
Ramipril from Altace™ capsule (35)	16.1 ± 8.0	13.3 ± 5.3	14.1 ± 5.4	0.6 ± 0.2	0.7 ± 0.3	1.5 ± 1.5
Ramiprilat						
Ramiprilat from Polycap™ capsule (35)	16.7 ± 9.9	271.7 ± 86.6	373.0 ± 121.6	3.6 ± 1.4	0.01 ± 0.01	74.9 ± 39.7
Ramiprilat from Altace™ capsule (35)	14.3 ± 8.1	259.9 ± 83.1	359.0 ± 132.2	3.6 ± 1.4	0.01 ± 0.01	69.2 ± 28.1
Simvastatin						
Simvastatin from Polycap™ capsule (49)[a]	7.8 ± 4.5	25.7 ± 14.7	27.9 ± 15.2	1.4 ± 0.7	0.2 ± 0.1	4.2 ± 2.6
Simvastatin from Zocor™ tablet (49)	10.4 ± 6.9	32.6 ± 18.9	36.8 ± 20.5	1.8 ± 1.8	0.2 ± 0.1	6.2 ± 8.2
Simvastatin acid						
Simvastatin acid from Polycap™ capsule (49)[b]	3.9 ± 2.1	32.0 ± 15.1	35.9 ± 15.6	5.3 ± 4.9	0.2 ± 0.1	5.2 ± 2.6
Simvastatin acid from Zocor™ tablet (49)	2.5 ± 1.6	19.0 ± 10.4	24.9 ± 13.4	4.6 ± 2.0	0.1 ± 0.1	7.9 ± 6.3
Atenolol						
Atenolol from Polycap™ capsule (31)	390.8 ± 156.8	3206.3 ± 1318.9	3332.7 ± 1334.3	3.1 ± 0.8	0.1 ± 0.03	6.2 ± 1.5
Atenolol from Tenormin™ tablet (31)	418.4 ± 201.1	3374.5 ± 1706.5	3519.5 ± 1715.6	2.9 ± 1.3	0.1 ± 0.03	6.2 ± 1.7
Hydrochlorothiazide						
Hydrochlorothiazide from Polycap™ capsule (33)	102.0 ± 53.2	626.0 ± 263.4	664.8 ± 265.4	1.9 ± 1.0	0.1 ± 0.02	9.8 ± 2.7
Hydrochlorothiazide from Microzide™ capsule (33)	97.3 ± 33.6	668.8 ± 261.3	711.5 ± 257.9	1.7 ± 0.6	0.1 ± 0.02	9.2 ± 2.7

a For K_{el} calculations, n = 48; K_{el} could not be calculated in one participant.

b For K_{el} calculations, n = 46; K_{el} could not be calculated in three participants.

AUC_t = area under the plasma concentration-time curve from time zero to the last measurable concentration; **AUC_∞** = AUC from time zero to infinity; **C_{max}** = peak plasma concentration; **K_{el}** = apparent first-order elimination rate constant; **t_{max}** = time to C_{max}; **$t_{½}$** = apparent half-life.

Table III. Point estimates and relative bioavailability of the different Polycap™ (T; test) ingredients and two metabolites as compared with corresponding reference products (R)

Analyte	T/R point estimate multiplied by 100 (90% CI)		
	C_{max} (ng/mL)	AUC_t (ng • h/mL)	AUC_∞ (ng • h/mL)
Salicylic acid	80.6 (72.8, 89.3)	95.2 (85.7, 105.8)	95.5 (86.0, 106.1)
Ramipril	118.5 (99.7, 141.0)	110.0 (99.3, 121.8)	109.1 (98.9, 120.3)
Ramiprilat	117.5 (103.9, 132.9)	105.3 (99.9, 111.0)	105.9 (98.0, 114.5)
Simvastatin	77.0 (67.6, 87.7)	79.5 (68.1, 92.8)	76.7 (65.0, 90.4)
Simvastatin acid	158.7 (140.4, 179.4)	171.7 (152.0, 194.1)	150.2 (132.5, 170.3)
Atenolol	95.5 (85.0, 107.2)	97.1 (87.8, 107.3)	96.9 (88.2, 106.4)
Hydrochlorothiazide	101.1 (90.9, 112.5)	93.1 (86.9, 99.8)	92.7 (86.8, 99.0)

AUC_t = area under the plasma concentration-time curve from time zero to last measurable concentration; **AUC_∞** = AUC from time zero to infinity; **C_{max}** = peak plasma concentration.

among those with initial BP levels in the non-hypertensive range is smaller, as Wald and Law's estimates were largely derived from studies in individuals with much higher initial BP.[2]

For simvastatin, there was a slight loss of bioavailability with the Polycap™; the relative mean bioavailability parameters were 3–4% lower than the lower tolerance bound of 80%. However, there was an associated increase in the bioavailability of simvastatin acid with the Polycap™ compared with the reference drug. The bioavailability of simvastatin is known to be reduced in the presence of carbamazepine and rifampicin, which also reduce the bioavailability of simvastatin acid.[9,10] An increase in the bioavailability of simvastatin acid and simvastatin is known to occur with cytochrome P450 (CYP) inhibitors such as verapamil, clarithromycin, ketoconazole, protease inhibitors, grapefruit juice, etc.[11] However, an increase in the bioavailability of simvastatin acid with a simultaneous decrease in the bioavailability of simvastatin has not been reported thus far when given with other agents. Also, the contribution of the instability of simvastatin to this apparent interaction, if any, needs to be evaluated through a properly constructed study to assess *in vitro-in vivo* correlation (e.g. loss of dissolution resulting in loss of bioavailability).

There are two aspects to the observed lower relative bioavailability of simvastatin (<80%; the lower tolerance bound). First, despite this lower value, the active metabolite, simvastatin acid, showed a high relative bioavailability (>125%; the upper tolerance bound). Therefore, as an approximation, the overall bioavailability of active simvastatin and simvastatin acid is acceptable. Second, the lower bioavailability of simvastatin mirrors the results of the TIPS trial[3] in which a slight reduction in the efficacy of simvastatin was observed.

Because simvastatin acid is an active metabolite of simvastatin, the increased simvastatin acid level with the Polycap™, as observed in our study, should theoretically lead to a greater reduction in serum LDL cholesterol levels than with simvastatin administered alone. However, the findings of TIPS[3] are indicative of a slightly smaller reduction in LDL cholesterol levels with the Polycap™ than expected. We are not able to explain this finding based on our pharmacokinetic data, suggesting that other explanations should be sought. The three antihypertensive drugs contained in the Polycap™ are not known to induce such changes. Aspirin has been demonstrated to induce various CYP enzymes, including CYP3A,[12] and simvastatin and simvastatin acid are known substrates for these enzymes.[13,14] To elucidate the role of aspirin, we have planned a study comparing the bioavailability of simvastatin and simvastatin acid in Polycap™ with and without aspirin.

Conclusion

The present pharmacokinetic study of Polycap™ establishes the required bioavailability for all its component drugs, thus explaining its reported efficacy pharmacokinetically. Together with TIPS,[3] it corroborates the hypothesis of reducing cardiovascular risk factors by the use of multiple ingredients in a single pill. There was no indication of pharmacokinetic drug-drug interactions for any of the ingredients.

Acknowledgments

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candesartan plus hydrochlorothiazide (16/12.5 mg/day) in addition to rosuvastatin (10 mg/day) (as separate agents), and observed that their combination reduced major cardiovascular events by 29% in persons at intermediate risk for developing CVD, with a 40% relative risk reduction (RRR) in those with elevated blood pressure.[3,4] Even larger reductions in CVD risk may be achievable with more intensive regimens, but data are needed that directly examine the clinical benefits and tolerance of such a strategy using a single FDC pill, which is the focus of this study.

TIPS-3 is a 2x2x2 factorial, RCT that will examine the effect of a FDC polypill on CVD outcomes in a primary prevention population. This study aims to determine whether the Polycap (comprised of atenolol, ramipril, hydrochlorothiazide, and a statin) reduces CV events in persons without a history of CVD, but who are at least at intermediate CVD risk. Additional interventions evaluated in the factorial design of the study compare the effect of (1) aspirin versus placebo on CV events (and cancer), (2) vitamin D versus placebo on the risk of fractures, and (3) the combination of aspirin and the Polycap on CV events (versus double-placebo).

Recruitment of TIPS-3 began in 2012 and we initially planned to enroll 5000 participants over a 2-year period. Despite the study testing a polypill comprised of commonly available and well tolerated medications, unanticipated regulatory challenges and restrictions on drug importation occurred in several countries. This contributed to substantial delays to study initiation and slowed down study enrolment, necessitating a substantial prolongation of the duration of the trial. Consequently, the enrollment of participants took 5 years (instead of 2 years), and interruptions in drug resupply during follow-up have led to higher than expected study drug discontinuation rates. To preserve statistical power this has required a larger sample size (N = 5713), and will require longer participant follow-up (i.e. until 2019–2020 as opposed to the original planned study end of Dec 2017). This article summarizes the design of TIPS-3, and baseline characteristics of the enrolled participants. Also, given that there is an increasing need for trials that include LICs and MICs, we examined the impact of regulatory factors on study recruitment and other aspects of study conduct.

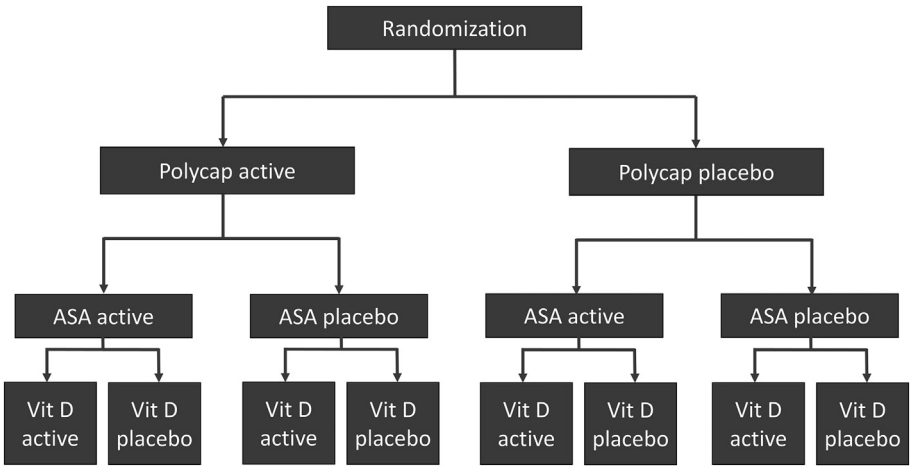
Methods

Study objectives, design, and interventions

TIPS-3 is a double-blind, randomized, placebo controlled trial. Using a 2x2x2 factorial design, first we are testing the effect of the Polycap (comprised of atenolol 100 mg/daily, ramipril 10 mg/daily, hydrochlorothiazide 25 mg/daily, and simvastatin 40 mg/daily) versus placebo on major CV events. In the second factorial, we are testing the effect of aspirin 75 mg/day versus placebo on major CV events (and cancer). In the third factorial, we are testing the effect of vitamin D 60,000 IU given monthly on the risk of fractures compared to placebo.

The purpose of the factorial design is to assess the effects of each of the three distinct treatments within one efficient design (using 3 separate randomizations) in the same study population (see Figure 1). Therefore, participants randomized to the Polycap will be compared to the participants randomized to its placebo; participants allocated to aspirin will be compared to those on placebo for aspirin; and participants allocated to vitamin D will be compared participants allocated to placebo for vitamin D. The net clinical benefit of aspirin in primary prevention remains unclear, and after debating whether the polypill we are evaluating should include ASA, we ultimately chose to randomize participants to ASA or its placebo in a

Figure 1



2x2x2 factorial study design of TIPS-3. Vit D = vitamin D.

factorial design to gain information on the effects of ASA alone.[5,6] However, the combined effect of the Polycap with aspirin (i.e. the double-treatment group) will also be compared to the double-placebo group as part of our pre-specified analysis. The net effect of ASA in the prevention of CVD and cancer is a secondary outcome measure. Finally, Vitamin D will be evaluated because Asian populations are considered to be deficient in Vitamin D, and several guidelines recommend its use despite the lack of an RCT showing clinical benefit in these populations.[7,8] In this paper, our focus is on the comparison of the Polycap versus its placebo.

Study population and eligibility

Eligibility criteria was based on absence of CVD, age, and the non-laboratory based INTERHEART risk score (IHRS), which is a validated tool for estimating CVD risk in multiple populations, without the need for laboratory-based measures (eg, cholesterol).[9,10] We included participants who were at least at intermediate risk of developing CVD based on their age and IHRS. Community-dwelling participants were recruited from primary care clinics, specialty clinics, or community outreach programs. Detailed information on study inclusion and exclusion criteria are summarized in Table I.

Primary, secondary, and additional pre-specified outcomes

Polycap versus placebo. The primary study outcome for this comparison is the composite of CV events, which includes major CVD (ie, CV death, non-fatal stroke, non-fatal MI), plus heart failure, resuscitated cardiac arrest, or arterial revascularization. Secondary outcomes are (1) major CVD and (2) the composite of major CVD, heart failure, resuscitated cardiac arrest, arterial revascularization, or angina with evidence of ischemia.

Aspirin versus placebo. The primary outcome of this comparison is the composite of major CVD (ie, CV death, non-fatal stroke, non-fatal MI). The secondary outcome is the composite of major CVD and cancer.

Vitamin D versus placebo. The primary outcome of this comparison is fractures. The secondary outcome is the composite of CV events (as described in Section 2.3.1), fractures, cancers, and falls.

Combined effects of the Polycap and aspirin. The primary outcome of this comparison is major CVD (CV death, non-fatal MI or non-fatal stroke), heart failure, resuscitated cardiac arrest, or arterial revascularization. Secondary outcomes are (i) major CVD and (ii) the composite of major CVD (CV death, non-fatal stroke, non-fatal myocardial infarction [MI]), heart failure, resuscitated cardiac arrest, arterial revascularization, or angina with evidence of ischemia.

Additional outcomes. Additional pre-specified outcomes include all-cause mortality, incident and recurrent CV events, visual acuity, age-related macular degeneration, cognitive function, adverse events (including bleeding), and economic analysis related outcomes.

TIPS-3 was started prior to the results of the HOPE-3 trial, which was published in 2016, and showed a benefit of statin therapy over placebo in individuals at intermediate CVD risk. After the results of HOPE-3 were published, the TIPS-3 steering committee decided to continue the current study design for several reasons. First, since HOPE-3 was the first long-term clinical trial to demonstrate this effect in an intermediate CVD risk primary prevention population, it was felt that confirmation of these findings were needed prior to

Table I. Inclusion and exclusion criteria of TIPS-3

Inclusion criteria:	1. Men aged ≥50 years and women aged ≥55 years with an INTERHEART risk score ≥ 10, or men and women aged ≥65 years with an INTERHEART risk score of ≥5.*
	2. Provision of informed consent
Exclusion criteria:	1. Participants with a clear clinical indication, contraindication, preference for or intolerance to statin, beta blocker (eg, bradycardia), ACE inhibitor, diuretic, aspirin or clopidogrel in the judgment of the physician.
	2. Regular use of vitamin D at doses higher than 400 IU per day.
	3. Hypercalcemia, hyperparathyroidism, osteomalacia or other contraindication or indication for vitamin D therapy.
	4. Peptic ulcer disease, frequent dyspepsia or bleeding.
	5. Expected long term use of anticoagulants
	6. Known vascular disease. (eg, Stroke, TIA, Angina, MI, ACS, PVD including claudication and amputation).
	7. Mean systolic BP below 120 mm Hg at run-in.
	8. Symptomatic hypotension (eg, dizziness with SBP <110 mm Hg systolic) during the run-in phase.
	9. Chronic liver disease or abnormal liver function, i.e. ALT or AST >3 × ULN.
	10. Inflammatory muscle disease (such as dermatomyositis or polymyositis) or creatine kinase (CK) >3 × ULN.
	11. Severe renal impairment (serum creatinine >264 μmol/L).
	12. History of malignancy affecting any organ system, except basal cell carcinoma of the skin, within the previous 5 years.
	13. Other serious condition(s) likely to interfere with study participation or with the ability to complete the trial.
	14. Concurrent use of any experimental pharmacological agent.
	15. Inability to attend follow-up as required by the protocol for at least 5 years.

*The original inclusion criteria for the study was men aged ≥55 years and women aged ≥60 years with an INTERHEART risk score ≥10. This was revised in February 2015 to include individuals at lower ages, as well as higher age groups with a lower INTERHEART risk score. This would still reflect an intermediate risk population (i.e. annual event rate >1%/year) since age is the strongest risk factor for CVD.

widespread adoption of such a strategy, which TIPS-3 can provide. Second, indications for statin use continue to vary between clinical guidelines in different countries, and even generic statins are relatively unaffordable in many LICs and MICs, and so their use even in secondary prevention is low.[11,12] Third, investigators have the option of discontinuing the Polycap and starting open label medications if a participant meets an indication for statin therapy based on local practice.

Sample size and data analysis

Reductions in cholesterol and blood pressure levels observed with the Polycap in prior studies suggest that a reduction in CV events of at least 35% is feasible, and likely necessary to be accepted in clinical practice (as lesser benefits can be achieved by using one BP lowering drug and a statin given separately). The study was originally designed to enroll 5000 participants over two-years, with a further 4 years of follow-up resulting in a mean follow-up of 5 years. Assuming a CV event rate of 1.0%/year in the placebo group, the study would have over 80% power to detect a 35% RRR in CV events with the Polycap compared to placebo, and over 90% to detect a 40% RRR. Ultimately recruitment required 5 years, and was skewed towards a higher enrollment in the final years. To compensate for this, a total of 5713 participants were enrolled in the study, and the anticipated completion of study follow-up will potentially be extended to a mean follow-up of up to approximately 4.25 years. The observed overall annual CV event rate in the study was 1.1% at the end of the recruitment phase. Based on this revised data, with extension of the study, it will maintain at least 80% power to detect a 35% RRR reduction in CV events, and over 90% power to detect a 40% RRR, comparing the Polycap to placebo. Further calculations outlining the statistical power of the study are available in the supplementary appendix of this paper.

The primary analysis for each treatment group will be based on the principle of intention to treat. For each comparison, survival curves for the primary and secondary outcomes will be generated using the Kaplan–Meier procedure. The primary analysis will be the time to a confirmed primary outcome event using the Cox proportional hazards model. Comparisons will be presented using hazard ratios with 95% confidence intervals, and a two-sided p-value of <0.05 will be considered statistically significant. Possible interactions between treatments will be tested by the inclusion of interaction terms in the model. Although interactions between the study medications are not anticipated, in the unlikely event of a significant interaction, treatment effects will be reported separately for each strata defined by the interacting treatment. Consistency of treatment effects on each primary outcome will be explored in a few predefined subgroups, including by thirds of pre-treatment LDL-cholesterol and blood pressure levels, thirds of the IHRS, gender, ethnicity and the presence or absence of dysglycemia (ie, diabetes or impaired fasting glucose). Whether treatments effects vary by subgroups will be analyzed using tests for interactions in the Cox regression model.

Study procedures

Following consent, eligible participants underwent a 3 to 4 week run-in phase, during which time they received low dose Polycap (consisting of atenolol 50 mg, ramipril 5 mg, HCTZ 12.5 mg and simvastatin 40 mg) and low dose aspirin daily. Participants who tolerated the study medications and did not meet run-in exclusion criteria were randomized to each of the study medications or their matching placebos. Allocation concealment was maintained by using a central randomization process that was stratified by center with fixed randomization blocks (of 8 participants). Follow up visits occur at 6 weeks, 3 months, 6 months, 9 months, 1 year, then at 6-month intervals until the end of the study. Blood pressure readings were collected prior to run-in, at randomization and during the follow up. Fasting lipids were collected prior to run-in and during follow up. As part of our pre-specified study outcomes, tools for measuring visual acuity, cognitive function, and quality of life were performed at baseline, and will be repeated during follow-up.

Study organization

The TIPS-3 study is being conducted at 86 centers in 9 countries. The study is funded through grants by the Wellcome Trust, Canadian Institutes for Health Research, Cadila pharmaceuticals, the Population Health Research Institute (PHRI), Heart and Stroke Foundation of Ontario, Philippines Council for Health Research and Development, Secretaria de Salud del Departamento de Santander (Colombia) and St. John's Research Institute (India). Ethics approvals were obtained at all participating centers, and regulatory approvals for conducting the trial and importation of the study drugs for the trial were obtained for each country. Written informed consent has been provided by all participants. Trial oversight occurs by an international steering committee comprised of the study's principal investigator and several co-investigators (see supplementary appendix). The central coordinating center of the study is the PHRI, Hamilton Health Sciences and McMaster University, in Hamilton, Ontario, Canada. Data are stored at the coordinating center using a secure electronic database, called iDataFax. Simple data collection forms are being used to collect baseline and follow-up data, which are sent to the central coordinating center via fax or entered at the site using the iDatafax software. To ensure data quality, automated checks have been developed within the software itself, and additional checks are performed at the coordinating center. An independent data monitoring and safety board, assisted

by a senior biostatistician who is independent of the everyday conduct of the trial, oversees the safety of each treatment and study conduct at six-month periods. In addition, three formal interim efficacy analyses are planned based on the number of primary outcome events that are expected to have accrued (see supplementary appendix for details of statistical guidelines and monitoring boundaries). Supporting documentation (eg, hospitalization records, diagnostic tests, and procedural notes) is requested for all primary outcome events, which then undergo adjudication by a committee that is blinded to the treatment assignments and using pre-specified criteria.

Results

Study enrollment

Of 7701 screened participants, 7539 were eligible for run-in. Of these 1826 (24.2%) were not eligible for randomization, resulting in 5713 participants being randomized to the study. The most common reason for not undergoing randomization was participant decision (20.6%), followed by <80% adherence to the Polycap (11.2%) or aspirin (10.9%). Only 4.7% of participants were ineligible due to syncope, dizziness or a SBP <110 mmHg. Only 1.4% were ineligible due to elevated blood tests meeting exclusion criteria; and 1% were ineligible due to peptic ulcer disease, dyspepsia or gastrointestinal bleeding.

Baseline characteristics

Key baseline characteristics of the study population are summarized in Table II. Most participants were recruited in India (47.9%) followed by the Philippines (29.3%). The mean age of the study population was 63.9 years, and 53.0% were female. A history of hypertension was self-reported in 77.6% of participants, and diabetes was reported in 32.2%. 1961 (34.3%) participants had a fasting glucose ≥6.1 mmol/L).

Table II. Baseline characteristics of the 5713 participants enrolled in TIPS-3

Variable	
Mean age, years (SD)	63.9 (6.6)
Female, N (%)	3026 (53.0%)
Country of recruitment, N (%)	
India	2739 (47.9)*
Philippines	1676 (29.3)
Colombia	489 (8.6)
Bangladesh	295 (5.2)
Canada	131 (2.3)
Malaysia	119 (2.1)
Indonesia	118 (2.1)
Tunisia	107 (1.9)
Tanzania	39 (0.7)*
Risk factors:	
Self-reported hypertension, N (%)	4436 (77.6)
Self-reported diabetes, N (%)	1841 (32.2)
Fasting glucose ≥6.1 mmol/L (%)	1961 (34.3)
Current smoker, N (%)	512 (9)
Mean INTERHEART Risk Score	16.8 (4.6)
Physiologic parameters:	
Mean heart rate, beats per minute (SD)	77.0 (10.6)
Mean systolic blood pressure, mmHg (SD)	144.5(16.8)
Mean diastolic blood pressure, mmHg (SD)	83.9(9.7)
Mean total cholesterol, mmol/L (SD)	5.1 (1.2)
Mean low density lipoprotein, mmol/L (SD)	3.1 (1.1)
Mean high density lipoprotein, mmol/L (SD)	1.2 (0.3)
Mean triglycerides, mmol/L (SD)	1.6 (0.8)
Mean fasting plasma glucose, mmol/L (SD)	6.3 (2.5)
Mean Creatinine, mmol/L (SD)	81.5 (23.3)
Mean BMI, kg/m^2 (SD)	25.8 (4.8)
Mean waist-to-hip ratio (SD)	
Males	0.96 (0.06)
Females	0.91 (0.07)

* After randomization, all patients from Tanzania (n = 39) and a small number in India (N = 18) were withdrawn because of regulatory barriers resulting in site closures. Participants at these sites were censored at the time of the site closure. Currently 5656 participants are actively in follow-up.

Regulatory factors, study initiation and study enrollment

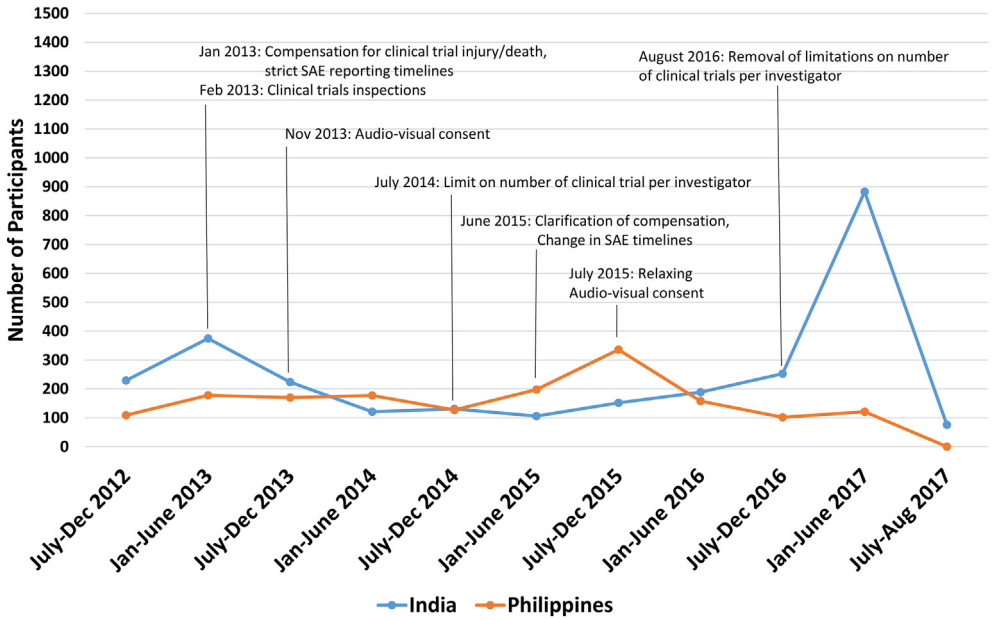
Time required to achieve regulatory approval in each country

Approval to conduct the study was granted in 10 countries, of which 9 enrolled participants (approval was also granted by the Food and Drug Administration, United States of America, although the study was not operationalized in this country). Approval times to start the study varied substantially, with Tunisia and Colombia granting approval in <3 months; India, Philippines, and Malaysia taking 3 to 6 months to approve the study; Canada and Bangladesh requiring approximately 9 months for approval; and Indonesia and Tanzania requiring approximately 1 year for approval. In addition, submissions were withdrawn in 3 countries (Brazil, China, and Argentina) after facing multiple challenges to approving the study despite extensive efforts over a 2-year period.

Regulatory changes in India and enrollment trends in TIPS-3

Between 2013 and 2014, several new regulatory requirements in India were created that directly impacted the conduct of ongoing clinical trials. These included a requirement for compensation for trial related injury or death, clinical trial inspections, audiovisual (AV) recording of the informed consent process, and limitations on the number of clinical trials that could be performed by an investigator.[13,14] In 2013, 22 sites within India were actively recruiting participants in TIPS-3. These regulatory changes contributed to the closure of 5 study sites. While most sites continued, the challenging regulatory environment was commonly cited by investigators as a

Figure 2



Number of participants randomized in six-month intervals within India and the Philippines, and in relation to major clinical trial regulatory changes that occurred within India.[13,14] Several regulatory changes that started in 2013 contributed to a reduction in randomization in India until approximately June 2015. The large increase in recruitment that occurred in 2017 was also partly the result of several new sites joining TIPS-3.

reason for higher operational costs, greater complexity of recruitment, and a substantial decline in recruitment rates. These changes also negatively impacted our ability to identify additional sites that were willing to participate in the study. Several of these regulatory requirements were subsequently amended (i.e. clarification of compensation for trial related injury, relaxing AV consent requirments) between 2015 and 2016.

A summary of study recruitment in India at 6-month intervals is provided in Figure 2. For comparison, a summary of recruitment in the Philippines (the second highest recruiting country in our study) is also provided. After the introduction of regulatory changes in early 2013, a substantial and prolonged decrease in recruitment occurred until late 2015, when many of the introduced changes were relaxed. During this time, from a peak 6 month enrollment of 375 participants (occurring from January to June 2013), enrollment declined by 72% to a trough of 106 participants (January to June 2015). Between 2013 and 2016, enrollment in the Philippines also declined but to a lesser extent (maximum decline of 32% per 6-month period), and recovered at a faster rate when compared with India.

Discussion

TIPS-3 will be the first large clinical trial to examine whether FDC therapy (using the Polycap) targeting aggressive blood pressure and cholesterol reduction is effective in the primary prevention of CVD in individuals at increased risk. This study will address key knowledge gaps that currently exist and limit the use of FDC therapy in the primary prevention of CVD. First, estimates of the benefits of FDC therapies are largely extrapolated from their impacts on blood pressure and cholesterol levels. However, determining their actual effects on CVD risk requires their examination in long-term clinical outcome trials, such as TIPS-3.[2] Second, TIPS-3 will determine the tolerability of FDC therapy in a broad range of participants at increased CVD risk, across several populations in LICs and MICs where its use is likely to be most applicable. Third, we will examine whether effects differ by key risk factor levels (eg, blood pressure, lipids, overall CVD risk) to better inform its application in primary CVD prevention.

Control of common risk factors for CVD is suboptimal in many regions of the world, particularly in LICs and MICs.[15] If a 35% to 40% reduction in CVD outcomes can be achieved with the Polycap, global adoption could potentially avert up to 10–13 million cases of CVD per year. Importantly, implementation of a FDC strategy as part of CVD prevention can have a significant impact on how CVD is managed across a wide range of health resource settings. In high-income countries, FDC therapy could address common barriers to medication non-adherence, such as the complexity of medication

regimens, as well as cost.[16] Medication access and affordability are more wide-spread barriers to CVD prevention in MICs and LICs, and the broad adoption of low-cost, FDC therapy by healthcare payers and providers in these regions could be a central strategy to CVD control at the population level.[17-19]

We have also provided a brief example of how changes in national regulations can adversely impact enrollment in a multi-national clinical trial. The highest priority of clinical trial regulation is ensuring that research participants are treated safely and ethically, while balancing the need to conduct ethical research in a productive manner. We identified two instances where regulatory factors significantly and adversely impacted the ability to conduct our clinical trial. The first was during initial approval, where we faced prolonged regulatory processes, resulting in significant delays to commencing the study in multiple countries. Furthermore, three countries did not provide approvals despite prolonged efforts over a 2-year period and repeated responses to questions from regulators. The large variation in time required to obtain regulatory approval between countries reflect the substantial differences in processes that currently exist, and highlights the need to better streamline current practices in several countries. Furthermore, this may have also reflected discomfort related to the concept of using a polypill (with 4 components) on the part of some regulators, despite the fact that all the components of the Polycap are safe, effective, and widely used in clinical practice; and that the Polycap was found to be well tolerated in two prior clinical studies.[20,21] The second instance occurred during the implementation of new regulatory guidelines in India that substantially increased the efforts and risk undertaken by investigators to participate in clinical research; and the complexity and costs of conducting the trial. Although we acknowledge that other factors impacted recruitment rates in India (eg, the addition of study centers, the relatively modest funding), trends in enrollment during the period in which the most restrictive regulatory requirements came into force strongly suggest that such regulatory policies dramatically impacted study conduct. Our data are also consistent with other analyses showing that the number of registered phase II or III clinical trials in India had decreased by >70% between 2013 and 2016.[22] Importantly, many of these policies were amended to a more pragmatic set of policies (without compromising ethical conduct or participant safety), but this process required over 2 years. These data show the profound impact that regulatory changes can have on the conduct of scientific research.

In addition to the above challenges, substantial regulatory barriers to the importation of study drugs have occurred in several countries, which has resulted in delays and interruptions in patients taking them. In some instances, this has led to worsening adherence of participants to the study medications, and additional efforts on the parts of the participants and local investigators (eg, added study visits), national leaders (eg, clearing drugs through customs, obtaining repeated approvals for importation for each batch of study drugs), staff at the coordinating center (eg, reallocating drugs to minimize the impact of a lack of availability), and the drug distribution team at Cadila (who have to obtain approval from the Drugs Controller General of India for each drug shipment outside India). These challenges also led to prolonged delays in receiving study drugs in Tanzania, and contributed to the study being stopped early in this country due to administrative delays. In future analyses of TIPS-3, characterizing the potential impact of temporary study drug discontinuation on clinical outcomes may be considered. As clinical trials research continues to expand to more regions of the world, there is a need to have greater collaboration between the scientific community and regulators (especially in LICs and MICs) in order to develop balanced regulatory and importation processes that do not compromise ethical integrity or participant safety, but are also designed to avoid unnecessary and onerous barriers to the conduct of scientific studies.

Conclusions

Results of TIPS-3 will be key to determining the appropriateness of FDC therapy as a strategy in the global prevention of CVD. If the study demonstrates that the Polycap reduces the risk of CVD by at least 35%, then the polypill will likely gain acceptance as a cost effective and convenient approach for CVD prevention.

Conflicts of Interest and Disclosures

None of the authors have any relevant conflicts of interest related to the study. SY and PP have received research grants from Cadila pharmaceuticals. SY has received honoraria from several companies (Bayer, Boehringer Ingelheim, Astra Zeneca, Ferrer) for separate activities unrelated to any of the treatments being evaluated in the trial. JB has received honoraria from Bayer. PLJ has received honoraria from Ferrer and Scandinavia pharmaceutical laboratories.

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Author Contributions

All authors contributed significantly to the work. Drs. PJ, PP, TK and SY contributed to the concepts of the paper. Drs. PJ, TK and SY contributed to data analysis or interpretation. Drs. PJ, PP, AD, JB, DX, PLJ, KY, ST, AS, HG, KY, PCL, KT, and SY contributed to drafting the manuscript, or revising it critically for intellectual content. All authors provided final approval of the manuscript.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ahj.2018.07.012.

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Acceptance of a Polypill Approach to Prevent Cardiovascular Disease Among a Sample of U.S. Physicians ☆

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ABSTRACT

Objective. To examine US physicians' self-reported knowledge about the Polypill, factors considered in deciding whether to prescribe it, and acceptance of prescribing it for cardiovascular disease (CVD) prevention.

Methods. Numerical scales of 0 (lowest) to 5 (highest) were used to assess self-reported knowledge and importance of factors relevant to making a decision to prescribe a Polypill. Characteristics of physicians indicating they would prescribe a Polypill were compared.

Results. Among 952 physicians surveyed February through March 2010, mean self-rated knowledge about the Polypill was 2.0 ± 1.5. Importance of degree of CVD event reduction, cost, and side effects were rated with means of 4.4, 4.3, and 4.3, respectively. 83% of respondents indicated they would "definitely" or "probably" prescribe it for high-risk patients; 62% would do so for moderate risk patients. Physicians with self-rated knowledge at $\geq$75th percentile were more likely to indicate they would prescribe a Polypill for moderate risk (adjusted OR 2.16; 95% CI 1.60–2.93) and high-risk (adjusted OR 1.57; 95% CI 1.07–2.32) patients.

Conclusion. Among this sample of physicians, there is relatively high acceptance of prescribing a Polypill for CVD prevention despite relatively modest knowledge about it.

Introduction

Cardiovascular disease (CVD) accounts for 1 of every 3 deaths in the United States (US), (Lloyd-Jones et al., 2010). Prevention of CVD therefore remains a high public health priority, and the high-rate of initial CVD events that are fatal or disabling makes primary prevention paramount. The conventional clinical approach to primary prevention of CVD relies on identification and treatment of individual threshold-based risk factors such as hyperlipidemia and hypertension. However, a sizeable proportion of CVD events occur among people with average levels of blood pressure (BP) and cholesterol (Law et al., 2004; Rose, 1985; Wald and Law, 2003). This "prevention paradox" occurs because there are many more people in the middle of the distribution of these risk factors (Rose, 1985).

An approach of only offering preventive pharmacotherapy to people with elevated risk factors based on the upper tail of the distribution does not take into full account the consistent increase in relative risk of CVD as BP or cholesterol increases, the combined effects of risk factors, or the fact that the strongest risk factor is age (Hingorani and Psaty, 2009; Lewington et al., 2002, 2007; Rose, 1985). An exclusive risk factor level approach therefore does little to help reduce the risk in the large portion of the population whose overall CVD risk is elevated but whose individual risk factors are only mildly elevated or "normal" (Hingorani and Psaty, 2009; Law et al., 2004; Persell et al., 2006).

In 2003 Wald and Law proposed a strategy to address this significant limitation of the clinical approach to CVD prevention (Wald and Law, 2003). They calculated that if a combination pill containing three half-standard doses of BP-lowering drugs, a statin (standard dose), low-dose aspirin, and folic acid was given to all adults 55 years and older (regardless of risk factor levels), the potential impact would be substantial, with reductions in coronary heart disease and stroke events of 80% and 88%, respectively. However, the actual efficacy of a population-level Polypill approach in reducing CVD events is unknown. Calculations based on data observed in The Indian Polycap Study (TIPS)

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suggest a risk reduction closer to 60%—still a tremendous potential impact (The Indian Polycap Study, 2009).

With the publication of TIPS, ongoing initial research in several countries, and at least three Indian pharmaceutical companies currently producing versions of a Polypill, it appears that the Polypill-type approach may become a viable option for CVD prevention, but additional studies are needed (Combination Pharmacotherapy and Public Health Research Working Group, 2005; Hingorani and Psaty, 2009; Wald and Wald, 2010). Currently, however, there are no Polypill trials in the US, and physician acceptance of a population-level Polypill approach may be limited by concerns such as potential side effects, cost, and inability to individualize therapy. A clinical-level approach, whereby people could be counseled about the potential risks and benefits of taking a Polypill and could be monitored, might be more acceptable to physicians than the population-level approach. The goal of this study was to examine US physicians' knowledge and attitudes regarding a Polypill approach with particular focus on whether physicians would prescribe a Polypill for primary prevention to patients at varying levels of increased cardiovascular risk.

Methods

Overall design

This study was a web-based survey of a national sample of family physicians, general internists, and cardiologists. The survey was designed by the investigators and revised after pretesting among a convenience sample of family physicians, general internists, and cardiologists. Some items were modified from a questionnaire used in a Polypill study in Sri Lanka (Soliman EZ et al., Wake Forest University, unpublished study, 2010). This study was approved by the Institutional Review Board of the University of North Carolina at Chapel Hill.

Study sample and invitations to participate

Personalized invitation letters were mailed to 8623 physicians randomly selected from databases of members of the American Academy of Family Physicians and the American College of Physicians. These letters described that the survey would ask about new ideas in CVD prevention and provided instructions for accessing it online. An individualized identification code allowed tracking of non-respondents. At 2 and 4 weeks after the initial invitation, non-respondents were mailed reminder letters. As an incentive to participate, physicians could have their name entered into a drawing for one of two $500 gift cards.

A total of 1238 physicians participated in the survey. Respondents who indicated they do not see patients in the office setting ($n=251$) or whose specialty was not family medicine, general internal medicine, or cardiology ($n=55$) were excluded. Seventy-four letters were returned as undeliverable, including 8 because the intended recipient was deceased, and 3 because of delivery refusal. The adjusted response rate was 15%. The final sample consisted of 390 family physicians, 272 general internists, and 290 cardiologists.

Variables

Data obtained included self-rated knowledge about the Polypill, factors considered important to the decision to prescribe a Polypill, and level of agreement with the idea that CVD risk factors would not need monitoring in patients receiving the Polypill. The numerical scale for items ranged from 0 to 5, with 0 being lowest level (of knowledge, agreement or importance) and 5 being the highest. For reporting associations with acceptance, self-rated Polypill knowledge and ratings of perceptions of problems with adherence to CVD prevention medications were dichotomized at ≥75th percentile of the sample. In order to assess acceptance of a clinical approach to using a Polypill, respondents were asked whether they would be likely to prescribe a Polypill for primary prevention to patients at moderate CVD risk and high CVD risk (not otherwise defined). For these items, respondents were told to assume that the Polypill halved the risk of CVD events. Information on specialty type, amount of patient care time, year in practice, type of practice setting, and region of the country was also collected.

Analysis

Responses to each of the items were tabulated and differences were compared by respondent characteristics. Testing for significant differences was performed using analysis of variance for numerically-scaled outcomes and chi-square for categorical outcomes. Because of multiple comparisons, statistically significant differences were defined as a p-value<0.01. Characteristics of physicians who indicated they would "definitely" or "probably" prescribe a Polypill for primary prevention were compared in unadjusted analyses and then by logistic regression to adjust for specialty, years in practice, region of country, self-rated knowledge and perceptions of patients' adherence to risk-reducing medications. All analyses were performed using Stata 10.1 software (StataCorp, College Station, TX).

Table 1
Characteristics of Respondents ($N=952$).

	All	Family physicians ($n=390$)	General internists ($n=272$)	Cardiologists ($n=290$)	p-Value
	%	%	%	%	
% Male	73.5	57.8	74.6	94.3	<0.001
Years in practice					<0.001
≥ 20	61.4	37.8	68.7	86.6	
10–19	17.0	21.8	19.1	8.7	
<10	21.6	40.4	12.2	4.7	
Region of country					0.018
Northeast	23.9	18.3	25.7	29.3	
South	33.2	34.3	33.6	31.4	
Midwest	24.2	24.5	24.2	23.9	
West	18.8	22.9	16.6	15.4	
Time spent in office-based patient care					<0.001
≥75%	56.6	71.0	63.5	30.3	
51% to 74%	14.6	9.5	11.1	25.1	
50%	8.5	5.6	6.6	14.3	
25% to 49%	10.2	9.0	6.6	15.3	
<25%	10.0	4.9	12.2	15.0	
Practice setting					<0.001
Solo practice	12.5	9.7	14.8	14.1	
Small group (2–9 clinicians)	32.0	36.7	32.6	25.2	
Large single specialty group (10+ clinicians)	11.8	9.7	4.8	21.0	
Large multi-specialty group (10+ clinicians)	14.0	13.9	18.5	9.7	
Academic group	20.6	21.8	17.0	22.4	
Other	9.1	8.2	12.2	7.6	

Physicians were surveyed in the United States from February to March 2010.

Results

Characteristics of respondents

Most respondents were male (74%), in practice ≥10 years (78%), and spent >50% time in office-based patient care (71%) (Table 1). The most common practice type was small group practice (2 to 9 clinicians). Family physicians and general internists spent more time in office-based care than cardiologists. Cardiologists were more likely to be in practice for a longer time frame.

Knowledge and attitudes about polypill

Self-rated knowledge about the Polypill ranged from 0 (lowest) to 5 (highest) with a mean of 2.0. Cardiologists' self-rated knowledge (2.7) was higher than that reported by family physicians (1.5) and general internists (1.9) ($p<0.0001$) (Table 2). In terms of factors important in the decision to prescribe a Polypill, respondents rated cost, degree of CVD event risk reduction, and side effects nearly equally important with means of 4.3, 4.4, and 4.3, respectively. Importance of patient's likely adherence and ability to modify doses were rated slightly less important. Among respondents of all three specialties there was low agreement (mean 1.0) with the idea to forgo routine monitoring of CVD risk factors in patients receiving the Polypill.

Acceptance of Prescribing Polypill

Assuming the Polypill halved the risk of cardiovascular events, 41.1% (95% CI 37.9%–44.2%) of respondents would "definitely" prescribe it and 41.4% (95% CI 38.2%–44.5%) would "probably" prescribe it for high-risk patients (Table 3). There was greater uncertainty among respondents about whether they would prescribe the Polypill for moderate risk patients. Still, 50.1% (95% CI 46.9%–53.3%) indicated that they "probably" would prescribe the Polypill to moderate risk patients, and 12.3% (95% CI 10.1%–14.4%) indicated they would "definitely" prescribe it to moderate risk patients. When asked whether the Polypill should be available without a prescription assuming that a well-done large clinical trial showed that it halved the risk of CVD events and it was approved for use in the US, 89.2% of respondents indicated "no."

Characteristics of physicians who would prescribe Polypill

Physicians who indicated that they would "definitely" or "probably" prescribe the Polypill to high risk patients as primary prevention were somewhat more likely to be in practice 10 to 19 years, live in the South, and believe that adherence to risk reducing medications was a problem in their practice (Table 4). Cardiologists were somewhat more likely than general internists and family physicians to be willing to prescribe Polypill for moderate risk patients (68.7% vs. 61.7% vs. 58.3%, $p=0.02$). Physicians with higher self-rated Polypill knowledge were more likely to be willing to prescribe it for moderate risk patients (73.2% vs. 54.7%, $p<0.001$). Other characteristics of physicians who would prescribe Polypill for moderate risk patients were similar to characteristics of those who would prescribe to high risk patients.

In adjusted models (Table 5), the factors associated with physicians' acceptance of prescribing a Polypill were self-rated knowledge about the Polypill and region of country. Physicians with self-rated knowledge about the Polypill at ≥75th percentile were more likely to indicate they would prescribe it as primary prevention for moderate risk (OR 2.16; 95% CI 1.60–2.93) and high-risk (OR 1.57; 95% CI 1.07–2.32) patients. Physicians practicing in the South were also more likely to indicate that they would prescribe the Polypill.

Discussion

This study is the first to the authors' knowledge to examine acceptance of a Polypill approach among a sample of US physicians. The findings can be summarized as follows: (1) based on risk/benefit tradeoff there is a high level of acceptance for prescribing a Polypill for primary prevention to high risk patients and a moderate level of acceptance for prescribing it to moderate risk patients, (2) physicians consider multiple relevant factors equally important when deciding on whether they would prescribe a Polypill, (3) self-rated knowledge about the Polypill is low, and higher knowledge is associated with greater acceptance, (4) perceptions of problems with adherence to CVD risk-reducing medications do not appear to be associated with greater acceptance, (5) physicians would prefer some ability to modify doses of a Polypill, and (6) physicians do not favor forgoing risk factor monitoring in patients taking a Polypill.

As initially proposed, the Polypill would be a population level strategy rather than a clinical one (Wald and Law, 2003). That is, it would be taken by all adults using some non-clinical criterion such as age (e.g., ≥55 years) without any known CVD (and who had no contraindication to its components) (Wald and Law, 2003; Wald and Wald, 2010). The clinical monitoring of risk factor levels and routine assessments for side effects (including laboratory parameters) would be major barriers to using such a strategy as would the need to see a physician to obtain a prescription for the Polypill. In other words, requiring the person interested in taking the Polypill to be a "patient" may limit its population-level potential (Wald and Wald, 2010). However, US physicians currently have very low agreement with the idea that CVD risk factors would not need routine monitoring in those taking the Polypill. Additionally, US physicians did not feel that the Polypill should be available without a prescription. Physicians were not asked to rate their level of agreement with the possibility of having the Polypill available by other means (e.g., pharmacists who could dispense the Polypill after an appropriate screening) (Wald and Wald, 2010). Nevertheless, the physicians sampled seemed generally unwilling to endorse a population-based approach to cardiovascular prevention, but could envision the implementation of a more clinical one.

The clinical type of Polypill approach that physicians in this sample find acceptable still would offer many advantages. While patients at high risk usually have their risk addressed because of their inherently higher level of risk factors, many people at moderate risk are not receiving appropriate risk-reducing therapies, particularly in combination (Persell

Table 2
Physician self-rated knowledge and attitudes about Polypill, rated 0 to 5[a].

	All	Family physicians	General internists	Cardiologists	*p*-Value
Self-rated knowledge about the Polypill	2.0	1.5	1.9	2.7	<0.0001
Importance of patient's likely adherence on decision to prescribe Polypill	4.0	4.0	3.8	4.0	0.13
Importance of ability to modify doses on decision to prescribe Polypill	3.9	3.9	3.8	4.1	0.04
Importance of cost of pill on decision to prescribe Polypill	4.3	4.4	4.2	4.4	0.12
Importance of degree of CVD event risk reduction on decision to prescribe Polypill	4.4	4.4	4.3	4.4	0.11
Importance of side effects on decision to prescribe Polypill	4.3	4.3	4.3	4.4	0.64
Agreement with idea that CVD risk factors would not need routine monitoring in patients receiving Polypill	1.0	1.0	1.0	1.0	0.80

Physicians were surveyed in the United States from February to March 2010.
[a] "0" is lowest level or lowest importance, and "5" is highest level or highest importance.

Table 3
U.S. physicians' acceptance of prescribing Polypill as primary prevention assuming it halved risk of cardiovascular events.

	All respondents, % (95% CI)	Family physicians, % (95% CI)	General internists, % (95% CI)	Cardiologists, % (95% CI)	*p*-Value
Moderate risk patients for primary prevention					0.04
Yes, definitely	12.3 (10.1–14.4)	9.6 (6.6–12.5)	13.2 (9.1–17.2)	15.3 (11.0–19.6)	
Yes, probably	50.1 (46.9–53.3)	48.7 (43.7–53.7)	48.5 (42.5–54.5)	53.5 (47.5–59.4)	
Uncertain	17.9 (15.4–20.3)	21.8 (17.7–25.9)	16.2 (11.7–20.6)	13.8 (9.7–17.9)	
No	19.8 (17.2–22.4)	20.0 (15.9–24.0)	22.2 (17.2–27.2)	17.5 (12.9–22.0)	
High-risk patients for primary prevention					0.02
Yes, definitely	41.1 (37.9–44.2)	38.4 (33.5–43.3)	42.1 (36.1–48.1)	43.5 (37.6–49.4)	
Yes, probably	41.4 (38.2–4.5)	45.6 (40.6–50.6)	40.6 (34.7–46.5)	36.6 (30.9–42.3)	
Uncertain	9.2 (7.4–11.1)	10.8 (7.7–13.9)	8.3 (4.9–11.6)	8.0 (4.8–11.2)	
No	8.4 (6.6–10.1)	5.2 (2.9–7.4)	9.0 (5.6–12.5)	12.0 (8.1–15.8)	

Physicians were surveyed in the United States from February to March 2010.

et al., 2006). It is for this group, estimated to be about 13% of the US adult population, that the Polypill could be targeted clinically (Ajani and Ford, 2006). The use of global CVD risk (e.g., Framingham-based) assessments could facilitate such an approach. Global risk takes into account the combined contributions of the major risk factors (including age), and can be used by clinicians to guide preventive pharmacotherapy without reliance on threshold BP and cholesterol levels (Pearson et al., 2002). As such, it would be important that the Polypill not be viewed as a pill for "treatment" of risk factors. Rather, its indication should be for "prevention" of CVD.

This study showed that physicians with higher self-rated knowledge about the Polypill have greater acceptance of prescribing a Polypill, particularly to patients at moderate CVD risk. Specific knowledge questions were not included in this study, however. Thus, it is not known what particular understandings about the Polypill approach influenced the physicians' acceptance. Respondents practicing in the

Table 4
Characteristics of physicians who would "definitely" or "probably" prescribe Polypill for primary prevention of cardiovascular disease.

	Moderate risk patients	*p*-Value	High risk patients	*p*-Value
	%		%	
Specialty		0.02		0.42
Family medicine	58.3		84.0	
General internal medicine	61.7		82.7	
Cardiology	68.7		80.1	
Sex		0.43		0.63
Male	62.9		82.7	
Female	60.0		81.3	
Years in practice		0.04		0.05
≥20	64.2		80.8	
10–19	66.9		89.1	
<10	55.3		83.4	
Region of country		0.02		0.04
Northeast	61.3		82.8	
South	68.3		86.4	
Midwest	61.4		81.3	
West	53.7		76.1	
Time spent in office-based patient care		0.33		0.62
≥75%	61.8		83.3	
Between 50% & 75%	68.7		82.1	
50%	58.2		83.8	
Between 25% and 50%	64.9		82.5	
<25%	56.2		76.4	
Practice setting		0.89		0.06
Solo practice	66.4		83.6	
Small group (2–9 clinicians)	61.4		87.3	
Large single specialty group (10+ clinicians)	64.6		79.1	
Large multi-specialty group (10+ clinicians)	59.2		76.3	
Academic group	61.8		82.3	
Other	62.3		77.1	
Self-rated Polypill knowledge ≥75th percentile		<0.001		0.06
Yes	73.2		85.3	
No	54.7		80.4	
Adherence to BP medications a problem in practice[a]		0.07		<0.001
Yes	65.7		87.9	
No	59.7		78.5	
Adherence to lipid lowering medications a problem in practice[a]		0.05		0.001
Yes	65.4		86.9	
No	59.1		78.3	
Adherence to aspirin a problem in practice[a]		0.02		0.01
Yes	66.6		86.0	
No	58.9		79.7	

[a] Based on being at or above 75th percentile of sample in response to question, "On a scale from 0 to 5, where 0 indicates not a problem at all and 5 indicates an extremely big problem, how big of a problem is nonadherence to [the medication] in your practice?" Physicians were surveyed in the United States from February to March 2010.

Table 5
Independent associations[a] of characteristics of physicians who would "definitely" or "probably" prescribe Polypill for primary prevention of cardiovascular disease.

	Moderate risk patients		High risk patients	
	OR	95% CI	OR	95% CI
Specialty				
Family medicine	ref		ref	
General internal medicine	1.04	0.73–1.48	0.91	0.57–1.45
Cardiology	1.22	0.83–1.80	0.69	0.43–1.12
Years in practice				
≥ 20	1.18	0.81–1.72	0.89	0.55–1.46
10–19	1.48	0.94–2.34	1.54	0.81–2.94
<10	ref		ref	
Region of country				
Northeast	1.36	0.89–2.07	1.75	1.05–2.94
South	1.98	1.33–2.96	2.20	1.34–3.62
Midwest	1.52	1.00–2.31	1.57	0.95–2.60
West	ref		ref	
Self-rated Polypill knowledge ≥75th percentile				
Yes	2.16	1.60–2.93	1.57	1.07–2.32
No	ref		ref	
Adherence to BP medications a problem in practice[b]				
Yes	1.03	0.72–1.48	1.48	0.93–2.36
No	ref		ref	
Adherence to lipid lowering medications a problem in practice[b]				
Yes	1.09	0.77–1.54	1.29	0.83–2.00
No	ref		ref	
Adherence to aspirin a problem in practice[b]				
Yes	1.31	0.95–1.81	1.13	0.74–1.71
No	ref		ref	

[a] Adjusted for all characteristics in table.
[b] Based on being at or above 75th percentile of sample in response to question, "On a scale from 0 to 5, where 0 indicates not a problem at all and 5 indicates an extremely big problem, how big of a problem is nonadherence to [the medication] in your practice?" Physicians were surveyed in the United States from February to March 2010.

South were somewhat more likely to indicate that they would "probably" or "definitely" prescribe the Polypill for primary prevention. This association may be related to the greater burden of CVD seen in the South (e.g., the "Stroke Belt") (Lanska and Kuller, 1995).

Limitations

The most important limitation of this study is the low response rate. If attitudes and acceptance as reported by physicians who responded are different from responses that would be reported by physicians who did not respond, then our results will be biased. If physicians who chose to respond to the survey were more passionate about CVD prevention, they might also be more accepting of a Polypill. In such a case our results will overestimate the acceptance of a Polypill. It is also possible that those especially opposed to the Polypill idea participated more than physicians whose opinions were in favor of or neutral towards the idea. In such an instance, our findings would underestimate the level of acceptance.

Whether or not the Polypill would contain aspirin was not specified. In the original Polypill description, aspirin was included as a component (Wald and Law, 2003). However, the efficacy of aspirin in primary prevention of CVD has been called into question (ATT, 2009; Fowkes et al., 2010; Ogawa et al., 2008). Further, the use of aspirin for CVD prevention needs to be weighed against the risk of gastrointestinal bleeding (Wolff et al., 2009). It is not known whether respondents considered such issues in formulating their answers, or whether respondents' acceptance would differ between a Polypill containing aspirin and one that did not.

Conclusions

US physicians' acceptance of a clinical approach to using Polypill for CVD prevention appears fairly high, but our findings suggest that US physicians are not ready to support a true population level Polypill approach. A clinical strategy using a Polypill for primary prevention of CVD in the US has tremendous potential and is worthy of study.

Conflict of interest statement
The authors declare that there are no conflicts of interest.

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Economic evaluation of a pharmacogenomic multi-gene panel test to optimize anti-hypertension therapy: simulation study

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ORIGINAL RESEARCH

Economic evaluation of a pharmacogenomic multi-gene panel test to optimize anti-hypertension therapy: simulation study

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ABSTRACT

Aims: Hypertension is the strongest modifiable risk factor for cardiovascular disease, affecting 80 million individuals in the US and responsible for ~360,000 deaths, at total annual costs of $93.5 billion. Antihypertension therapies guided by single genotypes are clinically more effective and may avert more adverse events than the standard of care of layering anti-hypertensive drug therapies, thus potentially decreasing costs. This study aimed to determine the economic benefits of the implementation of multi-gene panel guided therapies for hypertension from the payer perspective within a 3-year time horizon.

Materials and methods: A simulation analysis was conducted for a panel of 10 million insured patients categorized clinically as untreated, treated but uncontrolled, and treated and controlled over a 3-year treatment period. Inputs included research data; empirical data from a 11-gene panel with known functional, heart, blood vessel, and kidney genotypes; and therapy efficacy and safety estimates from literature. Cost estimates were categorized as related to genetic testing, evaluation and management, medication, or adverse events.

Results: Multi-gene panel guided therapy yielding savings of $6,256,607,500 for evaluation and management, $908,160,000 for medications, and $37,467,508,716 for adverse events, after accounting for incremental genetic testing costs of $2,355,540,000. This represents total 3-year savings of $42,276,736,216, or a 47% reduction, and 3-year savings of $4,228 and annual savings of $1,409 per covered patient.

Conclusions: A precision medicine approach to genetically guided therapy for hypertension patients using a multi-gene panel reduced total 3-year costs by 47%, yielding savings exceeding $42.3 billion in an insured panel of 10 million patients. Importantly, 89% of these savings are generated by averting specific adverse events and, thus, optimizing choice of therapy in function of both safety and efficacy.

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Introduction

Hypertension is the strongest modifiable risk factor for cardiovascular disease (CVD) and is the leading cause of death and disability-adjusted life-years worldwide[1,2]. Globally, 31.1% of the adult population (1.39 billion) had hypertension in 2010 (the last year that meaningful population data are available), and this number is projected to increase to 1.5 billion people worldwide by 2025[3,4]. In the US, from 2000 to 2010, the prevalence of hypertension rose from 27.8% to 31.1% in men and 30.9% to 31.8% in women, creating an affected population size of ~80 million individuals[3,5]. The problem is compounded by the addition of more than 5 million new diagnoses made each year in the US alone[3,5,6]. Furthermore, high blood pressure (BP) is responsible for ~360,000 deaths annually and, in 2009, had a direct cost to the US healthcare system of ~$51 billion dollars[7,8]. From 1979–1982 to 2003–2006, the proportion of hospitalizations associated with hypertension increased from 1.9% to 5.4%, resulting in cost increases from $40 billion to estimates as high as $113 billion[9,10]. Although new BP standards were released in 2017[11], their adoption has been slow and the BP categorization as used in recent meta-analyses prevails: normal BP (systolic BP [SBP] < 120 mmHg and diastolic BP [DBP] < 80 mmHg), elevated BP (SBP = 120–129 mmHg, DBP <80 mmHg), stage 1 hypertension (SBP = 130–139 mmHg, DBP = 80–89 mmHg), and stage 2 hypertension (SBP ≥140 mm, DBP ≥90 mmHg)[12–15].

Aggressive and intensive treatment for rapid reduction in BP is important for survival in patients with hypertension, as end organ damage occurs quickly, and small reductions (~5 mmHg) in BP can markedly improve survival[16]. Unfortunately, only an estimated 70% of hypertension

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patients are treated, and ~50% of those are defined as controlled (BP <140/90 mmHg), suggesting that the efficacy of anti-hypertensive therapy to achieve BP control goes beyond patient adherence and related medication behaviors[17]. Furthermore, each common class of prescribed BP medication (β-blockers, Ca^{+} channel blockers, ACE inhibitors, angiotensin II antagonists, diuretics) has an average effectiveness rate of ~50%, clearly suggesting a genetic component to therapy efficacy[18]. The lack of universal effectiveness for each class of antihypertensive medications is further demonstrated in the bell-curve response to most hypertension therapies. This bell-curve response leads to a proportion of patients having a desired reduction in BP, but a significant proportion of patients (10–20%) experiencing no change or even an *increase* in BP[19,20]. Therefore, the current standard of care to achieve the desired BP response is to increase dosage to the maximally tolerated dosage and then adding additional hypertension therapies when the prior line of therapy proves unsuccessful. Unfortunately, this approach of layering blood pressure drug therapies has many potential long- and short-term consequences in the form of increased side-effect profile, additional costs to the patient, increased healthcare service utilization, and reduced quality-of-life[21,22].

Like many diseases, research indicates a heritable component to the development of hypertension estimated at ~50%, with data suggesting treatment for hypertension may be heritable as well[19,23–26]. While genetics has been shown to improve responsiveness to antihypertensive monotherapy, few studies have explored the impact of genotype on responsiveness to therapy employing multiple genes and drug classes concurrently[19,27]. Much of this genetics work focused initially on genome-wide association studies (GWAS) and was followed later by studies of response rates to independent drug classes, typically in isolation[27–31]. This proves problematic, as recent meta-analyses have identified ~50 loci associated with hypertension, with each individual locus accounting for a small fraction (~ 2%) of heritability[32]. While GWAS have historically been valuable in clinical research, few variants identified as being associated with hypertension, or a response to pharmacotherapy, have been validated to demonstrate a meaningful functional response in follow-up prospective trials[24,27]. However, the exploration into gene–gene interactions of known functional variants selected with candidate-gene studies may explain more variance than a single locus alone[33]. Current enthusiasm for the field of pharmacogenetics remains high, but few commercial pharmacogenetic tests have completed research studies to provide evidence of effectiveness, and even fewer have provided economic analyses on how their panels can reduce healthcare costs, when compared to the standard of care.

We have developed a multi-gene panel that identifies functional genotypes within the heart, vasculature, and kidney that have previously demonstrated pharmacogenetic differences in target therapy. DNA is collected using buccal swabs. From the buccal swab, 14 alleles in 11 genes are assessed: two SNPs in ADRB1 (rs1801252 and rs1801253), two SNPS in ADRB2 (rs1042713 and rs1042714), SCNN1A (rs2228576), alpha-adducin (ADD1, rs4961), SLC12A3 (rs1529927), two in WNK1 (rs1159744 and rs2107614), angiotensin-converting enzyme (ACE, rs1799752), angiotensin (AGT, rs699), angiotensin receptor (AGTR1, rs5186), cytochrome P450 2D6 (CYP2D6*4, rs3892097), and renin (REN, rs12750834). We have demonstrated that the use of this panel to guide therapy is associated with improved BP medication success in hypertension patients[34]. In a Phase-I retrospective analysis we demonstrated that the multi-gene panel showed improvements in both changes in blood pressure (from the time of diagnosis until the time of office blood pressure measurement in the study) and control rates (using both 140/90 mmHg and 120/80 mmHg to determine "control"). In this study, using both survey data and chart review, we found that patients with a functional genotype within our multi-gene panel had better control rates (<140/90 mmHg) and a greater drop in blood pressure when compared to patients with functional genotypes who are not on the target therapy. The level of blood pressure reduction (SBP = 9 mmHg; DBP = 6.4 mmHG) has been shown to be associated with a 20–40% decrease in the risk of cardiovascular incidents in patients with uncomplicated hypertension and a 50–60% decrease in risk of cardiovascular incidents in patients with other co-morbidities[35,36].

The ineffectiveness of the current standard of care implies that implementing a multi-gene panel that takes into consideration common and functional genotypes of the organ systems important in mechanistic hypertension (heart, vasculature, and kidneys) could have significant economic benefits by decreasing costs of evaluation and management, medication usage, and adverse event costs incurred by payers. We report here on a simulation analysis to estimate the economic benefit of using a multi-gene panel to guide clinical decision-making about antihypertensive therapy. This simulation used data from a 100-individual trial comparing the standard of care vs genetically-guided antihypertensive treatment to determine the net savings that could be achieved from using a multi-gene panel. The analysis was conducted from the payer perspective, over a 3-year time horizon, for an insured panel of 10 million hypertension patients.

Methods

Economic analysis assumptions

To inform the simulation, the following assumptions regarding patient numbers in the US were made: 77,900,000 patients have hypertension; 82.7% of these patients are aware of their hypertension, having been diagnosed as such; 77.3% of these patients are treated for their hypertension, with 47.2% of these having their hypertension under control; and 5.4% of aware patients go untreated[37]. As shown in Figure 1, of the patients aware of their hypertension and receiving the standard of care, 60% are under control and 40% are not and are effectively hypertensive[37]. Further, previous data suggests the use of a multi-gene panel to guide hypertension therapy would improve the percentage of patients being treated and being under control to 85% (Table 1)[34,38] because of (1) choosing the correct medication

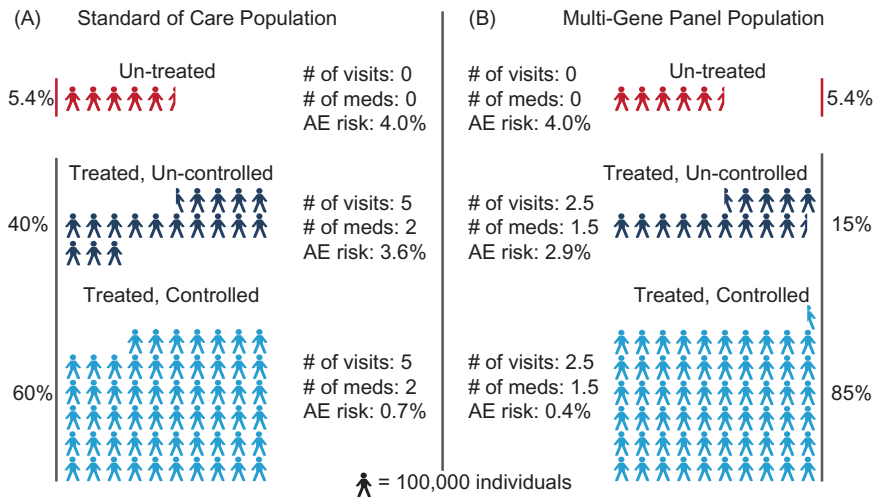

Figure 1. Distribution of treatment groups, interventions, and outcomes. Populations are represented as indicated from meta-analyses and retrospective clincal data. Interventions and risk were informed from these same data.

Table 1. Hypertension population.

Number and percentage of hypertension patients		
Number of patients with hypertension	77,900,000[37]	
Patients aware of hypertension	82.7%	
Patients aware of hypertension but not treated	5.4%[a]	
Patients with hypertension and being treated	77.3%[37]	
Total percentage of hypertension patients under control	47%[37]	
	Standard of care	Multi-gene panel
Care classification		
Treated/uncontrolled hypertension patients	40%[a]	15%[b]
Treated/controlled hypertension patients	60%[37]	85%[b]

[a]Per available data.
[b]Estimate.

first, (2) decreasing the total number of medications prescribed, and (3) telling a patient their drug regimen is based on their personal genetic make-up[39].

The following assumptions regarding costs associated with hypertension were made. Patients make 55 million annual visits for treatment of hypertension, resulting in $46 billion annual direct costs[10,40]. Adding $47.5 billion in indirect costs (loss of productivity due to presenteeism, work absence, and short-term disability) yields total annual hypertension costs of $93.5 billion; allowing a calculation of $590.50 per patient per year[10,40]. Medication costs were based on four 3-month generic prescription refills per year for each drug class at $16 each for treated patients[40]. The cost per clinic visit was assumed to be $143[40]. Previous research suggests an average of five visits to achieve BP control with standard of care[41], which we assumed would decrease to 2.5 visits if a multi-gene panel to guide hypertension therapy was implemented. Per expert opinion, treated patients were assumed to be on an average of two drug classes in standard of care practices, which would be decreased to an average of 1.5 drug classes with the use of a multi-gene panel. The cost of a multi-gene panel test was set at $249 (Table 2).

To calculate the probability of adverse events, 2-year incidence rates for men aged 30–39 (3.3%), women aged 30–39 (1.5%), men aged 70–79 (6.2%), and women aged 70–79 (8.6%) were used[42]. This allowed a weighted average 2-year incidence rate of 3.9% with a 4,833,483 assumed annual incidence and an estimated cost of $369,000 per adverse event. We assumed that the implementation of a multi-gene panel to guide hypertension therapy would result in a 20% decrease in adverse events in treated but uncontrolled patients, and a 40% decrease in treated and controlled patients (Table 3). The simulation was performed over 3 years, because this is the average time of impact to a payer-provider, and was performed using extrapolated 2-year data, because this is the most robust comprehensive data available on hypertension.

Economic simulation data

From these data, we ran simulations based on 10 million aware patients, using the above data to inform our classification of patients into three categories (Table 4): untreated patients ($n = 540,000$ for standard of care and multi-gene panel), treated and uncontrolled ($n = 3,784,000$ and $n = 1,419,000$ for standard of care and multi-gene panel, respectively), and treated and controlled ($n = 5,676,000$ and $n = 8,041,000$ for standard of care and multi-gene panel, respectively). This simulation was run utilizing data consistent with the standard of care and data consistent with the use

Table 2. Annual costs associated with hypertension.

Annual estimates		
Cost associated with hypertension	$46 billion[10,40]	
Cost associated with visits to treat hypertension	$55 million[10,40]	
Cost per patient	$590.50[a]	
Direct and indirect costs	$93.5 billion[10,40]	
	Standard of care	Multi-gene panel
Care classifications		
Average visits to BP control	5[b]	2.5[a]
Average number of drug classes	2[a]	1.5[a]

[a]Per available data above.
[b]Geneticure Phase I data.

Table 3. Two-year adverse events incidence rates and reductions associated with multi-gene panel directed therapy.

Rates	
Men (30–39 years)	3.3%[43]
Women (30–39 years)	1.5%[43]
Men (70–79 years)	6.2%[43]
Women (70–79 years)	8.6%[43]
Weighted average	3.9%[a]
Assumed adult annual rate	4,833,483[a]
Cost per event	$369,000[b]
Multi-gene panel adverse event reduction	
Treated/uncontrolled hypertension	20%[b]
Treated/controlled hypertension	40%[b]

[a]Per available data.
[b]Estimate.

Table 4. Simulation population.

Total	10,000,000	
Untreated patients	540,000	
	Standard of care	Multi-gene panel
Care classification		
Treated/uncontrolled patients	3,784,000	1,419,000
Treated/controlled patients	5,676,000	8,041,000

In total population: Untreated patients = 5.4% of total population; treated/uncontrolled = 40% (standard of care) and 15% (multi-gene panel); treated/controlled = 60% (standard of care) and 80% (multi-gene panel).

Table 5. Cost of adverse events in untreated hypertension patients over a 3-year care period.

Number of untreated patients	540,000
Probability	4%
Number of events	21,600
Total cost of adverse events	$7,970,400,000
Cost per patient	$14,760

of a multi-gene panel to guide hypertension therapy for the three categories.

Results

Untreated patients

For untreated patients ($n = 540{,}000$) at a 4% probability of adverse events, our simulation estimated 21,600 total adverse events at a cost of $369,000 per event; resulting in a total cost of $7,970,400,000 and a per patient cost of $14,760 over a 3-year period (Table 5).

Treated and uncontrolled patients

For treated/uncontrolled patients receiving the standard of care ($n = 3{,}784{,}000$), on an average of two drug classes, with a 3.6% probability of adverse events, we estimated the 3-year costs for evaluation and management at $8,116,680,000, for medications at $1,453,056,000, and for adverse events at $50,266,656,000; for a total 3-year cost of $59,836,392,000 or $15,813 per patient (Table 6).

Table 6. Cost of treated/uncontrolled hypertension patients over a 3-year care period.

	Standard of care	Multi-gene panel
Simulation population	3,784,000	1,419,000
Geneticure testing[12]	–	$353,331,000
Evaluation and management[12]	$8,116,680,000	$3,043,755,000
Medications[12]	$1,453,056,000	$408,672,000
Adverse events by care classification		
Probability	3.6%	2.9%
Number of events	136,224	40,867
Total cost of adverse events	$50,266,656,000	$15,079,996,800
Total cost	$59,836,392,000	$18,885,754,800
Cost per patient	$15,813	$13,309

Table 7. Costs associated with treated/controlled hypertension patients over a 3-year care period.

	Standard of care	Multi-gene panel
Simulation population	5,676,000	8,041,000
Geneticure testing[12]	–	$2,002,209,000
Evaluation and management[12]	$4,058,340,000	$2,874,657,500
Medications[12]	$2,179,584,000	$2,315,808,000
Adverse events		
Probability	0.7%	0.4%
Number of events	41,208	35,027
Total cost of adverse events	$15,205,663,440	$12,924,813,924
Total cost	$21,443,587,440	$20,117,488,424
Cost per patient	$3,778	$2,502

For treated/uncontrolled patients receiving hypertension therapy guided by a multi-gene panel ($n = 1{,}419{,}000$), on an average of 1.5 drug classes, with a 2.9% probability of adverse events, our simulation yielded 3-year costs for genetic testing at $353,331,000 for evaluation and management at $3,043,755,500, for medications at $408,672,000, and for adverse events at $15,079,996,800; for a total 3-year cost of $18,855,754,800 and $13,309 per patient.

Treated and controlled patients

For treated/controlled patients receiving the standard of care ($n = 5{,}676{,}000$); on an average of two drug classes, with a 0.7% probability of adverse events, we projected the 3-year cost for evaluation and management at $4,058,340,000, for

Table 8. Cost savings achieved with multi-gene enabled hypertension management over a 3-year care period.

	Standard of care	Genetic testing	Savings (loss)
Genetic testing			
Untreated patients	–	–	–
Treated/uncontrolled patients	–	$353,331,000	($353,331,000)
Treated/controlled patients	–	$2,002,209,000	($2,002,209,000)
Total		$2,355,540,000	($2,355,540,000)
Evaluation and management			
Untreated patients	–	–	–
Treated/uncontrolled patients	$8,116,680,000	$3,043,755,000	$5,072,925,000
Treated/controlled patients	$4,058,340,000	$2,874,657,500	$1,183,682,500
Total	$12,175,020,000	$5,918,412,500	$6,256,607,500
Medications			
Untreated patients	–	–	–
Treated/uncontrolled patients	$1,453,056,000	$408,672,000	$1,044,384,000
Treated/controlled patients	$2,179,584,000	$2,315,808,000	($136,224,000)
Total	$3,632,640,000	$2,724,480,000	$908,160,000
Adverse events			
Untreated patients	$7,970,400,000	$7,970,400,000	–
Treated/uncontrolled patients	$50,266,656,000	$15,079,996,800	$35,186,659,200
Treated/controlled patients	$15,205,663,440	$12,924,813,924	$2,280,849,516
Total	$73,442,719,440	$35,975,210,724	$37,467,508,716
Aggregated			
Untreated patients	$7,970,400,000	$7,970,400,000	–
Treated/uncontrolled patients	$59,836,392,000	$18,885,754,800	$40,950,637,200
Treated/controlled patients	$21,443,587,440	$20,117,488,424	$1,326,099,016
Total	$89,250,379,440	$46,973,643,224	$42,276,736,216

medications at $2,179,584,000, and for adverse events at $15,205,663,440; for a total 3-year cost of $21,443,587,440 and $3,778 per patient (Table 7).

For treated/controlled patients receiving hypertension therapy guided by a multi-gene panel ($n = 8,041,000$), on an average of 1.5 drug classes, with a 0.4% probability of adverse events, the simulation estimated the 3-year cost for genetic testing at $2,002,209,000, for evaluation and management at $2,874,657,500, for medications at $2,315,808,000, and for adverse events at $12,924,813,924; for a total 3-year cost of $20,117,488,424 and $2,502 per patient (Table 7).

Cost reductions and savings achieved from multi-gene panel guided antihypertensive therapy

In this simulation for a panel of 10 million covered beneficiaries, for patients receiving the standard of care for hypertension management with layering blood pressure medications, the estimated costs of evaluation and management were $12,175,020,000, of medications were $3,632,640,000, and of adverse events were $73,442,719,440; for a total 3-year cost of $89,250,379,440. This results in a 3-year total cost per patient of $8,952, and an annual cost per patient of $2,975 (Table 8).

In contrast, for patients receiving hypertension therapy guided by multi-gene panel genetic testing, the incremental 3-year cost of genetic testing was $2,355,540,000, whereas the 3-year treatment costs were $5,918,412,500 for evaluation and management, $2,724,480,000 for medication, and $35,975,210,724 for adverse events management; for a total 3-year cost of $46,973,643,224. This corresponds to a 3-year cost per patient of $4,697, and an annual cost per patient of $1,566 (Table 8).

Reconciling these 3-year figures, managing hypertension patients with multi-gene panel guided hypertension therapy returned decreases of 51% in evaluation and management costs for savings of $6,256,607,500; of 25% in medication costs for savings $908,160,000; and of 51% in adverse event costs for savings of $37,467,508,716 over 3 years, and this after accounting for the incremental $2,355,540,000 cost of genetic testing in the multi-gene panel scenario. Aggregated across cost categories, multi-gene panel guided hypertension management generated a 47% reduction in total 3-year costs, corresponding to total net savings of $42,276,736,216 for a panel of 10 million covered patients. This equals a 3-year net saving of $4,228 per patient, or $1,409 annual net savings (Table 8).

Discussion

The principal finding of this economic simulation analysis of a precision medicine approach to optimizing antihypertensive treatment is that genetic testing with a multi-gene panel and targeting treatment based on the genetic profile thus identified reduces the total cost of hypertension management by almost 50%. Importantly, 89% of these savings are generated by averting specific adverse events and, thus, optimizing choice of therapy in function of both safety and efficacy.

Specifically, under conservative assumptions, our economic simulation for 10,000,000 covered patients demonstrated that the use of a multi-gene panel to guide hypertension therapy would result in substantial net savings of $42.3 billion (rounded) over 3 years of treatment (a common duration of covering a patient), despite the incremental cost of $2.4 billion for the genetic testing. One significant benefit of the proposed genetic testing is the one-time upfront cost as opposed to the recurring differential costs of

evaluation and management, medications, and adverse events in non-tested patients. For instance, we assumed an improved time to BP control (5 vs 2.5 clinic visits per patient) would result in an estimated saving of $6.3 billion in evaluation and management costs, or a 51% reduction. We also projected that therapies guided by a multi-gene panel would be more effective, thus reducing drug layering and dosing. This reduced both adverse event rates and medication costs. Interestingly, our data revealed an increase of $136 million in medication costs for treated/controlled patients, which is attributable to improved efficacy of multi-gene enabled therapies in terms of increasing treated/controlled patients in numbers and as a proportion of the covered population. This incremental cost is small compared to both medication cost-savings and total overall cost-savings in treated/uncontrolled patients. The subsequent increase in the percentage of treated/controlled patients taking fewer drug classes was reflected in a greatly reduced adverse event rate, and, therefore, the costs of managing these adverse events. Economically, reduced adverse event rates are the main benefit of more effective hypertension therapies, constituting $37.5 billion of the $42.3 billion in total 3-year net savings. This amounts to $4,228 3-year net savings per patient and annual net savings of $1,409 per patient.

Hypertension is ~50% heritable (with a range of 20–65%)[44]. The heritable nature of hypertension and the limited clinical effectiveness of the current standard of care suggest a genetically tailored approach to hypertension therapy may be indicated for both clinical and safety reasons, and, therefore, be cost-effective over the standard of care. A great deal of the research on the genetics of hypertension has focused on genome-wide association studies that have demonstrated that genes in or within an area of proteins, enzymes, and receptors important to BP therapy are also important in the development of hypertension[45,46]. Previous work has demonstrated that single genes can help guide hypertensive therapy[44,47], and that multi-gene scoring can improve the response to common BP medications[27].

Current research examining genetic determinants to the response to hypertension therapy primarily focuses on genetic variations of thiazide and thiazide-like diuretic response. This includes lysine deficient protein kinase 1 (WNK1), alpha adducin (ADD1), sodium-chloride symporter (SLC12A3), and alpha subunit of the epithelial sodium channel (SCNN1A) variants[24,28,29]. These studies suggest genetic variations of WNK1 result in an ~6 mmHg difference in BP response to hydrochlorothiazide treatment[29]. Additionally, genetic variations of ADD1 and SLC12A3 have been shown to affect patient responsiveness to a diuretic[48]. Similarly, genetic variations in the β-adrenoceptors (both β_1 and β_2-adrenergic receptors, ADRB1 and ADRB2, respectively) have also been shown to mediate the response to β-blockade[48,49]. Specifically, evidence for the benefit of a multi-gene approach lies in the study of genetic variants of ADRB1 and β-blockade. Patients who are homozygous for functional variants at positions 49 and 389 (ser49/arg389) have an average reduction in blood pressure of 15 mmHg with β-blockade, while patients heterozygous for this haplotype demonstrate almost no reduction in blood pressure with β-blockers, and some combination of homozygosity for functionality and heterozygosity lie between these two extremes in a step-wise manner. Lastly, the response to vasodilation has primarily focused on genetic variation of the angiotensin-converting enzyme (ACE)-inhibitor, angiotensin, and the angiotensin-II receptor, demonstrating genetic variation alters the response to ACE-inhibition and angiotensin receptor antagonism[50,51]. Collectively, these previous findings demonstrate genetic variation plays a functional role in the variability of hypertension therapy efficacy and further supports the promise of genetically guided hypertension therapies. An interesting point of future research in multi-gene pharmacogenetics in hypertension is a focus on side-effect profiles. Most of the common hypertension therapies have well-established side-effect profiles, ranging from the development of type-II diabetes and bradycardia to development of an ACE-induced cough and angioedema. Interestingly, some of the variants that have been shown to be associated with improved response to treatment, from a blood pressure perspective, may also be those that can increase side-effect incident rates.

In this era of precision medicine, an effective multi-gene panel that includes functional variants in the three organ systems that are mechanistically important in hypertension (the heart, the vasculature, and the kidney) could guide individualized treatment decision-making considering both efficacy and adverse event profiles and medication. Therefore, contrary to the current standard of care of layering drugs and the likelihood of an worse side-effect profile, increased costs to the patient, increased healthcare service utilization, and reduced quality-of-life, with genetic testing patients can be prescribed drug classes based on their genetics, thus improving both efficacy and safety. The potential benefits of employing a multi-gene panel to guide pharmacological therapy in hypertension include: fewer clinic visits to achieve BP control; a higher percentage of treated patients with controlled BP; reduced adverse event rates; fewer drug classes prescribed per patient; and improved adherence rates through improved effectiveness, reductions in medications used, and lower adverse events. Cumulatively, this would result in lower costs associated with evaluation and management, medications, and managing adverse events, even after accounting for the incremental costs associated with genetic testing. In turn, as we demonstrated in this simulation, this translates into major reductions in the total cost incurred by payers.

Despite the short-term analysis of our study over a 3-year time horizon, an analysis with a longer time horizon is needed to estimate the extended savings that can be achieved by performing multi-gene panel genetic testing. Cost-effectiveness analyses over a lifetime horizon may support the long-term clinical and economic benefits of multi-gene panel genetic testing.

One limitation of this study is the need to use estimates for some inputs as there is limited research examining the efficacy of multi-gene panel guided therapies in hypertension. Therefore, we relied on data pertaining to gene panels

and gene–gene interactions in other pathologies as well as results from a Phase I trial on the multi-gene hypertension panel. Preventively, we used conservative assumptions to minimize the risk of bias. Additionally, it is likely that the increased blood pressure reduction from genetically-guided therapy will also improve adherence (less trial-and-error), which could further augment the economic benefits of such a panel. While further studies are needed on the association of multi-gene panel guided therapies to BP medication efficacy and safety in hypertension, our data suggests the potential for large economic impacts.

Conclusions

Collectively, our payer-focused economic simulation for the US of the implementation of multi-gene panel enabled therapies for hypertension patients demonstrates cost reductions of nearly 50% over 3 years in the management of hypertension. While certainly these findings are substantive to payers, the benefits to patients are just as significant in terms of targeted treatment, reductions in adverse events, and fewer clinic visits, not to mention the corresponding improvements in quality-of-life.

Transparency

Declaration of funding

The study was supported by funds from Geneticure Inc., which has developed multi-gene panels for blood pressure prescribing using pharmacogenetics. NSA and IA provided independent economic analysis advice to Geneticure Inc. pro bono without any monetary or other benefits.

Disclosure of financial/other interests

EFK declares no conflict of interest. EMS, SCS, RS, and TPO have significant financial interests in Geneticure Inc. NSA and IA provided independent economic analysis advice to Geneticure Inc. pro bono without any monetary or other benefits. They have no other conflicts to declare. Peer reviewers on this manuscript have received an honorarium from JME for their review work, but have no other relevant financial relationships to disclose.

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