The SCCS Polypill Pilot Trial

NCT02278471

Redacted Study Protocol

Version Date: 12/28/2016

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Table of Contents

1. BACKGROUND AND SIGNIFICANCE

1.1 The public health burden of cardiovascular disease

Heart disease represents a significant public health burden around the globe and remains the leading cause of death for both men and women in the United States. Coronary Heart Disease (CHD), the most common form of heart disease, kills nearly 400,000 Americans annually.[1] Each year, approximately 720,000 Americans suffer a heart attack, resulting in significant morbidity and lost quality of life.[2] Taking into account the cost of health care services, medications, and lost productivity, CHD alone costs the U.S. nearly $110 billion per year.[3]

1.2 Poor control of cardiovascular risk factors contributes to the problem

The disease-producing and disease-perpetuating roles of certain CHD risk factors, such as hypertension and dyslipidemia, have been well established. Effective management of these risk factors remains a key strategy in both the primary and secondary prevention of CHD.[4,5]

1.3 The challenge of primary prevention in low SES populations

Individuals of low socioeconomic status (SES) experience a disproportionately high risk of cardiovascular disease and cancer. [redacted]

Pharmacologic measures are frequently needed, but there is no consensus on how to optimally implement such measures. Two competing approaches have been advocated for cardiovascular risk reduction: the “high-risk strategy” and the “population-based strategy.”[6,7] In the high-risk strategy, preventive measures are targeted specifically at high-risk individuals, with medication therapy tailored to each patient’s risk factor profile (i.e. a personalized approach). The identification of high-risk patients typically relies on clinical and laboratory-based prediction algorithms, such as the Framingham Risk Score. This has been the traditional approach endorsed in major guidelines, such as JNC 8 and ATP 3. In contrast, the population-based strategy focuses on shifting the entire risk distribution, with measures implemented at the population level. This approach emphasizes low-cost interventions generally associated with a low incidence of side effects.

The relative merits of these competing approaches have stimulated active debate in cardiovascular prevention. The attractiveness of the high-risk strategy lies in its concentrated efforts on individuals who are most likely to develop a cardiovascular event.

On the other hand, it is estimated that two-thirds or more of cardiovascular events occur in individuals who are at low or intermediate risk by current prediction algorithms. Furthermore, the cost/benefit equation may differ in low SES populations.

The most recent cholesterol guidelines from the ACC/AHA (an update to ATP 3) endorse a hybrid of the high-risk and population-based approaches. The guidelines recommend statin pharmacotherapy for individuals with a predicted 10-year cardiovascular risk of 7.5% or higher.[9] Targeting individuals based on individual risk estimates embodies a high-risk approach. On the other hand, by moving the risk threshold from 20% over 10 years (in ATP 3) to 7.5% over 10 years, the guidelines seek to apply pharmacotherapy to a much broader population that is closer to that seen in population-based approaches. Furthermore, the guidelines no longer advocate specific LDL targets and recommend a standard dose of statin therapy for the majority of individuals, a shift toward a less personalized strategy.

1.4 The "polypill" approach and underserved populations

A relatively recent iteration of the population strategy is the "polypill" concept. The polypill refers to a fixed dose combination of medications with proven benefits for cardiovascular prevention,

The polypill offers several potential advantages to usual pharmacotherapies. The simplicity of a single daily pill is likely to improve adherence. For blood pressure control, the combination of multiple medications at low doses rather than 1 or 2 medications at higher doses may be better tolerated, as side effects are typically dose-dependent. Furthermore, components of the polypill could have offsetting side effects; for instance, adding an ACE inhibitor or ARB to a thiazide is likely to reduce the risk of hypokalemia.

Lastly, eliminating the need for dose titration may insulate against physician “inertia,” and may be rational in settings where frequent follow-up visits are impractical.

The feasibility of the polypill approach has been evaluated in several randomized trials outside the United States. In the Indian Polycap Study (TIPS), approximately 2,000 individuals in India were assigned to one of 9 arms, including 412 individuals to the Polycap (aspirin 100 mg, simvastatin 20 mg, atenolol 25 mg, HCTZ 12.5 mg, and ramipril 20 mg).[12] The other arms comprised various combinations of the individual component medications in the polypill. The polypill was well-tolerated and effectively reduced blood pressure and LDL cholesterol. Several smaller trials have been performed with similar findings (e.g. the PILL Study, TIPS-2, UMPIRE), with sample sizes ranging from 50 to 500 individuals.[13-15] Only 13 individuals from the U.S. have been enrolled in all of these studies combined, and none of the studies focused specifically on low SES individuals.

[redacted]

[redacted] we propose to test the feasibility and effectiveness of daily administration of a “polypill” in a medically-underserved population. The proposed study should establish whether larger outcomes trials are warranted to assess the effectiveness of the polypill in reducing the incidence of cardiovascular events.

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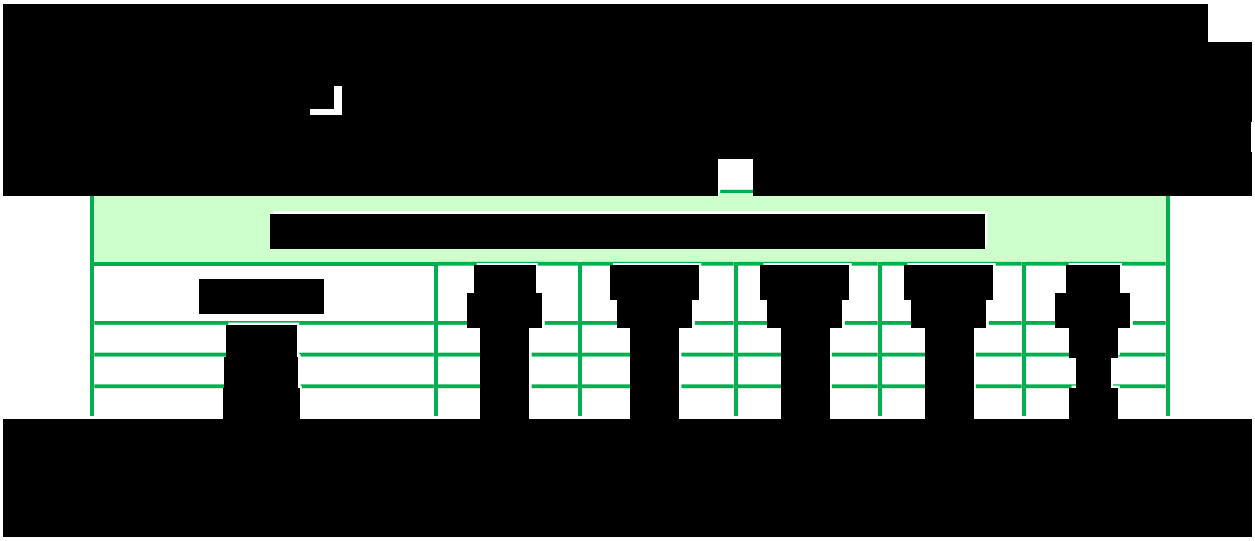

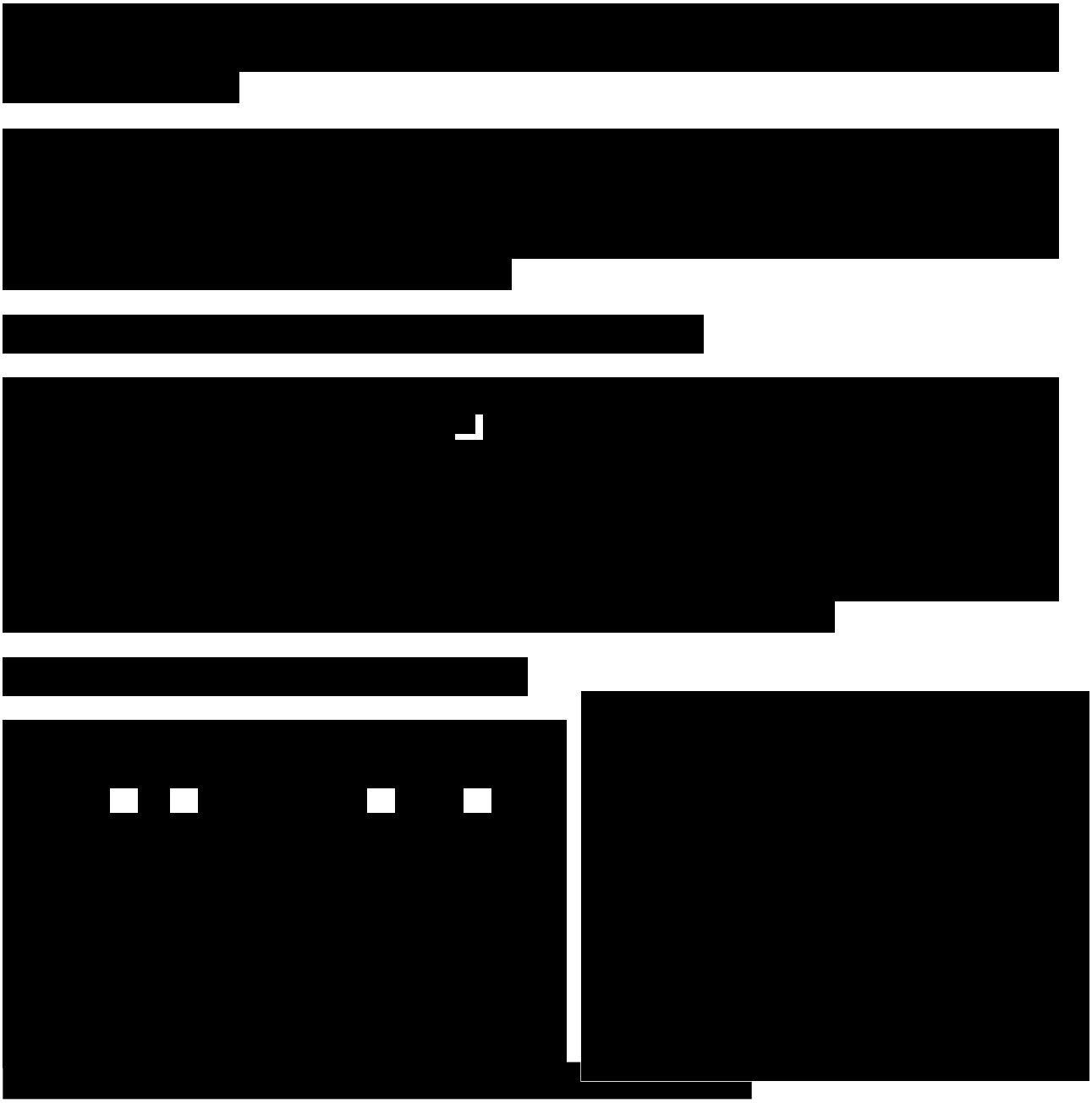

3. RESEARCH DESIGN AND METHODS

3.1 Overview and study hypothesis

The proposed study is a two-group, randomized, open-label comparison of polypill versus usual care in 300 individuals (150 per arm) without prior cardiovascular disease. The duration of treatment is 1 year, and outcomes will include medication adherence, blood pressure, and LDL cholesterol. ***We hypothesize that use of a polypill is feasible in a low SES, primary prevention setting, and will be associated with better cardiovascular risk factor control compared with usual care***.

3.2 Study sample

We will leverage an existing epidemiologic resource, the NCI-funded Southern Community Cohort Study (SCCS).

3.3 Study medication (polypill)

The study medication will be a fixed-dose combination pill (polypill) containing: atorvastatin 10 mg, amlodipine 2.5 mg, losartan 25 mg, and hydrochlorothiazide 12.5 mg. As this is an open-label trial, there will be no placebo provided in the "usual care" arm.
The polypill is formulated to be taken once daily, to maximize compliance. The lowest standard doses (or half-doses) of the component medications are used to minimize side effects that might lead to discontinuation of the entire combination. Fixed dosing is intended to obviate the need for titration and frequent follow-up visits. Nonetheless, physicians treating subjects in the polypill arm are free to prescribe add-on therapy at

their discretion. Individuals in the polypill arm on existing statin or anti-hypertensive monotherapy will be converted to the polypill at study initiation. Individuals taking more than 2 anti-hypertensive medications at baseline will not be included in the trial.

[redacted]

Atorvastatin. Evidence from 14 primary prevention trials randomizing nearly 50,000 individuals indicates that statins reduce coronary events by approximately 25%, and all-cause mortality by 14%.[18] Though myalgias and asymptomatic liver function test abnormalities may occur, they are often dose-dependent (i.e. more common at doses higher than the dose chosen for the polypill) and cease with drug discontinuation. In fact, rates of myalgia and liver function test abnormalities do not differ between statin and placebo groups enrolled in randomized trials. The same is true for rates of adverse events or drug discontinuation. Clinically overt liver failure and rhabdoymyolysis with statins are exceedingly rare, particularly in the absence of interacting drugs, which will be excluded by protocol.[19] Recent trials suggest a small excess risk of incident diabetes among patients randomized to statins, though this risk appears to be substantially outweighed by the reduction in cardiovascular risk.[20,21]

[redacted]

Anti-hypertensive therapy. The proposed anti-hypertensive combination (amlodipine, HCTZ, and losartan at half doses) is identical to that used in the trial by Wald and colleagues.[22] In that randomized, cross-over study, the pill was effective and well tolerated, with no side effects requiring discontinuation.

[redacted]

[redacted]

[redacted]

[redacted]

3.4 Participant recruitment

We will send an introductory letter and pre-screening questionnaire to participants at the Franklin Primary site who are age-eligible and not known to meet any of the exclusion criteria listed above. The letter will describe the nature of the study, its goals, and the risks and benefits of participating, and invite the participant to call the study team if questions arise and to complete the questionnaire and mail it back in the provided prepaid mailer. The questionnaire will seek updated information on medication use, health status, and other characteristics to assess potential eligibility into the trial. Participants not returning the questionnaire after a three-week lapse will be sent a second packet. Phone calls will then be made to non-responders to seek their involvement and, if desired by the person being called, to complete the questionnaire over the phone and schedule a clinic visit. Calls will also be made to those who returned the questionnaires and remain potentially eligible to arrange a study screening visit at the clinic. We estimate that we will attempt contact with up to 1,050 Franklin-SCCS participants over a 15-month period to enroll 300 participants into the feasibility study trial (see **3.2**). [redacted]

Eligible participants, who are not enrolled in the SCCS, may also be identified and approached about participation by the site investigator (or a trained member of his staff) at one of their regularly scheduled visits to Franklin Primary Health Center.

[redacted]

4. Participant selection and withdrawal criteria

4.1 Overview

We will recruit individuals at risk for cardiovascular disease, but without prevalent disease, who have no contraindications to any of the components of the polypill. The inclusion and exclusion criteria are similar to those of previous primary prevention studies involving the polypill that have been performed outside the U.S.[12-15]

4.2 Inclusion criteria

Participants eligible for enrollment in the study must meet all of the following criteria:

- Enrolled at the SCCS site in Mobile, Alabama, obtain care at Franklin Primary Health Center, or live in the surrounding area.
- Aged 45 to 75 years
- Baseline systolic blood pressure ≥120 mm Hg. In this open-label trial, the study physicians are permitted to prescribe any additional medication deemed appropriate to achieve blood pressure control.

4.3 Exclusion criteria

Participants meeting any of the following criteria will not be enrolled in the study:

- History of coronary heart disease or stroke
- History of cancer, except for basal cell skin cancer
- History of advanced liver disease, not including chronic, clinically-stable hepatitis
- Laboratory evidence of hepatic dysfunction (an alanine aminotransferase level more than three times the upper limit of the normal range)
- Known renal disease, estimated creatinine clearance < 60,
- Current use of more than 2 anti-hypertensive medications
- LDL cholesterol ≥190 mg/dl
- Insulin-dependent diabetes
- Known intolerance to any of the components of the polypill
- Potassium <3.4 or >5.5 mEq/L
- Use of medications that interact with statins, including those affecting the cytochrome P450 system
- Current use of diuretics for indications other than hypertension
- Comorbidities that might be expected to limit lifespan during the 12-month follow-up period
- Inability to provide informed consent.

4.4 Study withdrawal and early termination

Participants have the right to withdraw their consent for further participation in the study (i.e., precluding continued data collection). A participant may also be asked to stop study

participation at the investigator's discretion. In participants withdrawing their consent to provide any additional information, no further study visits or study-related telephone contacts can be conducted.

4.5 Preliminary eligibility data from Franklin SCCS participants

We applied the inclusion and exclusion criteria to the Franklin SCCS sample based on data collected at entry and during routine follow up of the cohort. Even restricting the Franklin population to SCCS participants who participated in the routine follow-up contacts (and thus have demonstrated recent continuing active interest in participating in SCCS follow up activities), we estimate that nearly 1,000 individuals would be eligible for entry into the trial, with greater numbers available should participants who did not complete a follow-up survey be considered. One of the study's aims will be to estimate and measure recruitment rates, [redacted]

5. Study treatments

5.1 Polypill

The polypill will be produced and dispensed by the Vanderbilt Investigational Drug Service (IDS). [redacted] Participants will be instructed to take one pill per day for the duration of the study.

All polypill medication, including unopened or partially-used containers, must be maintained at the study site for eventual return to the Vanderbilt IDS.

5.2 Treatment assignment

Participants who meet eligibility criteria after the initial Franklin visit will be invited to participate in the study, and randomized to polypill versus usual care. Block randomization will be performed according to baseline hypertension status. The randomization key will be maintained at the International Epidemiology Institute (IEI). Physicians at the Franklin Primary site will prescribe the polypill to those in the active arm.

5.3 Blinding

This is an open-label study and thus will not be blinded. Please see Section 8.1.

5.4 Product accountability

In accordance with local regulatory requirements, the investigator or designated site staff must document the quantity of polypill dispensed and/or administered to study participants, the amount returned by study participants, and the amount received from and returned to the Vanderbilt IDS when applicable. Product accountability records must be maintained throughout the course of the study.

5.5 Concomitant medications

Medications and non-drug therapies not specifically prohibited by the study are allowed. All concomitant medications taken during the study will be recorded by study staff.

Prohibited medications include all medications that interact with statins, including those affecting the cytochrome P450 system, and diuretics used for indications other than hypertension.

6. Study assessments and procedures

Procedures	Screening/Baseline Visit 1	2 month follow-up Visit 2	12 month follow-up Visit 3
Introductory letter (sent prior to visit)	X		
Pre-screening questionnaire (sent prior to visit)	X		
Written informed consent	X		
Medical history	X		
Inclusion exclusion criteria	X		
Vital Signs (blood pressure/heart rate)	X	X	X
Weight	X	X	X
Height	X	X	X
Social History	X		
Follow-up questionnaire (sent prior to visit)		X	X
Self-reported adherence		X	X
Moriskey questionnaire		X	X
Medication packaging return		X	X
Adverse events		X	X
Fasting blood draw (20 mL)	X	X	X
Urine Pregnancy Test	Xa		

a. **Urine pregnancy test will be performed for pre-menopausal women.**

6.1 Baseline visit

Individuals will be asked to fast for at least 8 hours prior to the clinic visit. At the visit, responses to the baseline questionnaire will be reviewed by a study coordinator as a final check on inclusion and exclusion criteria and current medication use. Blood pressure will be measured twice in the left-arm of the seated subject, and results will be averaged. Following the informed consent process, a 5mL blood sample will be obtained for eligibility screening laboratories: comprehensive metabolic panel, lipid panel. Any pre-menopausal women will also undergo a rapid urine pregnancy test. [redacted] Subjects will be randomized at this visit to either the polypill or usual care arm. When the baseline lab results are received, they will be reviewed for any values meeting exclusion criteria. [redacted] if any exclusion criteria are found to be met at this time the subject will be contacted and removed from the study.

6.2 Follow-up visits

At 2 and 12 months post-randomization, participants will be sent follow-up questionnaires and scheduled for a follow-up visit at the health center. At these follow-up visits, the study coordinators will review questionnaires for completeness, measure blood pressure, and collect a fasting blood sample for repeat laboratories. Procedures for blood collection, analysis, shipment, and storage will be identical to those of the baseline visit. Information on tolerability and side effects will be collected. Additional clinic visits as desired by the participants' physicians will be allowed at their discretion.

Pill vials will be collected for pill counts. Self-reported adherence will also be ascertained for all medications, recorded as the number of days the medication was taken in the week prior to the study visit. [redacted]

6.3 Remuneration

Subjects will receive $50 per study visit. In addition, subjects in the polypill arm will receive $10 every three months when they return to the Franklin Primary Health Center to pick up their next three month supply of medication and return the previous months used pill vials.

7. Outcome measures and statistical analysis

7.1 Primary and secondary outcome measures

Primary outcomes
The co-primary outcomes will be medication adherence (based on pill count and self-report), systolic blood pressure, and LDL cholesterol, at 12 months.

Secondary outcomes
Medication adherence, systolic blood pressure, and LDL cholesterol at 2 months. The primary endpoint variables will also be measured at the interim, 2-month visit.

Drug metabolite profile. Medication adherence will be further assessed using a novel drug screening panel [redacted]

Insulin resistance. At baseline and 12 months, we will measure HOMA-IR using fasting glucose and insulin as previously described.[34]

Inflammatory profile. The measures of inflammation will include plasma levels of IL-17, IFN-g, IL-6, IL-10 and high-sensitivity C-reactive protein. [redacted]

Recruitment response rates. Recruitment response rates will be tracked [redacted]

7.2 Statistical analyses and power

In our primary analyses, we will evaluate systolic blood pressure (SBP) and low-density lipoprotein cholesterol (LDL) using multivariable regression models with treatment group as the primary covariate, and age, gender, racial/ethnic group as additional covariates.

The baseline measurement of each outcome will be included in the respective model. Note that even though systolic blood pressure is used in stratified randomization, we will include it in the SBP model following the recommendations by Senn and Raab.[35,36] To allow for the treatment effect estimates to differ between subgroups, in exploratory additional analyses interaction terms will be considered between treatment and each of age, gender, and racial/ethnic group. Secondary outcomes will be analyzed in the same fashion. A two-sided p-value of 0.05 will be considered statistically significant. Because this is a pilot study, we will not divide the p-value for these 2 co-primary outcomes.

	Sample size in each arm	Correlation between baseline and 12-month measures			
		r=0.5	r=0.6	r=0.7	r=0.8
Detectable Difference for SBP, mmHg	N = 150	6.8	6.1	5.3	4.3
	N = 135	7.2	6.4	5.6	4.5
	N = 120	7.6	6.8	5.9	4.8
Detectable Difference for LDL, mg/dl	N = 150	12.7	11.3	9.8	8.0
	N = 135	13.3	11.9	10.3	8.4
	N = 120	14.2	12.7	11.0	9.0

Detectable treatment effects for SBP and LDL depend on the true correlation between the baseline and 12 month data. The **Table** above summarizes the detectable difference with sample size of 150 in each group at 80% power for plausible correlations between two time points. We expect a high correlation between the time points, suggesting that the scenarios shown for r=0.7 or r=0.8 are most likely. Estimates of baseline variability (SD) are based on existing SCCS data, and closely approximate those obtained in other cohorts with large minority representation, such as the Jackson Heart Study.[16,17]

We also incorporated the possibility of 10% and 20% dropout (n=135 and n=120 in each arm, respectively). Type I error rate was controlled at 5%. As shown, we have excellent power to detect clinically meaningful differences. Indeed, the detectable differences for SBP and LDL are far lower than those found using a similar polypill in the Wald study, though that study used a placebo comparison rather than usual care, which likely overestimates the differences.[22] Further, these power analyses are based on simple univariate tests; our proposed multivariable regression models should be more powerful because they take into account covariates.

For recruitment, with 1,050 contacts to potential enrollees, we can estimate recruitment response rates to within ±3%. For adherence, our sample size is large enough to estimate a simplified adherence measure (Yes/No) with a precision of ±8%. In additional regression models, pill count will be square-root transformed if necessary to satisfy the regression assumption (normality of the residuals).

8. Study risks and discomforts

8.1 Fasting
Participants will be required to fast prior to each study visit. Risks related to overnight fasting include hypovolemia. Study participants will be instructed to drink plenty of fluids on the day prior to their visit.

8.2 Phlebotomy
Risks related to phlebotomy are rare and include syncope, hematoma formation, and phlebitis. A total of approximately 45 mL (equivalent to a few tablespoons) will be drawn from study participants, with no more than 15 mL drawn at any study visit. The risk associated with this amount of phlebotomy should be minimal.

8.3. Overview of study medication risks
The medications in the polypill have been extensively evaluated individually and in combination. Each of the medications in the polypill is approved by the United States Food and Drug Administration (FDA) and widely administered in the US for the treatment of cardiovascular disease. The doses of each medication included in the polypill are low, which should minimize the change of any potential side-effects. Prior studies using a polypill with the identical medications have confirmed high tolerability.

Patients in the usual care arm will be informed of the risks of the medications they are prescribed. The risks associated with each drug contained in the polypill are detailed in subsequent sections.

The first study visit on medication will take place at 2 months, with additional visits at the discretion of the participants' physicians. During the trial, all adverse events will be reported to the study IRB in a timeframe consistent with IRB policies. The trial will also be monitored by an independent Data Safety and Monitoring Committee and by the FDA under an approved IND (#124626).

8.3.1 Atorvastatin risks
The most common side effects of atorvastatin are myalgias and liver function test abnormalities without symptoms. The risk of these side effects is very low at the dose delivered by the polypill. Discontinuation of atorvastatin eliminates these side effects of the drug. The most serious side effects of atorvastatin are liver failure and myositis, which occur, if at all, in less than 1% of patients receiving a statin.

8.3.2 Amlodipine risks
Potential side effects of amlodipine are swelling, rapid heart rate, dizziness, fatigue, and flushing. These side effects are rare (likely to be less than 5%) and are likely to cease as soon as the medication is discontinued.

8.3.3 Losartan risks

Potential side effects of losartan are dizziness, cough, diarrhea, weakness/fatigue, hypoglycemia, anemia, and hyperkalemia. These side effects are rare (likely to be less than 5%) and are likely to cease as soon as the medication is discontinued. Furthermore, the theoretical risk of hyperkalemia is offset by the concomitant administration of hydrochlorothiazide.

8.3.4 Hydrochlorothiazide risks

Uncommon side effects of hydrochlorothiazide are weakness, jaundice, diarrhea, vomiting, imbalances and abnormalities in blood electrolyte levels (e.g., hypokalemia), rash, photophobia, and impotence. Serious side effects of hydrochlorothiazide include kidney disease or kidney failure. However, these serious side effects generally occur at high medication doses (≥25mg). For the 12.5 mg dose contained in the polypill, the chance of serious side effects is likely to be less than 1%. Furthermore, the theoretical risk of hypokalemia is offset by the concomitant administration of Losartan.

8.4 Adverse events

The investigator or site staff will be responsible for detecting, documenting and reporting events that meet the definition of an AE or SAE. All AEs and SAEs will be collected from the time of the first dose of study medication through the final study visit. All SAEs will be reported to the DSMB and to the IRB within 24 hours.

8.4.1 Definition of an Adverse Event (AE)

Any untoward medical occurrence in a participant, temporally associated with the use of the polypill or any usual care medications. Note: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of the polypill.

Events meeting the definition of an AE include:

- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after medication administration even though it may have been present prior to the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of study medication or a concomitant medication (overdose per se will not be reported as an AE/SAE).

Events that **do not** meet the definition of an AE include:

- Medical or surgical procedure (e.g., endoscopy, appendectomy); the condition that leads to the procedure is an AE.
- Situations where an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition.

8.4.2 Definition of a Serious Adverse Event (SAE)

A SAE is any untoward medical occurrence that, results in:

a. death

b. a life-threatening experience
NOTE: The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. inpatient hospitalization
NOTE: In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or out-patient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d. persistent or significant disability or incapacity, or
NOTE: The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g. sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption.

e. requires, based on reasonable medical judgment, a medical or surgical intervention to prevent an outcome described in list a – d.
NOTE: Medical judgment should be exercised in deciding whether reporting is appropriate in situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious. Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

9. Monitoring and quality assurance

9.1 Data and Safety Monitoring and Quality Assurance

Informed consents, case report forms and data will be reviewed by the principal investigators and a DSMB every 3 months to ensure the safety of study participants. The DSMB will consist of a group of three individuals; Harvey J. Murff, M.D, M.P.H, Associate professor of Medicine, Vanderbilt University, Chang Yu, Ph.D; Associate Professor, Department of Biostatistics, Vanderbilt University, and Michael Blaha, M.D., M.P.H; Assistant Professor, Division of Cardiology, Johns Hopkins Hospital. The safety data that will be reviewed includes: all reported AEs, any participants with early study termination or withdrawal of consent and any protocol deviations. Other data to be reviewed includes appropriate handling and processing of blood samples and laboratory data and maintenance of patient confidentiality.

The review and decision regarding altering or stopping the protocol will be performed by the principal investigators and an independent data and safety monitor. Reasons to stop the study include an unexpected incidence of AEs attributed to the polypill.

The principal investigator will review any AEs immediately following their occurrence and report them to the IRB in accordance with their guidelines. All SAEs will be reported by phone, fax or email within 24 hours to both the IRB and the data safety monitor, followed by a full written report within 10 business/14 calendar days.

9.2 Privacy and Confidentiality

All participant data, including case report forms, blood samples, and written study questionnaires will be coded by an identification number to maintain participant confidentiality. The master key to the identification numbers will be kept in a locked storage at each site accessible only by the principal investigator.

9.3 Records Retention

Following closure of the study the investigators must maintain and store complete study records for a period of 5 years in a safe and secure location.

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