Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Yusuf S, Joseph P, Dans A, et al. Polypill with or without aspirin in persons without cardiovascular disease. N Engl J Med 2021;384:216-28. DOI: 10.1056/NEJMoa2028220

SUPPLEMENTARY APPENDIX: THE INTERNATIONAL POLYCAP STUDY 3 (TIPS 3)

THE INTERNATIONAL POLYCAP STUDY 3 (TIPS 3)

Supplementary Appendix Table of Contents

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SECTION S2: Eligibility Criteria

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. Indication, contraindication, preference for or intolerance to statins, beta blockers, angiotensin converting enzyme inhibitors, diuretics, 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.
7. Systolic BP below 120 mm Hg.
8. Symptomatic hypotension (e.g., 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 x ULN.
10. Inflammatory muscle disease or creatine kinase (CK) > 3 x 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 for at least 5 years.

*This criterion was revised in February 2015. The original criteria was Men aged ≥ 55 years and women aged ≥ 60 years with an INTERHEART risk score of 10 or greater.

SECTION S3: Measurement Protocol

Blood Pressure:

Sitting Blood Pressure & Heart Rate: Blood pressure was measured at screening or run-in, randomization, 6 weeks, 6 months, 12 months and yearly thereafter. The following guidelines were provided to sites:

1. Use Omron automatic blood pressure monitor.
2. Ask the participant to remove tight-fitting clothing from his/her arm.
3. The participant must be sitting for ≥ five (5) minutes
4. Put the participant's arm through the cuff loop making sure the bottom edge of the cuff is approximately one-half inch (1.25) above the elbow and the arrow on the cuff is above the brachial artery. The entire cuff should be evenly tight around the participant's arm. Ask the participant to remain still until the measurement is complete
5. Press the ON/OFF button. After the heart symbol (♥) appears on the digital panel, press the START button. The cuff will start to inflate automatically and stop when completed.
6. The cuff will deflate and when the measurement is complete, the systolic/diastolic and heart rate measurements will appear on the screen.
7. Take 2 readings on the right arm at least 1-minute apart
8. Record all readings on the RI1
9. The participant must be sitting for 3 additional minutes prior to 2nd reading and again prior to the 3rd reading
10. Please record the time (24-hour clock) at which each blood pressure reading was taken

Collection and Measurement of Lipids:

Summary of local laboratory collection of lipid measurements: Fasting blood was collected prior to run-in, and at 6 months, 12 months, and 2 years during follow-up for analysis of lipids (see Table 1). These were measured locally.

Table 1: Fasting Lipids:

Collection Time Point	Local Analysis (All countries)	Central Analysis
Screening/Run-in (3-4wks)	X	X (Philippines, Colombia & India, Indonesia, Bangladesh Canada, Malaysia, Tanzania)
6 Months	X	
12 Months	X	
24 Months	X	X (Philippines, Colombia & India)

Collection of blood for central lipid analysis: In a subset of participants, fasting blood samples were collected for lipid analyses at central locations (see Table 1 and 2). At run-in, lipids were collected for central analysis in all countries except Tunisia. Lipids for central analysis have been collected during follow-up in three countries: India, Philippines, and Colombia. Due to COVID-19 restrictions there have been delays in the central analysis of lipid measures. Analysis is expected to be completed by October 2020 (and these data will be included in the final report). Data are currently reported based on local measurements.

Measurements were made at three laboratories for the central analysis; the Core Laboratory at the Population Health Research Institute in Hamilton, Canada, SRL Diagnostics Limited in Bangalore, India using a Roche Cobas 8000 and the Hi-Precision Diagnostics Laboratory in Manila Philippines. Lipid testing was performed on the Beckman Coulter UniCel DxC600 System using turbimetric methods for timed endpoint methods for Cholesterol (CHOL), High Density Lipoprotein (HDL), Low Density Lipoprotein (LDL) and Triglycerides (TG).

Measurements for Indonesia run-in measurements were made at P.T. Prodia Dia CRO Laboratories in Jakarta, Indonesia using an Architect C-8000 machine and Abbott reagent.

Table 2: Summary of central lipid collection during run-in and follow-up by country

Country	Collection Time Point	Central or Local Analysis	Lab for Analysis	LDL measurement completed
India	2 year	Central	SRL (India)	1175
Philippines	2 year	Central	HPD (Philippines)	873
Colombia	2 year	Central	PHRI (Canada)	237
Indonesia	Run-in	Central	Prodia (Indonesia)	94
Philippines	Run-in	Central	PHRI (Canada)	1544
Malaysia	Run-in	Central	PHRI (Canada)	74
Canada	Run-in	Central	PHRI (Canada)	114
India	Run-in	Central	SRL (India)	2166
Colombia	Run-in	Central	PHRI (Canada)	449
Tanzania	Run-in	Central	PHRI (Canada)	11

No samples were analyzed from Bangladesh or Tanzania

SECTION S4: Definitions of Adjudicated Outcome Events

Cardiovascular death
Defined as a death for which a definite non-cardiovascular cause (e.g. cancer) has not been identified. *Uncertain causes of deaths are presumed to be cardiovascular unless proven otherwise*. Cardiovascular deaths include any of the following:

Unwitnessed unexpected death
Death due to presumed cardiovascular cause in which the patient was well or stable and last seen alive prior to discovery of death (*example: patient found dead in his/her bed*). In this case, the interval between the time the patient was last seen and the time the death became known will be recorded.

Sudden witnessed unexpected death
Defined as death that occurred suddenly and unexpectedly in a patient who was well or had a stable cardiovascular status prior to the death. Death was witnessed, and due to:

- An identified arrhythmia (documented ECG or ECG monitor recording, or arrhythmia witnessed on a monitor by a trained health care provider).
- Cardiac arrest or cardiovascular collapse (*example: patient walking with a friend and suddenly collapses*).
- Patients resuscitated from a sudden cardiac arrest who later die of the sequelae of the event *(later may be hours, days or weeks),* or patients who die during an attempted resuscitation.

Non-sudden arrhythmic death
Death due to documented arrhythmia when death is expected, not sudden and not associated with evidence of myocardial ischemia (*e.g. patient with recurrent tachyarrhythmia or bradyarrhythmia who died 6 hours after admission to the hospital*).

Fatal myocardial infarction (MI)
Fatal MI may be adjudicated in any one of the following three circumstances:

- Death occurring within 30 days of a documented MI in which there is no conclusive evidence of another cause of death. Patients who are being treated for MI and who have a sudden death as the terminal event related to the MI will be classified as having an MI-related death.
- Autopsy evidence of a recent infarct with no other conclusive evidence of another cause of death.
- A fatal MI may be adjudicated for death that has suggestive criteria for an infarct but does not meet the strict definition of an MI. The suggestive criteria are presentation of chest pain considered to be due to myocardial infarction **and** one of the following:
    - ECG changes indicative of a myocardial injury (including new left bundle branch block)

    OR
    - Abnormal cardiac markers below the level of diagnostic myocardial necrosis: CKMB > 1.0 but < 1.5 x upper limit of normal (ULN) or troponin increase not

reaching the level for diagnosis of MI or other markers above normal range but < 2.0 x ULN (*e.g. in such an event patient died before a subsequent draw*)

OR

- Imaging evidence of new wall motion abnormality.

Heart failure death
Death primarily due to congestive heart failure (CHF). Cardiogenic shock is included. *There should be no evidence of ischemia such as the presence of myocardial infarction or arrhythmia such as ventricular fibrillation. Patient with documented CHF with systolic dysfunction who dies suddenly during an admission for worsening CHF will be considered as a CHF death.*

Death after invasive cardiovascular intervention
This includes death occurring within 30 days of cardiovascular surgery or limb amputation, or within 7 days of catheterization, arrhythmia ablation, angioplasty (with or without stent placement), atherectomy (coronary, cerebral or peripheral artery disease), or other invasive coronary or peripheral vascular intervention.

Death due to stroke
Death due to stroke and occurring within 30 days of signs/symptoms of stroke or autopsy evidence of a recent stroke with no other conclusive evidence of another cause of death. If death occurs within 24 hours of onset of stroke signs, this will be considered a death due to stroke.

Other cardiovascular causes of death
Other vascular events, including pulmonary emboli and ruptured abdominal aortic aneurysm.

Presumed cardiovascular death
Death suspicious of cardiovascular death with supporting clinical evidence that may not fulfill other criteria (*e.g. patient with chest pain typical for MI, but without ECG tracing or cardiac enzyme or marker documentation that fulfill MI criteria*).

Death from unknown cause
Qualifies as a cardiovascular event unless clear evidence of extraneous disease exists.

Non-cardiovascular death
Defined as any death for which clear evidence of a non-cardiovascular cause exists. Categories of non-cardiovascular death include:

Malignancy death
Death due to cancer or as a consequence of cancer related treatment complications.

Definite Non-procedural MI
EITHER
Cardiac Ischemic Symptoms lasting > 20 minutes, determined by the site investigator to be secondary to ischemia

OR
ECG or changes consistent with acute infarction or ischemia MI:

- New diagnostic Q waves (Q wave in leads V2 and V3 ≥ 0.02 sec or QS complex in leads V2 and V3; Q wave ≥ 0.03 sec and ≥ 0.1 mV deep or QS complex in leads I, II, aVL, aVF or V4-V6 in any two leads of a contiguous lead grouping (I and aVL; V1-V6; II, III, aVF, R wave ≥ 0.04 sec in V1 and V2 and R/S ≥ 1 with a concordant positive T wave)) in the absence of conduction abnormalities
- New significant ST-segment- T-wave changes in two or more contiguous leads: ST elevation at the J point ≥ 0.1 mV in all leads other than leads V2 and V3 where the following cut points apply: ≥ 0.2 mV in men ≥ 40 years; 0.25 mV in men < 40 years, or ≥ 0.15 mV in women. ST depression horizontal or downsloping ≥ 0.05 mV; or T wave inversion ≥ 0,1mV with prominent R wave or R/S ratio ≥ 1.
- Development of new left bundle branch block (LBBB)
- Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality
- Intracoronary thrombus by angiography

AND
Elevated cardiac biomarkers (values according to each hospital's laboratory):
A rise and/or fall in cardiac biomarker values (preferably troponin, CKMB, AST, LDH or myoglobin) with at least one value above the 99th percentile of the upper reference limit.

Probable Non-procedural MI
In cases of missing cardiac biomarkers:

- Ischemic symptoms lasting ≥20 minutes considered to be of cardiac origin and requiring hospitalization with ECG changes consistent with acute ischemia or with thrombolysis or coronary revascularization within 12 hours.

In cases of missing information on symptoms and ECG report or tracing:

- History of hospitalization for MI with cardiac enzymes showing a typical pattern of

MI as for definite MI. However, the local PI should find out if the participant had chest pain or if the event occurred in a peri-operative period.
In cases of missing information on cardiac markers, ECG findings and duration of typical symptoms:

- History of hospitalization for MI with a documented finding compatible with recent

MI on follow-up ECG or on imaging (cardiac echocardiography, nuclear scan, MRI) in a participant without previous MI or in a participant with previous MI having a new ECG or imaging finding compatible with MI in comparison to a previous ECG or imaging finding.

MYOCARDIAL INFARCTION

Procedural MI: PCI-related MI
An MI after a PCI is defined as:
EITHER
Cardiac ischemic symptoms as above
OR
ECG or imaging changes consistent with MI, as above, or angiographic findings consistent with a procedural complication,

AND
Increased troponin values greater than 5 X 99th percentile URL in patients with normal baseline values (less than 99th percentile URL), or a rise of troponin values greater than 20% if baseline values are elevated and are stable or falling.

CABG-related MI
An MI after CABG surgery is defined as:
ECG changes consistent with MI, including new pathological Q waves or new LBBB; or angiographic documented new graft or new native coronary artery occlusion, or imaging evidence of new loss of viable myocardium or new regional wall motion abnormality,
AND
Increased cardiac biomarker values (greater than 10 X 99th percentile URL) during the first 48 hours following CABG in patients with normal troponin values.

Procedural MI: MI related to other cardiac procedures
For cardiac catheterization same criteria as for 'Definite Non-procedural MI'. For transcatheter aortic valve implantation or mitral clip procedure same criteria as for as 'CABG-related MI'.

MI associated with non-cardiac procedures (within 48 to 72 hours of procedure)
Same criteria a as for 'Definite Non-procedural MI'

Unrecognized (silent) MI
MI documented on ECG that may not have been clinically recognized. If the investigator (based on review of the clinical status and ECGs) feels that this occurred, he/she should submit information supporting the diagnosis of a clinically unrecognized MI. Such documents could be an ECG showing new and significant Q-waves not attributed to intraventricular conduction defect, left ventricular hypertrophy, pre-excitation syndrome, idioventricular rhythm, or electronic pacer. In addition, confirmation may be achieved by echocardiographic or other evidence of new regional wall motion or perfusion abnormalities.

The timing of that event would be the earliest ECG showing new Q-waves. The PI has to send with the ECG copy showing the new signs of MI, a copy of the previous ECG without the new MI. The EAC may request additional ECG tracings.

Stroke
Stroke is defined as the presence of acute focal* neurological deficit thought to be of vascular origin. The duration of the neurological deficit should be > 24 hours if no imaging is done or there is no acute stroke on imaging. The duration of symptoms may be less than 24 hours if a new stroke is documented on CT or MRI. On the basis of clinical symptoms or signs, and CT or MRI imaging, strokes will be classified as:

- definite ischemic stroke
- definite hemorrhagic stroke
- subarachnoid hemorrhage
- uncertain or unknown stroke

* *Subarachnoid hemorrhage may not have focal deficit.*

Definite ischemic
Stroke with CT or MRI performed within 3 weeks that is either normal or shows infarct in the clinically expected area:

Lacunar infarct
Cerebral infarction with:

- Consciousness and higher mental functions maintained.
- One of the typical lacunar syndromes such as pure motor stroke, pure sensory stroke, mixed sensori-motor stroke or ataxic hemiparesis.
- CT/MRI performed within 3 weeks that is either normal (CT only) or shows a small (< 2 cm) subcortical infarct in the basal ganglia, internal capsule, brain stem or elsewhere.

Cardioembolic infarct
Cerebral infarction with:

- Absence of lacunar syndrome suggesting cortical involvement.
- No definite evidence of large artery disease in the neck.
- Major cardioembolic source present (e.g. atrial fibrillation, MI in the last 6 weeks, cardiomyopathy, endocarditis or prosthetic heart valve).
- CT/MRI performed within 3 weeks that is either normal (CT only) or shows a > 2 cm or cortically-based infarct.

Large artery infarct

- Absence of lacunar syndrome suggesting cortical involvement.
- No major cardioembolic source present.
- Evidence of large artery disease in the neck (e.g. a bruit or duplex scan evidence of arterial stenosis of more than 50%).
- CT/MRI performed within 3 weeks that is either normal (CT only) or shows a > 2 cm cortically- or subcortically-based infarct but not in the classical lacunar region.

Cerebral infarction that is not lacunar, cardioembolic or large artery in origin. This category also includes patients who have more than one potential cause for stroke (e.g. atrial fibrillation and large artery disease) if it is not possible to determine which mechanism is the cause of the stroke.

Definite hemorrhagic stroke (Intracerebral hemorrhage)
Definite stroke with CT/MRI evidence of cerebral hemorrhage. (Note: Does not include hemorrhage secondary to cerebral infarct, post-traumatic intracerebral hemorrhage, hemorrhage into a tumor and hemorrhage into a vascular malformation.)

Subarachnoid hemorrhage
Typical clinical syndrome of sudden onset headache, with or without focal signs*, and CT or cerebrospinal fluid evidence of bleeding primarily in the subarachnoid space.
* *Subarachnoid hemorrhage may not have focal deficit.*

Non traumatic subarachnoid hemorrhage documented by imaging is considered a hemorrhagic stroke.

Stroke, type uncertain or unknown
Definite stroke that does not meet the above criteria for cerebral infarction or hemorrhage (CT scan or MRI not done).

Significant CHF
CHF with the following symptoms: dyspnea (at rest or on exertion), orthopnea, paroxysmal nocturnal dyspnea; and signs: rales, edema, elevated jugular venous pressure includes:

Hospitalization for CHF
Defined as hospitalization for CHF or attendance in an acute care setting (Emergency Room) for administration of intravenous diuretic, escalation of diuretic doses and/or inotropes, and/or evidence of CHF from chest X-rays or elevated B-type natriuretic peptide (BNP) > 300 pg/ml or NT-pro B-type natriuretic peptide > 900 pg/ml.

Significant CHF not requiring hospitalization (participant evaluated at physician's office or in outpatient clinic):
Defined as at least one sign plus one symptom, plus either one positive diagnostic test (such as BNP > 300 pg/ml or NT-pro BNP > 900 pg/ml or chest X-ray showing pulmonary congestion, edema or pleural effusion) OR needing intravenous diuretic or inotropic agent.

Note*:* *If CHF was not the PRIMARY reason for hospitalization then the CHF is not coded as a primary outcome but coded as secondary outcome. Example of secondary CHF: CHF with MI. For cases of CHF associated with atrial fibrillation with rapid ventricular response, or with infection, the adjudicator has to decide based on the information received or requested if CHF was the preponderant event. If CHF is the preponderant event, it should be coded 05.01 or 05.02.*

Resuscitated cardiac arrest
Resuscitated cardiac arrest is defined as sudden cardiac arrest, with or without premonitory CHF or MI, following which the patient is resuscitated by defibrillation, medication and/or cardiopulmonary resuscitation. The patient should not be dependent on respiratory mechanical assistance and should have a meaningful recovery of consciousness. This definition excludes known transient losses of consciousness such as seizure or vasovagal episodes that do not reflect significant cardiac dysfunction.

Angina

New angina definite
Defined as new onset of typical angina with documented ischemia by stress testing (ECG, ECHO, or nuclear) in a patient previously not known to have angina at baseline. For ischemic ECG changes, the ST depression should be ≥ 2 mm in comparison to the tracing at rest obtained in the same position.
New angina also includes the following two types of cases:

- Angina occurring 6 months or more after the CABG/PCI
- Angina occurring any time after CABG/PCI if the subject did not have angina before the procedure

New angina probable
Defined as new onset of typical angina without documented ischemia by stress test. In such a case the local PI has to confirm that there is typical ischemic pain

- characterized by pressure, squeezing or burning touching the retrosternal area or cervical region or arm
- occurring on exertion
- relieved by rest and/or nitroglycerine.

Worsening angina
Defined as known angina increasing in frequency, duration, and/or severity, and requiring new or increased dosage of antianginal medication or coronary revascularization.

Unstable angina definite
Defined as ischemic symptoms: (pain, dyspnea, pressure) at rest or accelerated ischemic symptoms that the investigator determines is secondary to ischemia and requires hospitalization
AND
Ischemic ECG changes as compared to the most recent ECG or during the previous stable phase:

- > 0.5 mm transient ST segment depression in two contiguous limb or precordial leads
- > 1 mm transient ST elevation of two contiguous leads (or ST depression in V1 or V2)
- > 2 mm transient T wave change in two or more contiguous leads

OR
Cardiac Markers (CKMB and/or other enzymes or myoglobin) suggestive of myocardial injury, > ULN but not sufficient to meet MI criteria. Examples: CKMB > 1.0 < 1.5 ULN or other cardiac enzymes > 1.0 < 2.0 ULN.

Unstable angina probable
In cases of missing cardiac markers and ECG findings report:

- Ischemic symptoms considered to be of cardiac origin and having required hospitalization and treated as acute coronary syndrome

Revascularization Procedures

1. Percutaneous coronary intervention (PCI): Balloon only or other procedure with or without stent insertion.
2. Coronary artery bypass (CABG) surgery
3. Carotid endarterectomy or carotid bypass
4. Other arterial angioplasty with or without stent.
5. Other arterial surgery: This includes aortic (thoracic or abdominal) aneurysm repair (AAR) including stent for aortic aneurysm, aortobifemoral bypass (ABF), femoropopliteal bypass (FPB) femoral-tibial bypass (FTB), and cerebral aneurysm (CA).

Diabetes mellitus

New diagnosis of diabetes

Clinical diagnosis of diabetes with either elevated fasting or plasma glucose to ≥ 7 mmol/L (≥ 126 mg/dL) or locally measured 2 hour glucose ≥ 11.1 mmol/L (≥ 200 mg/dL) following a 75 gm oral glucose tolerance test (OGTT) or elevated HbA1c ≥ 6.5 % (if measured according to the NGSP certified and standardized to the DCCT assay) or HbA1c ≥ 110 % ULN of the local laboratory if any other methods are used, or the initiation of insulin or oral hypoglycemic agents.

Cancer

Cancer will be adjudicated according to the primary site, whether it is new or recurrent. In addition to the site of the cancer, the events will be adjudicated as definite, probable or possible cancer depending on the supporting documentation received. The event adjudicator will use the cancer report and supporting documentation provided by the site to complete their adjudication.

New Primary cancer

Cancer that is diagnosed for the first time and is a new cancer six months after randomization will be considered new cancer. The original site of the cancer is called the primary site and is usually named for the part of the body in which it begins e.g. lung cancer, prostate cancer.

Recurrent cancer

Recurrent cancer is a previously diagnosed cancer that was thought to be completely eradicated (whether with surgery, radiation, chemotherapy or other treatment) but has reoccurred either as a:

Local recurrence: recurrence at the same site or

Regional recurrence: recurrence to lymph nodes near the primary tumor or

Metastasis: Recurrence to other organs or lymph nodes other than those near the primary tumor.

Levels of evidence of cancer

Definite cancer: A cancer event will be considered definite if histological evidence of malignancy is available.

Probable cancer: A cancer event will be considered probable if imaging reports, evidence of treatment of cancer (surgery, radiotherapy, chemotherapy) lab tests or tumor marker tests are available.

Possible cancer: A cancer event will be considered possible if only the physician's note mentioning cancer or the death certificate (if no previous information on the cancer has been obtained before the fatal event) is available.

SECTION S5: Barriers to recruitment and adherence during the conduct of TIPS-3

This appendix summarizes unexpected barriers that impeded recruitment and adherence that occurred during the conduct of TIPS-3, and how they were addressed. A description of some of these barriers has been published in the design paper.[1] This document provides further information and additionally describes barriers to continuing the study, especially those that affected adherence:

1 Barriers to recruitment: Recruitment for the TIPS-3 study started 2012, with the initial plan of recruiting 5000 participants over a period of 2 years, and further follow-up of 4 years, which would have resulted in the mean duration of follow-up being 5 years. The trial was initially planned in two countries: India and China. However, several barriers occurred during the recruitment phase which required revisions of our initial recruitment plans. First, regulatory approval was not granted in China despite extensive efforts that spanned over a year and half. In addition the regulators in Argentina and Brazil did not approve the conduct of the study in the countries. In Canada after extensive discussions with the regulators over 9 months, permission was granted to conduct the study using the lower dose of the Polycap. Second, several new regulatory requirements came into force that affected the conduct of clinical trials in India between 2013-2014 (while recruitment was ongoing). These significantly restricted the ability to conduct trials, and resulted in the closure of many sites in India. These new requirements included compensation for any injury, adverse events or death (even if unrelated to the drugs being tested), excessive inspections at the sites which interfered with the ability of the sites to devote time for their usual activities, and audiovisual (AV) recording of consent (which increased the efforts and costs at sites and also decreased acceptance by participants to consent). These new requirements in India resulted in a 72% decline in the rate of recruitment of participants per month within the country. This partially recovered when some of the above restrictions were removed between 2015 and 2016. Tsunamis and floods also disrupted recruitment twice for extended periods of time in the Philippines.

Response to recruitment barriers: The unforeseen regulatory barriers that were faced during recruitment required frequent and numerous changes in our strategies during the course of the trial. First, it was necessary to expand the study to additional countries to compensate for the lack of participation from China (which was expected to enroll half the projected sample size), and recruitment barriers in India. Ultimately, the study was implemented in 9 countries after obtaining additional regulatory approvals. Regulatory approval (from the Food and Drug Administration) to conduct the study was also obtained in the United States of America (although the trial was not implemented there) as a means of persuading some countries to approve implementation of the study in their countries. The trial was also expanded to additional centers in India (86 in total instead of the originally planned number of 50 sites).

Most regulatory concerns were related to the use of multiple blood pressure and lipid lowering agents in a primary prevention population, although the components of Polycap are used extensively in clinical practice (with minimal side effects), and the safety of the Polycap had already been evaluated in two large Phase II trials. While clinical trials should be conducted in a manner to ensure participant safety, our experience highlights how excessive restrictions can adversely impact the ability to conduct trials. Ultimately, with the inclusion of additional countries

and sites, we were able to enroll 5713 participants (minimum target of 5000 and optimal target of 7000) although recruitment required 5 years (instead of 2 years) to complete. This substantially increased the overall operational complexity and costs of the trial and delayed its completion by about 3 years.

2 Barriers to adherence and follow-up: During the trial, complexities in the processes of drug distribution resulted in drug supply delays to many sites. First, the extended period of recruitment and follow-up required additional manufacturing of study drugs. Second, regulations in India required Cadila Pharmaceuticals to obtain approval from the Drugs Controller General of India prior to ***each*** shipment of study drugs outside the country. Third, drug shipments would often require extended periods of time (several months) to clear customs within a given country. These factors substantially increased the complexity of the drug supply chain, resulting in delays in sites receiving drug shipments. This also meant that a substantial proportion of participants could not be resupplied with drugs on time and lead to discontinuation of study medications (as patients were reluctant to restart the 'experimental' medications). These delays also shortened the time that the drugs could be used prior to the expiry date. In Bangladesh, the delays were nearly a year and required us to arrange for additional chemical tests to ensure drug stability as it was unclear whether the drugs had been stored in appropriate conditions in the customs ware-house. Finally, the trial was scheduled to be completed in June 2020, but significant local restrictions which prevented travel (lockdowns) due to the COVID-19 pandemic restricted site operations in virtually all countries beginning in March 2020. This impeded the ability of participants to physically return to sites, obtain study medications, and complete end of study visits.

Response to barriers: Several methods were employed to manage restrictions in drug supply. The co-ordinating center and Cadila Pharmaceuticals worked to extend timelines within the supply chain to account for unforeseen delays and prevent future supply issues. The coordinating center also worked with national leaders and sites to reallocate existing drug supplies within countries based on individual site needs. Efforts were made at national project offices to minimize custom delays. Sites arranged additional visits to restart study medications if interruptions occurred for participants. In Tanzania, persistent delays in drug supply with prolonged gaps in patients receiving drugs were largely responsible for the decision to ultimately close enrollment prematurely. Various efforts helped to improve the availability of study drugs. Attempts were made to restart study medications when they had been stopped for non-medical reasons. These efforts were only partly successful and fewer than half of the participants who had discontinued their medications restarted them. Despite all these efforts, drug shortages contributed to a higher non-adherence rates than anticipated.

The **COVID-19 pandemic** presented unique challenges to study conduct during the final phase of follow-up. In response, intensive efforts were made by the coordinating center, national project offices, and sites to develop strategies to complete the study. Several processes were considered. Sites were given the option of dividing data collection at the final visits, with some part of the follow-up being conducted by phone (to collect information on clinical outcomes) and other data (e.g. physical measures such as BP or questionnaires on cognitive function) to be collected at a future in person visit (which could include participants being seen in their homes by study staff

when possible -- these efforts are still ongoing). Extension of drug expiry was explored in several countries. Added funds for additional visits were provided to sites to cover the extra costs related to travel and personal protective equipment for participants who agree to in-person assessments. Collection of some types of data (e.g. cognitive function, vision tests, physical measures) require in person visits and so we are currently exploring remote assessments for certain measures at sites where travel is severely restricted. These processes have resulted in successful completion of clinical outcome events in the majority of participants, with vital status available in 99.2% of participants. At present, efforts to collect other data in person are ongoing. Restrictions to drug distribution did result in further worsening of study drug adherence in the final phase of the trial. To account for the impact of drug discontinuation for non–medical reasons, sensitivity analyses excluding events that occurred 30 days after stopping study medications were specified in the Statistical Analysis Plan.

3 Support from Wellcome Trust: The above barriers substantially increased the duration, complexity and costs of the trial. As a result, the investigators applied for and were granted additional funding from the Wellcome Trust, which allowed the trial to continue follow-up until its expected completion in June 2020. This was crucial to accruing the planned number of clinical outcome events initially projected (250 projected and 280 events documented) in order to maintain study power. In addition, due to the unforeseen costs related to operations in the context of the COVID-19 pandemic, additional funding has been provided by the Wellcome Trust for extended coordination and close-out procedures.

Section S6: Statistical Analyses

Proportional hazards assumptions:

For each comparison, the plausibility of the proportional hazards assumption for the primary and secondary outcomes were assessed by including a time-treatment interaction term in the Cox model (time log transformed). The interaction p –values were not statistically significant. The proportion hazards assumption was satisfied.

Interactions between treatment groups:

For the primary outcome analysis of the effect of the polypill versus placebo, there were no significant interactions with the aspirin/placebo group (p-value for interaction = 0.9788) or with vitamin D/placebo group (p-value for interaction = p = 0.9539). For the primary outcome analysis of the effect of aspirin versus placebo, there were no significant interaction with the polypill/placebo group (p-value for interaction = p = 0.8710), or with vitamin D/placebo group (p-value for interaction = 0.8886).

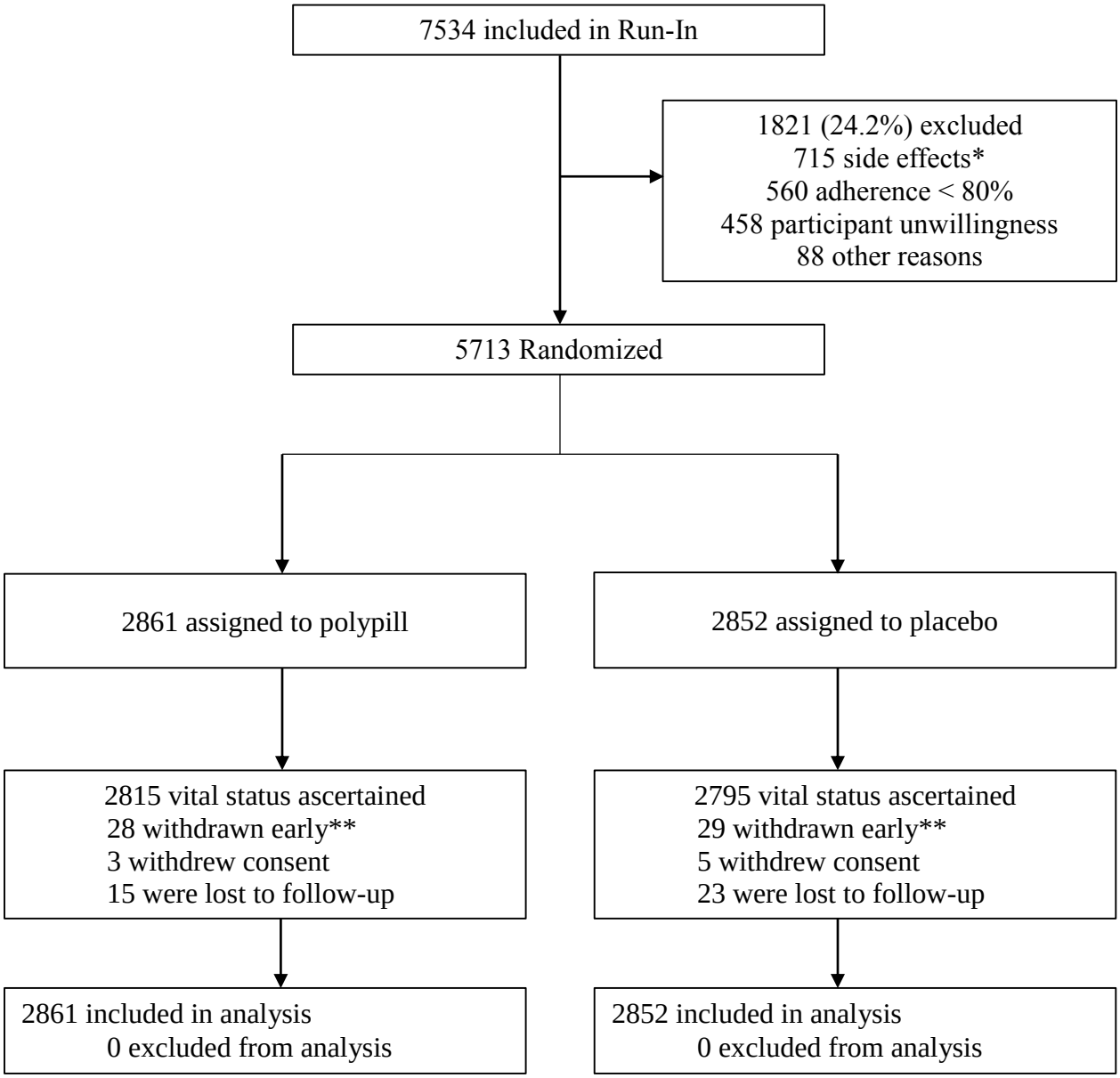
Section S7: Non-adherence data and open-label drug use data

Polypill vs Placebo: Among participants assigned to receive the polypill, 81.1% were taking trial medications at 24 months compared to 81.3% in the placebo group; at 48 months adherence was 67.7% and 69.4%. Open label statins were taken by 1.8% and 4.5% of participants in the polypill group at 24 and 48 months compared to 2.2% and 6.3% respectively in the placebo group. The corresponding proportion of individuals taking 2 or more open label BP medications were 1.7% at 24 months and 2.8% at 48 months in the polypill group and 3.1% and 5.2% in the placebo group. A high proportion of participants (14.5% polypill and 13.8% placebo) discontinued their medications because study drugs had run out, due to delays in resupply for different reasons (e.g. delays in shipment, regulatory barriers, and restrictions related to the COVID pandemic at the end of the study) (Supplementary Appendix 5, Table S10, S11). *As a result, the overall discontinuation of study medications was 42.2%, which was higher than the anticipated 20% in the protocol*. *The average contrast between the active and control groups in statin use was 81.6%, and in the use of 2 or more BP lowering agents was 80.9%* (Table S2). At study end, of the 3302 receiving blinded study medications, 2839 (86.0%) were on the full dose of the polypill, 279 (8.4%) were on the low dose and 184 (5.6%) were on the polypill without an ACE-inhibitor.

Aspirin vs Placebo: Among participants assigned to receive aspirin, 82.0% were taking their trial medications at 24 months and 73.0% at 48 months compared to 82.1% and 71.0% in the placebo group. Open label aspirin was taken by 0.9% and 1.6% in the active group and 0.7% and 2.2% in the placebo group at 24 months and 48 months respectively. *This represents a weighted mean contrast of 83.8% in aspirin use between the two randomized groups* (Table S3). A high proportion of participants (15.2% aspirin group and 14.8% in the placebo group) permanently discontinued their study medication due to delays in drug supply. *As a result, the overall discontinuation of study medications was 39.7% at the end of study, which was higher than the 20% anticipated in the protocol* (Table S9).

Polypill + Aspirin vs Double Placebo: The pattern of non-adherence in the polypill plus aspirin active group compared to the double placebo group mirrored that for the polypill or aspirin versus their respective placebo groups described above. (Tables S4, S5, S26). *The mean contrasts in the use of multiple BP-lowering agents, statins, and aspirin were 80.6%, 81.3%, and 83.5% respectively*.

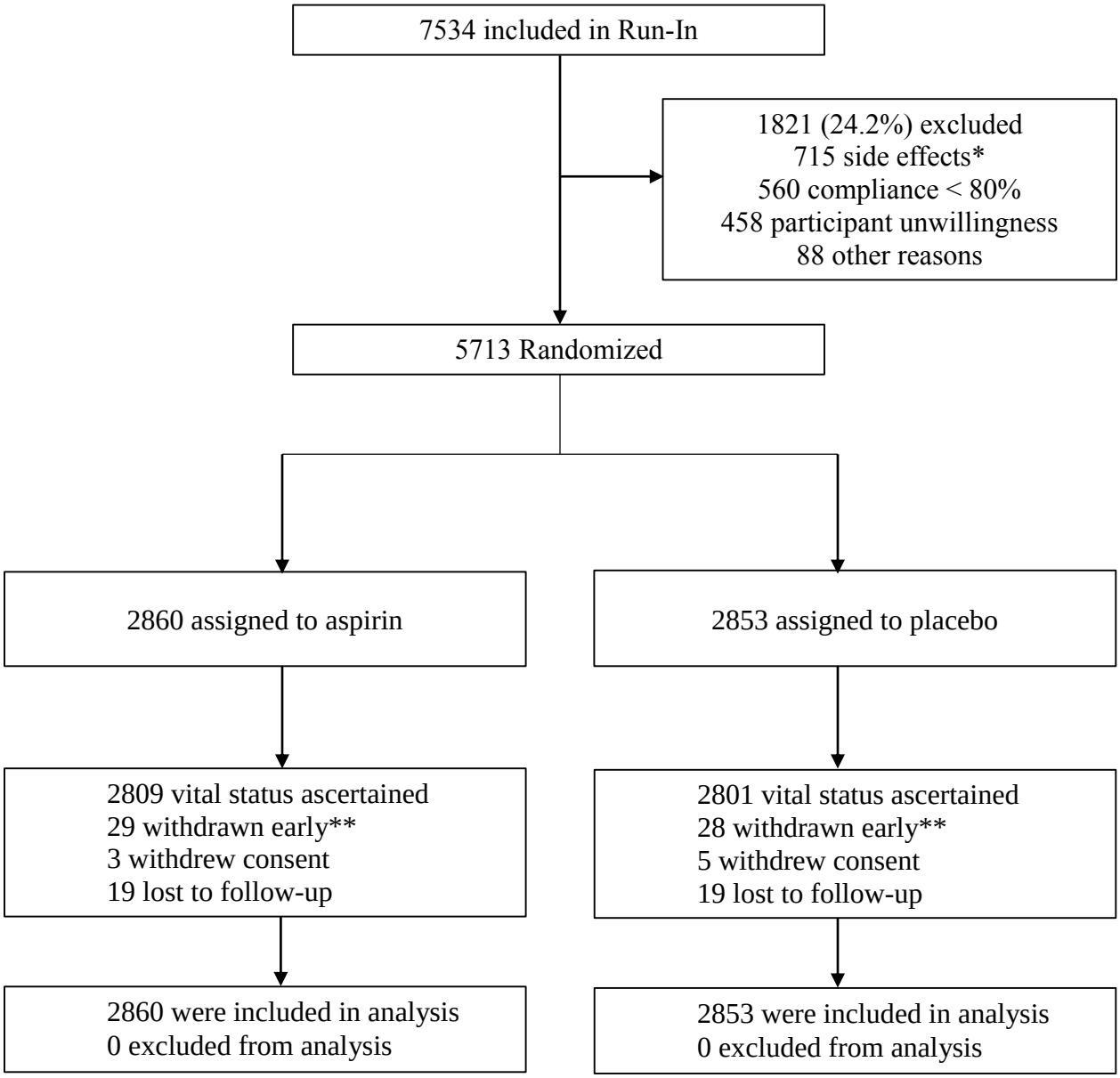
Figure S1: CONSORT Diagram for the Polypill versus Placebo Comparison



* The most common side effects resulting in run-in failure were syncope or dizziness with systolic blood pressure <110 mmHg, N=355 (4.7%). Participants could report more than one side effect.

**18 participants withdrew early from 2 centers in India due to new regulations that limited the numbers of trials an individual center could participate in, and 39 from Tanzania because of difficulties in importing study drugs. Participants at these sites had a final follow-up visit completed at the time of site closure and where censored thereafter. Follow-up events that occurred prior to termination of these centers are included in the analyses. Vital status was ascertained at the end of follow-up in 5667 (99.2%) participants, and clinical outcome data ascertained in 5649 (98.9%).

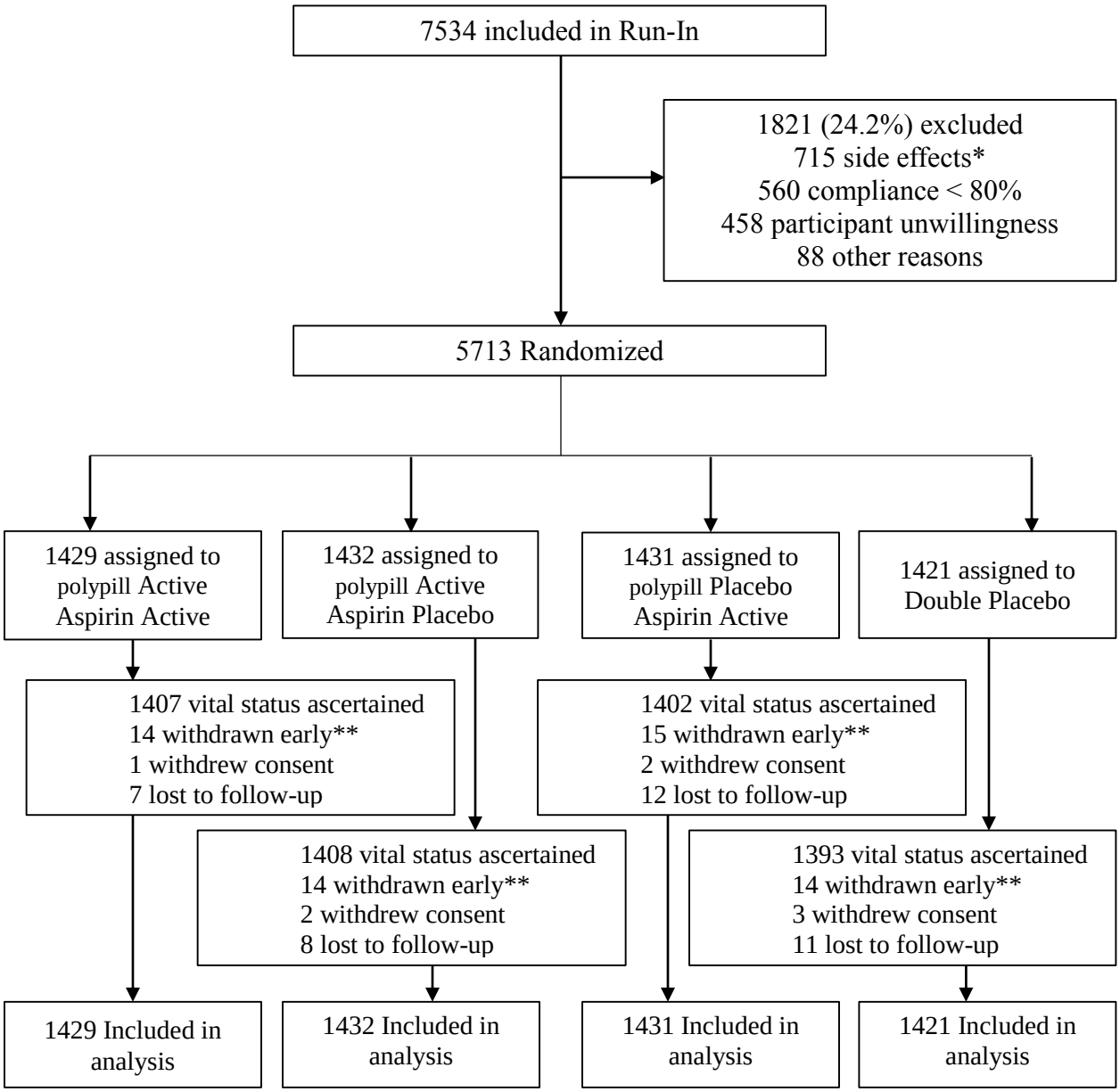
Figure S2: CONSORT Diagram for the Aspirin versus Placebo Comparison



* The most common side effects resulting in run-in failure were syncope or dizziness with systolic blood pressure <110 mmHg, N=355 (4.7%). Participants could report more than one side effect.

**18 participants withdrew early from 2 centers in India due to new regulations that limited the numbers of trials an individual center could participate in, and 39 from Tanzania because of difficulties in importing study drugs. Participants at these sites had a final follow-up visit completed at the time of site closure and where censored thereafter. Follow-up events that occurred prior to termination of these centers are included in the analyses. Vital status was ascertained at the end of follow-up in 5667 (99.2%) participants, and clinical outcome data ascertained in 5649 (98.9%).

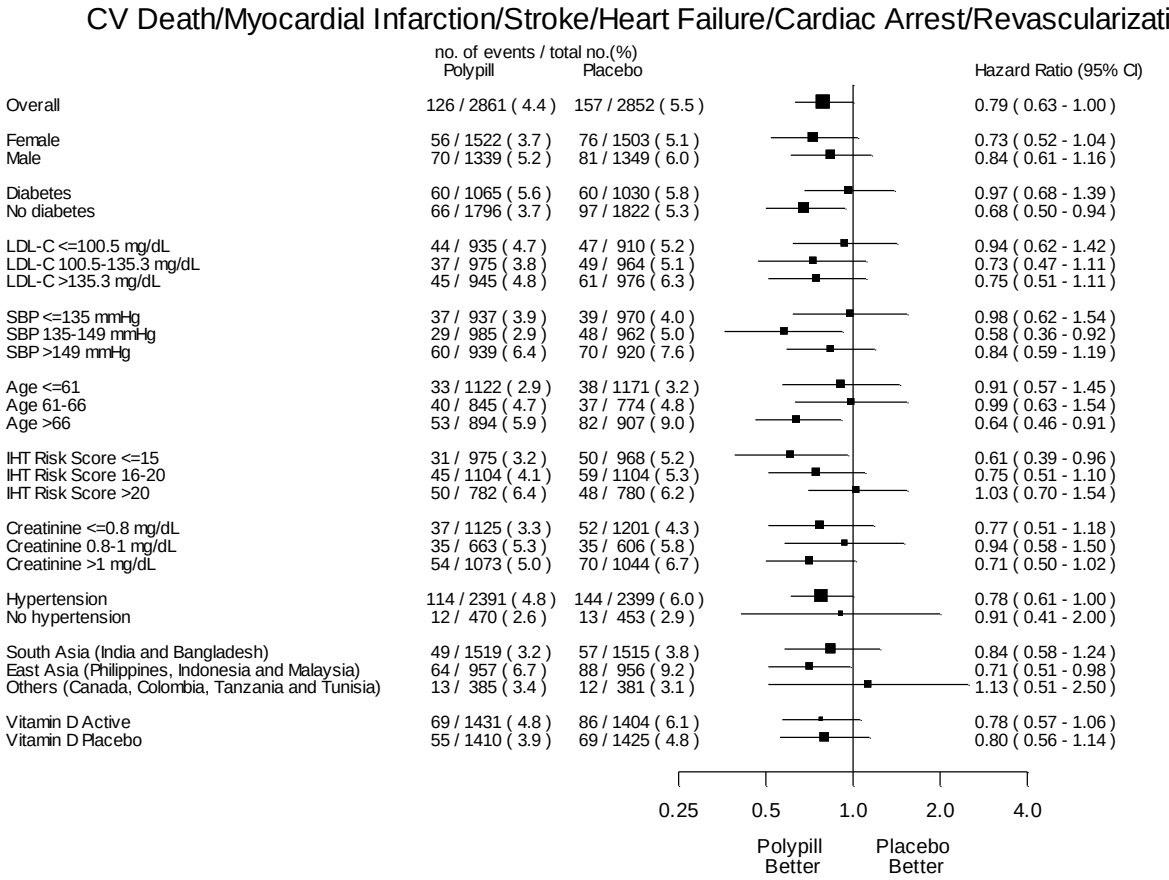
Figure S3: CONSORT Diagram for the Polypill + Aspirin versus Double Placebo Comparison



* The most common side effects resulting in run-in failure were syncope or dizziness with systolic blood pressure <110 mmHg, N=355 (4.7%). Participants could report more than one side effect.

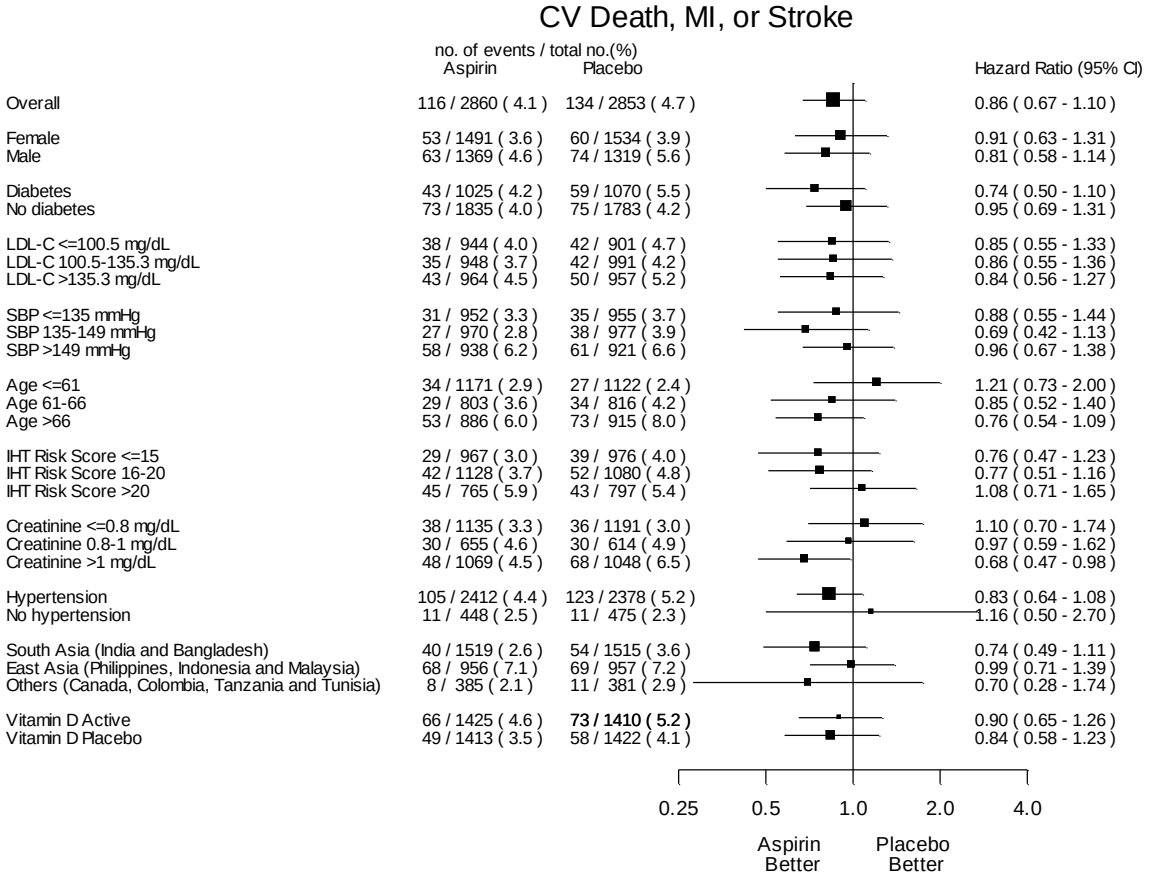
**18 participants withdrew early from 2 centers in India due to new regulations that limited the numbers of trials an individual center could participate in, and 39 from Tanzania because of difficulties in importing study drugs. Participants at these sites had a final follow-up visit completed at the time of site closure and where censored thereafter. Follow-up events that occurred prior to termination of these centers are included in the analyses. Vital status was ascertained at the end of follow-up in 5667 (99.2%) participants, and clinical outcome data ascertained in 5649 (98.9%).

Figure S4: Effect of the Polypill versus Placebo in Prespecified Subgroups for the Primary Outcome



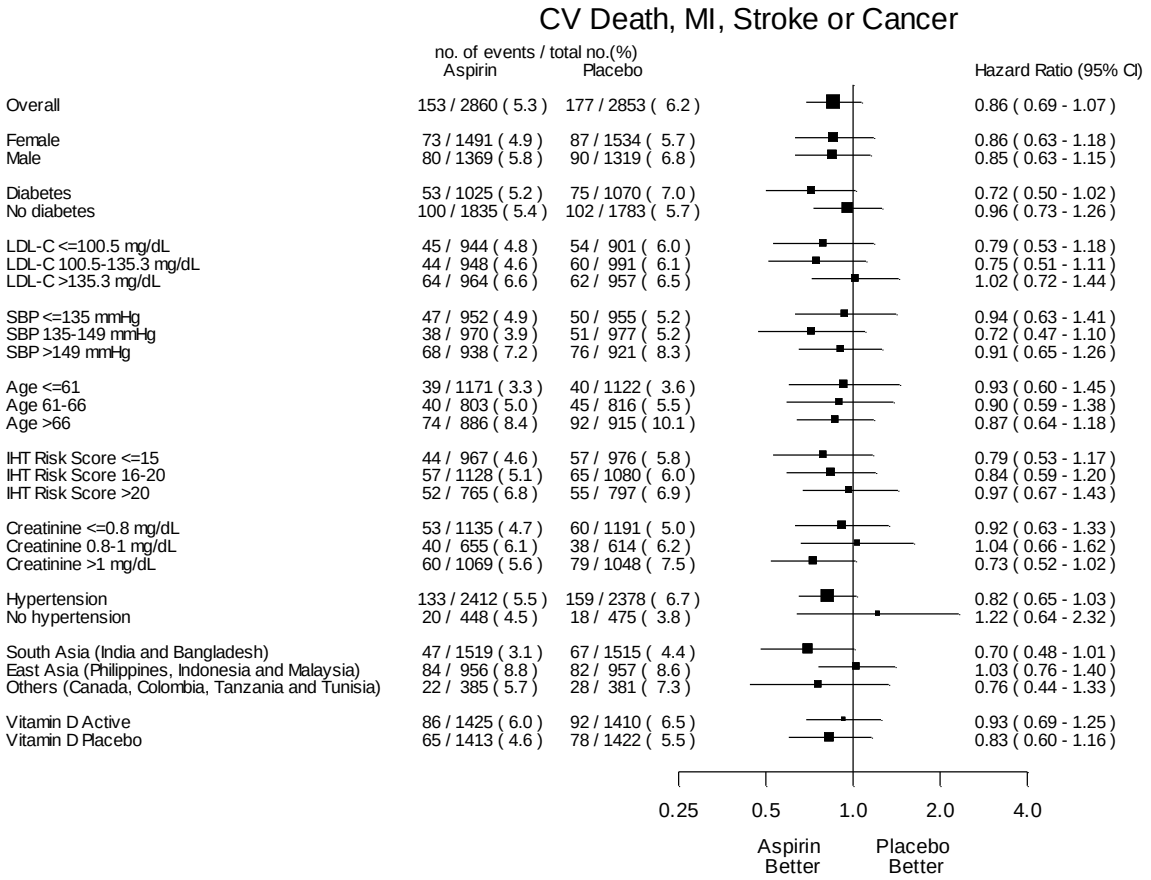
LDL = Low-Density Lipoprotein, SBP = Systolic Blood Pressure, IHT = INTERHEART

Figure S5: Effect of Aspirin versus Placebo in Prespecified Subgroups for the Primary Outcome



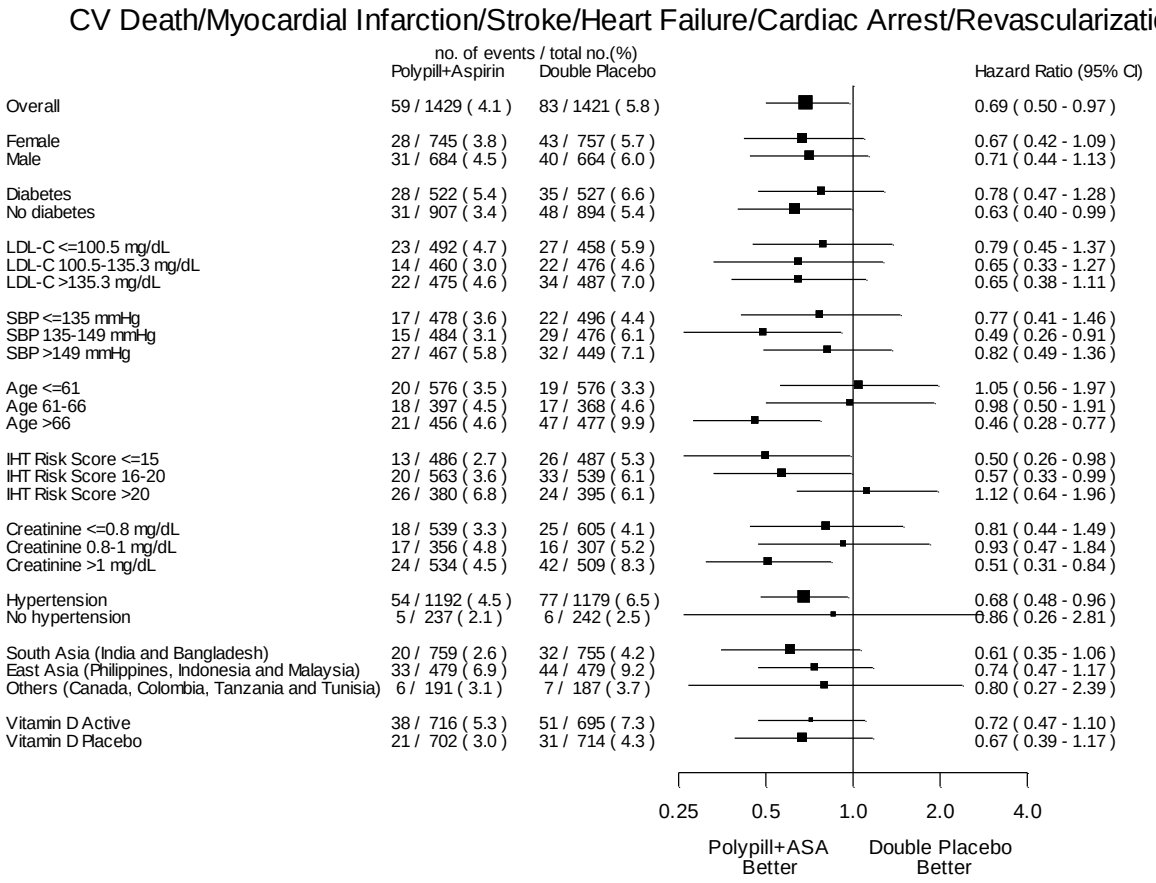
LDL = Low-Density Lipoprotein, SBP = Systolic Blood Pressure, IHT = INTERHEART

Figure S6: Effects of Aspirin versus Placebo in Prespecified Subgroups for the Primary Outcome plus Cancer



LDL = Low-Density Lipoprotein, SBP = Systolic Blood Pressure, IHT = INTERHEART

Figure S7: Consistency of the Effects of the Polypill + Aspirin versus Double Placebo in Prespecified Subgroups for the Primary Outcome



LDL = Low-Density Lipoprotein, SBP = Systolic Blood Pressure, IHT = INTERHEART

Table S1: Reasons for Participant Withdrawal During the Run-In Period

	Overall	
	n	Percent (%)
Reasons for withdrawing during Run-In		
Study Medication Side Effects*	715	9.5
Local blood tests elevated above acceptable levels	111	1.5
Peptic ulcer disease, dyspepsia or gastrointestinal bleeding	94	1.2
Syncope or dizziness and have a systolic blood pressure <110 mmHg	355	4.7
Cough	24	0.3
Muscle pain, muscle weakness or myalgia	10	0.1
Other events that prevent randomization	123	1.6
Compliance < 80%	560	7.4
Participant unwillingness	458	6.1
Other	88	1.2

**Multiple reasons can apply to one participant*

Table S2: Open Label Medication: Contrast Polypill Active vs Placebo

	Polypill Active						
	Visit	Discontinuation of Polypill n (%)	Taking Polypill n (%)	Use of 2 or more open label blood pressure lowering Meds n (%)	A: Taking polypill or 2 or more open label blood pressure lowering Meds n (%)	Open label Statins n (%)	B:Taking polypill or Statins n (%)
Randomization	2861	0 (0.0)	2861 (100)	15 (0.5)	2861 (100)	1 (0.0)	2861 (100)
12 Month	2787	357 (12.8)	2430 (87.2)	33 (1.2)	2449 (87.9)	28 (1.0)	2455 (88.1)
24 Month	2715	514 (18.9)	2200 (81.1)	47 (1.7)	2237 (82.4)	48 (1.8)	2239 (82.5)
36 Month	2260	530 (23.5)	1730 (76.5)	46 (2.1)	1772 (78.4)	67 (3.0)	1794 (79.4)
48 Month	1451	468 (32.3)	983 (67.7)	41 (2.8)	1019 (70.2)	65 (4.5)	1047 (72.2)
60 Month	886	284 (32.1)	602 (67.9)	32 (3.6)	631 (71.2)	37 (4.2)	638 (72.0)
72 Month	568	194 (34.2)	374 (65.2)	20 (3.5)	392 (69.0)	20 (3.5)	394 (69.4)
Weighted mean Contrast							

The contrast between active and placebo groups for blood pressure lowering treatment was calculated by subtracting the percentage of participants in the placebo group that were taking at least 2 open label blood pressure medications from the percentage of participants in the active group that received equivalent treatment (i.e. either the polypill or at least 2 open label blood pressure lowering medications). The weighted average contrast represents the average contrast across visits accounting for the varying number of participant with data at each visit. The same process was used to calculate the contrast in statin use, and the contrast in aspirin use, between treatment and placebo groups.

Polypill Placebo				Contrast	
Visit	Discontinuation of Polypill Placebo n (%)	C: Use of 2 or more Open label blood pressure lowering Meds n (%)	D: Open label statin n (%)	Blood pressure meds (%) Column A - C	Statin (%) Column B - D
2852	0 (0.0)	17 (0.6)	0 (0.0)	99.4	100
2759	340 (12.3)	55 (2.0)	37 (1.3)	85.9	86.8
2690	502 (18.7)	82 (3.1)	60 (2.2)	79.3	80.3
2220	468 (21.1)	77 (3.5)	83 (3.7)	74.9	75.7
1435	439 (30.6)	74 (5.2)	90 (6.3)	65	65.9
856	271 (31.7)	43 (5.0)	46 (5.4)	66.2	66.6
558	206 (36.9)	33 (5.9)	39 (7.0)	63.1	62.5
				80.9	81.6

Table S3: Open Label Medications: Contrast Aspirin Active vs Placebo

	Aspirin Active					Aspirin Placebo			Contrast
	Visit	Discontinuation of Aspirin n (%)	Taking Aspirin n (%)	Open label Aspirin n (%)	A: Taking Aspirin or open label Aspirin n (%)	Visit	Discontinuation of Aspirin n (%)	B: Open label Aspirin n (%)	Aspirin (%) Column A-B
Randomization	2860	0 (0.0)	2860 (100)	2 (0.1)	2860 (100)	2853	0 (0.0)	2 (0.1)	99.9
12 Month	2772	325 (11.7)	2447 (88.3)	10 (0.4)	2457 (88.6)	2774	343 (12.4)	14 (0.5)	88.1
24 Month	2703	486 (18.0)	2217 (82.0)	23 (0.9)	2238 (82.8)	2702	484 (17.9)	20 (0.7)	82.1
36 Month	2253	456 (20.2)	1797 (79.8)	22 (1.0)	1818 (80.7)	2227	468 (21.0)	37 (1.7)	79
48 Month	1446	391 (27.0)	1055 (73.0)	23 (1.6)	1077 (74.5)	1440	418 (29.0)	32 (2.2)	72.3
60 Month	866	248 (28.6)	618 (71.4)	14 (1.6)	632 (73.0)	876	268 (30.6)	15 (1.7)	71.3
72 Month	557	191 (34.3)	366 (65.7)	10 (1.8)	376 (67.5)	569	198 (34.8)	12 (2.1)	65.4
Weighted Mean Contrast									83.8

Table S4: Open Label Medication: Contrast for Polypill + Aspirin vs Double Placebo

	Polypill + Aspirin						
	Visit	Discontinuation of Polypill n (%)	Taking polypill n (%)	Use of 2 or more Open label blood pressure lowering Meds n (%)	A: Taking polypill or 2 or more blood pressure lowering meds n (%)	Open label Statins n (%)	B:Taking polypill or Open label Statins n (%)
Randomization	1429	0 (0.0)	1429 (100)	8 (0.6)	1429 (100)	0 (0.0)	1429 (100)
12 Month	1388	182 (13.1)	1206 (86.9)	12 (0.9)	1215 (87.5)	16 (1.2)	1220 (87.9)
24 Month	1352	251 (18.6)	1101 (81.4)	25 (1.9)	1121 (82.9)	30 (2.2)	1125 (83.2)
36 Month	1133	262 (23.1)	871 (76.9)	22 (1.9)	889 (78.5)	32 (2.8)	903 (79.7)
48 Month	725	231 (31.8)	494 (68.1)	21 (2.9)	512 (70.5)	29 (4.0)	523 (72.0)
60 Month	442	140 (31.7)	302 (68.3)	17 (3.9)	317 (71.7)	19 (4.3)	321 (72.6)
72 Month	281	95 (33.8)	186 (66.2)	10 (3.6)	194 (69.0)	8 (2.9)	194 (69.0)
Weighted Mean Contrast							

Double Placebo				Contrast	
Visit	Discontinuation of Polypill n (%)	C: Use of 2 or more Open label blood pressurelowering Meds n (%)	D: Statin use n (%)	BP meds n (%) Column A - C	Statin n (%) Column B - D
1421	0 (0.0)	8 (0.6)	0 (0.0)	99.4	100
1375	170 (12.4)	30 (2.2)	19 (1.4)	85.3	86.5
1339	247 (18.5)	41 (3.1)	35 (2.6)	79.8	80.6
1101	235 (21.4)	36 (3.3)	48 (4.4)	75.2	75.3
715	223 (31.2)	44 (6.2)	49 (6.9)	64.3	65.1
430	149 (34.5)	29 (6.8)	28 (6.5)	64.9	66.1
282	105 (37.2)	22 (7.8)	25 (8.9)	61.2	60.1
				80.6	81.3

Table S5: Open Label Medication: Contrast Polypill + Aspirin versus double placebo

	Polypill + Aspirin					Double Placebo			Contrast
	Visit	Discontina-tion of Aspirin n (%)	Taking Study Aspirin n (%)	Open label Aspirin n (%)	A: Study Aspirin or open label Aspirin n (%)	Visit	Discontinua-tion of Aspirin n (%)	B: Open label Aspirin use n (%)	Aspirin n (%) Column A-B
Randomization	1429	0 (0.0)	1429 (100)	1 (0.1)	1429 (100)	1421	0 (0.0)	2 (0.1)	99.9
12 Month	1388	168 (12.1)	1220 (87.9)	5 (0.4)	1225 (88.3)	1375	169 (12.3)	8 (0.6)	87.7
24 Month	1352	236 (17.5)	1116 (82.5)	8 (0.6)	1124 (83.1)	1339	235 (17.6)	9 (0.7)	82.4
36 Month	1133	233 (20.6)	900 (79.4)	7 (0.6)	907 (80.1)	1100	212 (19.3)	22 (2.0)	78.1
48 Month	726	200 (27.5)	526 (72.5)	6 (0.8)	532 (73.3)	715	210 (29.4)	23 (3.2)	70.1
60 Month	442	126 (28.5)	316 (71.5)	5 (1.1)	321 (72.6)	432	134 (31.0)	8 (1.9)	70.7
72 Month	281	89 (31.7)	192 (68.3)	4 (1.4)	196 (69.8)	282	99 (35.1)	8 (2.8)	67.0
Weighted Mean Contrast									83.5

*Column A – B

Table S6: Causes of Temporary or Permanent Discontinuation for Polypill versus Placebo

	Polypill		Placebo	
	n	Percent	n	Percent
Randomized	2861	100%	2852	100%
Any stop Polypill/Placebo	1715	59.9%	1690	59.3%
Physician/participant decision due to side effects	234	8.2%	160	5.6%
Dizziness	28	1.0%	17	0.6%
Hypotension	51	1.8%	14	0.5%
Dizziness or Hypotension	77	2.7%	31	1.1%
Muscle pain	9	0.3%	11	0.4%
Muscle weakness	5	0.2%	4	0.1%
Muscle pain or Muscle weakness	14	0.5%	15	0.5%
Cough	31	1.1%	17	0.6%
Wheezing	1	0.0%	2	0.1%
High Potassium	1	0.0%	0	0.0%
Renal Failure	2	0.1%	0	0.0%
Other	122	4.3%	109	3.8%
Physician/participant decision, no side effects	1569	54.8%	1586	55.6%
On open-label medication	60	2.1%	88	3.1%

	Polypill		Placebo	
	n	Percent	n	Percent
Participant moved	130	4.5%	148	5.2%
Participant refused	670	23.4%	658	23.1%
Forgot/lost Drug	6	0.2%	7	0.2%
Ran out of Drug	550	19.2%	528	18.5%
Drug expired in June/July 2020	89	3.1%	85	3.0%
No resupply due to COVID-19 restrictions (not for COVID-19 infections)	282	9.9%	300	10.5%
Last 3 above reasons	837	29.3%	835	29.3%
Other	132	4.6%	133	4.7%
Reason missing	1	0.0%	1	0.0%

Table S7: Causes of Permanent Discontinuation for Polypill versus Placebo

	Polypill		Placebo	
	n	Percent	n	Percent
Randomized	2861	100%	2852	100%
Permanent stop Polypill/Placebo	1221	42.7%	1190	41.7%
Physician/ participant decision due to side effects	155	5.4%	112	3.9%
Dizziness or Hypotension	45	1.6%	25	0.9%
Muscle pain or Muscle weakness	13	0.5%	10	0.4%
Cough	13	0.5%	5	0.2%
Wheezing	1	0.0%	2	0.1%
High Potassium	0	0.0%	0	0.0%
Renal Failure	2	0.1%	0	0.0%
Other	87	3.0%	73	2.6%
Physician/participant decision, no side effects	1065	37.2%	1078	37.8%
On open label medication	48	1.7%	77	2.7%
Participant moved	93	3.3%	95	3.3%
Refused/Refused-pt family member's decision	430	15.0%	424	14.9%
Forgot/lost Drug	2	0.1%	5	0.2%

	Polypill		Placebo	
	n	Percent	n	Percent
Ran out of Drug	170	5.9%	145	5.1%
Drug expired in June/July 2020	45	1.6%	44	1.5%
No resupply due to COVID-19 restrictions (not for COVID-19 infections)	199	7.0%	204	7.2%
Last 3 above reasons	414	14.5%	393	13.8%
Other	82	2.9%	87	3.1%
Reason missing	1	0.0%	0	0.0%

Table S8: Causes of Temporary or Permanent Discontinuation for Aspirin versus Placebo

	Aspirin		Placebo	
	n	Percent	n	Percent
Randomized	2860	100%	2853	100%
Any stop Aspirin/Placebo	1681	58.8%	1692	59.3%
Physician/ participant decision due to side effects	115	4.0%	140	4.9%
Gastritis	35	1.2%	46	1.6%
Dyspepsia	5	0.2%	4	0.1%
Peptic Ulcer	5	0.2%	5	0.2%
Gastrointestinal Bleeding	5	0.2%	1	0.0%
Hematemesis	0	0.0%	0	0.0%
Hematuria	1	0.0%	2	0.1%
Hematochezia	0	0.0%	1	0.0%
Other	77	2.7%	99	3.5%
Physician/ participant decision, no side effects	1643	57.4%	1628	57.1%
Participant on open-label medication	44	1.5%	50	1.8%
Participant moved	138	4.8%	151	5.3%
Refused	674	23.6%	674	23.6%

	Aspirin		Placebo	
	n	Percent	n	Percent
Forgot/lost Drug	7	0.2%	9	0.3%
Ran out of Drug	650	22.7%	648	22.7%
Drug expired in June/July 2020	112	3.9%	111	3.9%
No resupply due to COVID-19 restrictions (not for COVID-19 infections)	338	11.8%	314	11.0%
Last 3 above reasons	986	34.5%	953	33.4%
Other	99	3.5%	81	2.8%
Reason missing	1	0.0%	1	0.0%

Table S9: Causes of Permanent Discontinuation for Aspirin versus Placebo

	Aspirin		Placebo	
	n	Percent	n	Percent
Randomized	2860	100%	2853	100%
Permanent stop Aspirin/Placebo	1117	39.1%	1153	40.4%
Physician/pts decision due to side effects	79	2.8%	104	3.6%
Gastritis	26	0.9%	33	1.2%
Dyspepsia	3	0.1%	2	0.1%
Peptic Ulcer	5	0.2%	4	0.1%
Gastrointestinal Bleeding	3	0.1%	0	0.0%
Hematemesis	0	0.0%	0	0.0%
Hematuria	0	0.0%	2	0.1%
Hematochezia	0	0.0%	1	0.0%
Other	51	1.8%	72	2.5%
Physician/ participant decision, no side effects	1037	36.3%	1049	36.8%
Participant on open-label medication	31	1.1%	39	1.4%
Participant moved	96	3.4%	101	3.5%
Refused	420	14.7%	438	15.4%
Forgot/lost Drug	2	0.1%	4	0.1%

	Aspirin		Placebo	
	n	Percent	n	Percent
Ran out of Drug	169	5.9%	157	5.5%
Drug expired in June/July 2020	43	1.5%	48	1.7%
No resupply due to COVID-19 restrictions (not for COVID-19 infections)	223	7.8%	218	7.6%
Last 3 reasons from above	435	15.2%	423	14.8%
Other	60	2.1%	48	1.7%
Reason missing	1	0.0%	0	0.0%

Table S10: Reasons for Temporarily or Permanently Stopping Polypill or Placebo in the 4 randomized groups

	Polypill + Aspirin		Polypill Alone		Aspirin Alone		Double Placebo	
	n	Percent	n	Percent	n	Percent	n	Percent
Randomized	1429	100%	1432	100%	1431	100%	1421	100%
Any stop Polypill/Placebo	848	59.3%	867	60.5%	842	58.8%	848	59.7%
Physician/participant decision due to side effects	113	7.9%	121	8.4%	69	4.8%	91	6.4%
Dizziness	17	1.2%	11	0.8%	5	0.3%	12	0.8%
Hypotension	29	2.0%	22	1.5%	4	0.3%	10	0.7%
Dizziness or Hypotension	45	3.1%	32	2.2%	9	0.6%	22	1.5%
Muscle pain	3	0.2%	6	0.4%	7	0.5%	4	0.3%
Muscle weakness	2	0.1%	3	0.2%	1	0.1%	3	0.2%
Muscle pain or Muscle weakness	5	0.3%	9	0.6%	8	0.6%	7	0.5%
Cough	16	1.1%	15	1.0%	5	0.3%	12	0.8%
Wheezing	0	0.0%	1	0.1%	0	0.0%	2	0.1%
High Potassium	1	0.1%	0	0.0%	0	0.0%	0	0.0%
Renal Failure	0	0.0%	2	0.1%	0	0.0%	0	0.0%
Other	52	3.6%	70	4.9%	51	3.6%	58	4.1%
Physician/ participant decision, no side effects	779	54.5%	790	55.2%	796	55.6%	790	55.6%
On open-label medication	29	2.0%	31	2.2%	50	3.5%	38	2.7%

	Polypill + Aspirin		Polypill Alone		Aspirin Alone		Double Placebo	
	n	Percent	n	Percent	n	Percent	n	Percent
Participant moved	56	3.9%	74	5.2%	72	5.0%	76	5.3%
Refused	332	23.2%	338	23.6%	329	23.0%	329	23.2%
Forgot/lost Drug	2	0.1%	4	0.3%	3	0.2%	4	0.3%
Ran out of Drug	276	19.3%	274	19.1%	263	18.4%	265	18.6%
Drug expired in June/July 2020	43	3.0%	46	3.2%	43	3.0%	42	3.0%
No resupply due to COVID-19 restrictions (not for COVID-19 infections)	150	10.5%	132	9.2%	151	10.6%	149	10.5%
Last 3 reasons from above	429	30.0%	408	28.5%	417	29.1%	418	29.4%
Other	66	4.6%	66	4.6%	66	4.6%	67	4.7%
Reason missing	1	0.1%	0	0.0%	1	0.1%	0	0.0%

Table S11: Reasons for Permanently Stopping Polypill or Placebo in the 4 randomized groups

	Polypill + Aspirin		Polypill Alone		Aspirin Alone		Double Placebo	
	n	Percent	n	Percent	n	Percent	n	Percent
Randomized	1429	100%	1432	100%	1431	100%	1421	100%
Permanent stop Polypill/Placebo	600	42.0%	621	43.4%	590	41.2%	600	42.2%
Physician/ participant decision due to side effects	73	5.1%	82	5.7%	48	3.4%	64	4.5%
Dizziness or Hypotension	28	2.0%	17	1.2%	8	0.6%	17	1.2%
Muscle pain or Muscle weakness	5	0.3%	8	0.6%	5	0.3%	5	0.4%
Cough	6	0.4%	7	0.5%	0	0.0%	5	0.4%
Wheezing	0	0.0%	1	0.1%	0	0.0%	2	0.1%
High Potassium	0	0.0%	0	0.0%	0	0.0%	0	0.0%
Renal Failure	0	0.0%	2	0.1%	0	0.0%	0	0.0%
Other	37	2.6%	50	3.5%	36	2.5%	37	2.6%
Physician/ participant decision, no side effects	526	36.8%	539	37.6%	542	37.9%	536	37.7%
On open-label medication	19	1.3%	29	2.0%	42	2.9%	35	2.5%
Participant moved	43	3.0%	50	3.5%	50	3.5%	45	3.2%
Refused/Refused-pt family member's decision	213	14.9%	217	15.2%	210	14.7%	214	15.1%
Forgot/lost Drug	0	0.0%	2	0.1%	2	0.1%	3	0.2%
Ran out of Drug	93	6.5%	77	5.4%	72	5.0%	73	5.1%

	Polypill + Aspirin		Polypill Alone		Aspirin Alone		Double Placebo	
	n	Percent	n	Percent	n	Percent	n	Percent
Drug expired in June/July 2020	21	1.5%	24	1.7%	21	1.5%	23	1.6%
No resupply due to COVID-19 restrictions (not for COVID-19 infections)	100	7.0%	99	6.9%	105	7.3%	99	7.0%
Last 3 reasons from above	214	15.0%	200	14.0%	198	13.8%	195	13.7%
Other	40	2.8%	42	2.9%	43	3.0%	44	3.1%
Reason missing	1	0.1%	0	0.0%	0	0.0%	0	0.0%

Table S12: Change in Low Density Lipoprotein levels in participants with central laboratory lipid measurements both at baseline and in follow-up

		Polypill		Placebo		Difference	
Lipid		N	Mean (SD)	N	Mean (SD)	Mean (mg/dL)	95% CI
Low-Density Lipoprotein	Baseline	972	108.28 (44.90)	985	109.94 (43.29)	1.66	-2.25 - 5.57
	Follow-up *	978	90.83 (37.80)	994	106.98 (38.28)	16.15	12.79 - 19.52
	Follow-up*-Baseline	949	-17.97 (44.55)	966	-2.83 (41.99)	15.14	11.26- 19.02

*Bloods for follow-up lipid measures for central analysis was obtained at a mean of 50 months after randomization.

Table S13: Polypill vs Placebo: Outcome Events during treatment or within 30 days of discontinuation of medications for non-medical reasons and events which occurred after censoring

	Participants with Events *prior* to censoring			**Participants with Events occurring *after* censoring**		**All Events**		
	Polypill	Placebo	**HR (95% CI)**	Polypill	Placebo	Polypill	Placebo	**HR (95% CI)**
Cardiovascular Death/Myocardial Infarction/Stroke/ Heart Failure/Cardiac Arrest/Arterial Revascularization	95	126	**0.74 (0.57-0.97)**	31	31	126	157	**0.79 (0.63-1.00)**
Cardiovascular Death death/Myocardial Infarction/Stroke	82	107	**0.76 (0.57-1.01)**	29	32	111	139	**0.79 (0.61-1.01)**
Primary + Angina	103	135	**0.75 (0.58-0.97)**	29	29	132	164	**0.79 (0.63-1.00)**

Table S14: Safety Related Outcomes: Serious Adverse Events with Polypill versus placebo

System organ class	Polypill n(%)	Placebo n(%)
Randomized	2861	2852
Total Patient with SAE	23 (0.8)	33 (1.2)
Blood and lymphatic system disorders	0 (0.0)	1 (0.0)
Cardiac disorders	3 (0.1)	5 (0.2)
Ear and labyrinth disorders	1 (0.0)	0 (0.0)
Eye disorders	2 (0.1)	0 (0.0)
Gastrointestinal disorders	6 (0.2)	4 (0.1)
General disorders and administration site conditions	3 (0.1)	6 (0.2)
Hepatobiliary disorders	0 (0.0)	3 (0.1)
Infections and infestations	2 (0.1)	3 (0.1)
Injury, poisoning and procedural complications	1 (0.0)	3 (0.1)
Investigations	1 (0.0)	0 (0.0)
Metabolism and nutrition disorders	3 (0.1)	2 (0.1)
Musculoskeletal and connective tissue disorders	0 (0.0)	2 (0.1)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2 (0.1)	4 (0.1)
Nervous system disorders	3 (0.1)	5 (0.2)
Renal and urinary disorders	2 (0.1)	1 (0.0)

System organ class	Polypill n(%)	Placebo n(%)
Reproductive system and breast disorders	1 (0.0)	0 (0.0)
Respiratory, thoracic and mediastinal disorders	3 (0.1)	0 (0.0)
Surgical and medical procedures	2 (0.1)	2 (0.1)
Vascular disorders	1 (0.0)	1 (0.0)

Table S15: Safety Related Outcomes: Hospitalizations with Polypill versus Placebo

	Polypill		Placebo	
	N	%	N	%
Randomized	2861	100.0	2852	100.0
Patients Hospitalized	220	7.7	232	8.1
Patients with Any Cardiovascular Hospitalization	83	2.9	104	3.6
Myocardial Infarction	15	0.5	28	1.0
Stroke/Transient Ischemic Attack	28	1.0	35	1.2
Heart Failure	8	0.3	10	0.4
Angina	9	0.3	18	0.6
Atrial fibrillation/flutter	4	0.1	4	0.1
Cardiac arrest	10	0.3	5	0.2
Sustained ventricular tachycardia	2	0.1	0	0.0
Supraventricular arrhythmia	2	0.1	0	0.0
Pulmonary embolism	1	0.0	1	0.0
Other Cardiovascular	16	0.6	31	1.1

	Polypill		Placebo	
	N	%	N	%
Percutaneous Coronary Intervention/ Percutaneous transluminal coronary angioplasty	10	0.3	18	0.6
Coronary Artery Bypass Graft Surgery	0	0.0	7	0.2
Carotid endarterectomy/ Carotid bypass	0	0.0	0	0.0
Other arterial angioplasty	0	0.0	1	0.0
Other arterial surgery	1	0.0	1	0.0
Patients with Any Non-Cardiovascular Hospitalization	166	5.8	156	5.5
Renal failure	10	0.3	5	0.2
Cancer	23	0.8	15	0.5
Fall	11	0.4	12	0.4
Fracture	11	0.4	13	0.5
Other injury	7	0.2	5	0.2
Anemia	7	0.2	8	0.3

	Polypill		Placebo	
	N	%	N	%
Dementia	0	0.0	1	0.0
Pneumonia and other lung infections	30	1.0	25	0.9
Hematologic	1	0.0	2	0.1
Genito-urinary	23	0.8	11	0.4
Gastrointestinal	30	1.0	28	1.0
Other non-cardiovascular	87	3.0	84	2.9

Table S16: Distribution of Cancers by Site: Aspirin versus Placebo

Site	Aspirin (N=2,860) n (%)	Placebo (N=2,853) n (%)
Individuals with Any Cancer*	38 (1.3)	46 (1.6)
Cancer by Sites:		
Gastrointestinal/Pancreas/Liver/Colorectal	8 (0.3)	12 (0.4)
Breast	8 (0.3)	12 (0.4)
Lung	5 (0.2)	5 (0.2)
Prostate	6 (0.2)	4 (0.1)
Skin	5 (0.2)	3 (0.1)
Female Reproductive	2 (0.1)	3 (0.1)
Kidney	1 (0.0)	1 (0.0)
Hematologic	2 (0.1)	1 (0.0)
Brain cancer	0 (0.0)	1 (0.0)
Musculoskeletal	0 (0.0)	1 (0.0)
Other genito-uirnary	1 (0.0)	2 (0.1)
Thyroid	0 (0.0)	1 (0.0)
Mouth	0 (0.0)	1 (0.0)
Other	0 (0.0)	1 (0.0)
Site unknown	0 (0.0)	0 (0.0)

*Individuals may report more than one type of cancer during the study

Table S17: Aspirin vs Placebo: Outcome Events occurring during treatment or within 30 days of discontinuation of study medications for non-medical reasons and events after censoring

	Participants with Events during treatment or <30 days of Med stopped			Participants with Events > 30 days of Med stopped		All Participants		
	Aspirin	Placebo	HR (CI)	Aspirin	Placebo	Aspirin	Placebo	HR (CI)
Cardiovascular Death/Myocardial Infarction/Stroke	83	100	**0.83 (0.62-1.10)**	33	34	116	134	**0.86 (0.67-1.10)**
Cardiovascular death/ Myocardial Infarction /Stroke + Cancer	111	137	**0.81 (0.63-1.03)**	42	40	153	177	**0.86 (0.69-1.07)**

Table S18: Safety Outcomes: Bleeding Events with Aspirin versus Placebo

Outcome	Aspirin (N=2,860) n (%)	Placebo (N=2,853) n (%)
Major Bleeding*	21 (0.7)	19 (0.7)
Minor Bleeding	17 (0.6)	14 (0.5)
Gastrointestinal Bleeds	12 (0.4)	10 (0.4)

*Major Bleeding based on the International Society on Thrombosis and Haemostasis (ISTH) criteria, defined as: 1) fatal bleeding; 2) bleeding in a critical site or area (retroperitoneal, cardiac tamponade, hemoptysis, intraocular, intracranial, definite hemorrhagic stroke or subarachnoid hemorrhage), or 3) bleeding causing a fall in hemoglobin level of 20 g/L or more or leading to transfusion of 2 or more units of blood.[2]

Table S19: Safety related outcomes: Serious Adverse Events with Aspirin versus Placebo

System organ class	Aspirin n(%)	Placebo n(%)
Randomized	2860	2853
Total Patient with SAE	29 (1.0)	27 (0.9)
Blood and lymphatic system disorders	1 (0.0)	0 (0.0)
Cardiac disorders	4 (0.1)	4 (0.1)
Ear and labyrinth disorders	1 (0.0)	0 (0.0)
Eye disorders	2 (0.1)	0 (0.0)
Gastrointestinal disorders	3 (0.1)	7 (0.2)
General disorders and administration site conditions	3 (0.1)	6 (0.2)
Hepatobiliary disorders	2 (0.1)	1 (0.0)
Infections and infestations	2 (0.1)	3 (0.1)
Injury, poisoning and procedural complications	3 (0.1)	1 (0.0)
Investigations	1 (0.0)	0 (0.0)
Metabolism and nutrition disorders	1 (0.0)	4 (0.1)
Musculoskeletal and connective tissue disorders	2 (0.1)	0 (0.0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	3 (0.1)	3 (0.1)

Nervous system disorders	5 (0.2)	3 (0.1)
Renal and urinary disorders	2 (0.1)	1 (0.0)
Reproductive system and breast disorders	1 (0.0)	0 (0.0)
Respiratory, thoracic and mediastinal disorders	2 (0.1)	1 (0.0)
Surgical and medical procedures	2 (0.1)	2 (0.1)
Vascular disorders	1 (0.0)	1 (0.0)

Table S20: Safety related outcomes: Hospitalizations with Aspirin versus Placebo

	Aspirin		Placebo	
	N	%	N	%
Randomized	2860	100.0	2853	100.0
Patients Hospitalized	219	7.7	233	8.2
Patients with Any Cardiovascular Hospitalization	87	3.0	100	3.5
Myocardial Infarction	19	0.7	24	0.8
Stroke/Transient Ischemic Attack	25	0.9	38	1.3
Heart Failure	9	0.3	9	0.3
Angina	15	0.5	12	0.4
Atrial fibrillation/flutter	4	0.1	4	0.1
Cardiac arrest	7	0.2	8	0.3
Sustained ventricular tachycardia	1	0.0	1	0.0
Supraventricular arrhythmia	1	0.0	1	0.0
Pulmonary embolism	1	0.0	1	0.0
Other Cardiovascular	28	1.0	19	0.7

	Aspirin		Placebo	
	N	%	N	%
Percutaneous Coronary Intervention/ Percutaneous transluminal coronary angioplasty (PCI/PTCA)	14	0.5	14	0.5
Coronary Artery Bypass Graft Surgery	3	0.1	4	0.1
Carotid endarterectomy/ Carotid bypass	0	0.0	0	0.0
Other arterial angioplasty	1	0.0	0	0.0
Other arterial surgery	1	0.0	1	0.0
Patients with Any Non-Cardiovascular Hospitalization	165	5.8	157	5.5
Renal failure	5	0.2	10	0.4
Cancer	17	0.6	21	0.7
Fall	12	0.4	11	0.4
Fracture	13	0.5	11	0.4
Other injury	10	0.3	2	0.1
Anemia	7	0.2	8	0.3
Dementia	1	0.0	0	0.0

	Aspirin		Placebo	
	N	%	N	%
Pneumonia and other lung infections	30	1.0	25	0.9
Hematologic	2	0.1	1	0.0
Genito-urinary	12	0.4	22	0.8
Gastrointestinal	26	0.9	32	1.1
Other non-cardiovascular	96	3.4	75	2.6

Table S21: Outcome Events Based on Participants Receiving Polypill + Aspirin or Double Placebo (Within 30 Days of Discontinuation) and 30 days After Discontinuation for Medical Reasons

	Events during treatment or <30 days of Med stopped			**Events > 30 days of Med stopped**		**All Events**		
	Polypill + Aspirin	Double Placebo	**HR (CI)**	Polypill + Aspirin	Double Placebo	Polypill + Aspirin	Double Placebo	**HR (CI)**
Cardiovascular Death/ Myocardial Infarction /Stroke/ Heart Failure/Cardiac Arrest/Arterial Revascularization	40	64	**0.61 (0.41-0.91)**	19	19	59	83	**0.69 (0.50- 0.97)**
Cardiovascular death/ Myocardial Infarction /Stroke	35	56	**0.61 (0.40-0.93)**	17	19	52	75	**0.68 (0.47-0.96)**
Cardiovascular death/Myocardial Infarction/Stroke/Heart Failure/Resuscitated Cardiac Arrest/Arterial Revascularization/Angina	43	67	**0.63 (0.43-0.92)**	18	19	61	86	**0.69 (0.50-0.96)**

Table S22: Safety Related Outcomes: Serious Adverse Events with Polypill + Aspirin versus Double placebo

System organ class	Double Active	Double placebo
Randomized	1429	1421
Total Patient with SAE	12 (0.8)	16 (1.1)
Blood and lymphatic system disorders	0 (0.0)	0 (0.0)
Cardiac disorders	1 (0.1)	2 (0.1)
Ear and labyrinth disorders	1 (0.1)	0 (0.0)
Eye disorders	2 (0.1)	0 (0.0)
Gastrointestinal disorders	1 (0.1)	2 (0.1)
General disorders and administration site conditions	1 (0.1)	4 (0.3)
Hepatobiliary disorders	0 (0.0)	1 (0.1)
Infections and infestations	0 (0.0)	1 (0.1)
Injury, poisoning and procedural complications	1 (0.1)	1 (0.1)
Investigations	1 (0.1)	0 (0.0)
Metabolism and nutrition disorders	0 (0.0)	1 (0.1)
Musculoskeletal and connective tissue disorders	0 (0.0)	0 (0.0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2 (0.1)	3 (0.2)
Nervous system disorders	2 (0.1)	2 (0.1)

System organ class	Double Active	Double placebo
Renal and urinary disorders	1 (0.1)	0 (0.0)
Reproductive system and breast disorders	1 (0.1)	0 (0.0)
Respiratory, thoracic and mediastinal disorders	2 (0.1)	0 (0.0)
Surgical and medical procedures	1 (0.1)	1 (0.1)
Vascular disorders	1 (0.1)	1 (0.1)

Table S23: Safety Related Outcomes: Hospitalizations in Polypill + Aspirin versus Double placebo groups

	Polypill + Aspirin		Double Placebo	
	N	%	N	%
Randomized	1429	100.0	1421	100.0
Patients Hospitalized	102	7.1	115	8.1
Patients with Any Cardiovascular Hospitalization	40	2.8	57	4.0
Myocardial Infarction	6	0.4	15	1.1
Stroke/Transient Ischemic Attack	11	0.8	21	1.5
Heart Failure	4	0.3	5	0.4
Angina	4	0.3	7	0.5
Atrial fibrillation/flutter	2	0.1	2	0.1
Cardiac arrest	6	0.4	4	0.3
Sustained ventricular tachycardia	1	0.1	0	0.0
Supraventricular arrhythmia	1	0.1	0	0.0
Pulmonary embolism	0	0.0	0	0.0
Other Cardiovascular	12	0.8	15	1.1

	Polypill + Aspirin		Double Placebo	
	N	%	N	%
Percutaneous Coronary Intervention/ Percutaneous transluminal coronary angioplasty (PCI/PTCA)	4	0.3	8	0.6
Coronary Artery Bypass Graft Surgery	0	0.0	4	0.3
Carotid endarterectomy/ Carotid bypass	0	0.0	0	0.0
Other arterial angioplasty	0	0.0	0	0.0
Other arterial surgery	0	0.0	0	0.0
Patients with Any Non-Cardiovascular Hospitalization	80	5.6	71	5.0
Renal failure	4	0.3	4	0.3
Cancer	11	0.8	9	0.6
Fall	4	0.3	4	0.3
Fracture	5	0.3	5	0.4
Other injury	6	0.4	1	0.1
Anemia	4	0.3	5	0.4

	Polypill + Aspirin		Double Placebo	
	N	%	N	%
Dementia	0	0.0	0	0.0
Pneumonia and other lung infections	19	1.3	14	1.0
Hematologic	1	0.1	1	0.1
Genito-urinary	5	0.3	4	0.3
Gastrointestinal	14	1.0	16	1.1
Other non-cardiovascular	45	3.1	33	2.3

Table S24: Safety outcomes: Bleeding with Polypill + Aspirin versus Double Placebo

	Polypill + Aspirin (N=1,429) n (%)	Double Placebo (N=1,421) n (%)
Major Bleeding	9 (0.6)	12 (0.8)
Minor Bleeding	10 (0.7)	6 (0.4)

*Major Bleeding based on the International Society on Thrombosis and Haemostasis (ISTH) criteria, defined as: 1) fatal bleeding; 2) bleeding in a critical site or area (retroperitoneal, cardiac tamponade, hemoptysis, intraocular, intracranial, definite hemorrhagic stroke or subarachnoid hemorrhage), or 3) bleeding causing a fall in hemoglobin level of 20 g/L or more or leading to transfusion of 2 or more units of blood.[2]

Table S25: Reasons for Temporary or Permanently Stopping Aspirin or Placebo in the 4 randomized groups

	Polypill + Aspirin		Polypill Alone		Aspirin Alone		Double Placebo	
	n	Percent	n	Percent	n	Percent	N	Percent
Randomized	1429	100%	1432	100%	1431	100%	1421	100%
Any stop Aspirin/Placebo	840	58.8%	856	59.8%	841	58.8%	836	58.8%
Physician/ participant decision due to side effects	53	3.7%	74	5.2%	62	4.3%	66	4.6%
Gastritis	19	1.3%	24	1.7%	16	1.1%	22	1.5%
Dyspepsia	3	0.2%	1	0.1%	2	0.1%	3	0.2%
Peptic Ulcer	3	0.2%	2	0.1%	2	0.1%	3	0.2%
Gastrointestinal Bleeding	3	0.2%	0	0.0%	2	0.1%	1	0.1%
Hematemesis	0	0.0%	0	0.0%	0	0.0%	0	0.0%
Hematuria	0	0.0%	1	0.1%	1	0.1%	1	0.1%
Hematochezia	0	0.0%	1	0.1%	0	0.0%	0	0.0%
Other	29	2.0%	56	3.9%	48	3.4%	43	3.0%
Physician/participant decision, no side effects	822	57.5%	826	57.7%	821	57.4%	802	56.4%
Participant on open-label medication	16	1.1%	26	1.8%	28	2.0%	24	1.7%
Participant moved	63	4.4%	73	5.1%	75	5.2%	78	5.5%
Refused	339	23.7%	342	23.9%	335	23.4%	332	23.4%
Forgot/lost Drug	3	0.2%	5	0.3%	4	0.3%	4	0.3%

	Polypill + Aspirin		Polypill Alone		Aspirin Alone		Double Placebo	
	n	Percent	n	Percent	n	Percent	N	Percent
Ran out of Drug	337	23.6%	335	23.4%	313	21.9%	313	22.0%
Drug expired in June/July 2020	53	3.7%	57	4.0%	59	4.1%	54	3.8%
No resupply due to COVID-19 restrictions (not for COVID-19 infections)	173	12.1%	146	10.2%	165	11.5%	168	11.8%
Last 3 reasons from above	507	35.5%	474	33.1%	479	33.5%	479	33.7%
Other	50	3.5%	41	2.9%	49	3.4%	40	2.8%
Reason missing	1	0.1%	0	0.0%	0	0.0%	1	0.1%

Table S26: Reasons for Permanently Stopping Aspirin or Placebo in the 4 randomized groups

	Polypill + Aspirin		Polypill Alone		Aspirin Alone		Double Placebo	
	n	Percent	n	Percent	n	Percent	n	Percent
Randomized	1429	100%	1432	100%	1431	100%	1421	100%
Permanent stop Aspirin/Placebo	558	39.0%	583	40.7%	559	39.1%	570	40.1%
Physician/participant decision due to side effects	31	2.2%	51	3.6%	48	3.4%	53	3.7%
Gastritis	13	0.9%	15	1.0%	13	0.9%	18	1.3%
Dyspepsia	2	0.1%	1	0.1%	1	0.1%	1	0.1%
Peptic Ulcer	3	0.2%	1	0.1%	2	0.1%	3	0.2%
Gastrointestinal Bleeding	2	0.1%	0	0.0%	1	0.1%	0	0.0%
Hematemesis	0	0.0%	0	0.0%	0	0.0%	0	0.0%
Hematuria	0	0.0%	1	0.1%	0	0.0%	1	0.1%
Hematochezia	0	0.0%	1	0.1%	0	0.0%	0	0.0%
Other	14	1.0%	37	2.6%	37	2.6%	35	2.5%
Physician/ participant decision, no side effects	526	36.8%	532	37.2%	511	35.7%	517	36.4%
Participant on open-label medication	8	0.6%	23	1.6%	23	1.6%	16	1.1%
Participant moved	45	3.1%	50	3.5%	51	3.6%	51	3.6%
Refused/Refused-participant family member's decision	214	15.0%	225	15.7%	206	14.4%	213	15.0%
Forgot/lost Drug	0	0.0%	2	0.1%	2	0.1%	2	0.1%

	Polypill + Aspirin		Polypill Alone		Aspirin Alone		Double Placebo	
	n	Percent	n	Percent	n	Percent	n	Percent
Ran out of Drug	97	6.8%	80	5.6%	72	5.0%	77	5.4%
Drug expired in June/July 2020	22	1.5%	25	1.7%	21	1.5%	23	1.6%
No resupply due to COVID-19 restrictions (not for COVID-19 infections)	113	7.9%	107	7.5%	110	7.7%	111	7.8%
Last 3 reasons from above	232	16.2%	212	14.8%	203	14.2%	211	14.8%
Other	30	2.1%	24	1.7%	30	2.1%	24	1.7%
Reason missing	1	0.1%	0	0.0%	0	0.0%	0	0.0%

References:

1) Joseph P, Pais P, Dans A, Bosch J, Xavier D, Lopez-Jaramillo P, Yusoff K, Santoso A, Talukder S, Gamra H, Yeates K, Lopez P, Tyrwhitt J, Gao P, Teo K, Yusuf S on behalf of the TIPS-3 Investigators. The International Polycap Study-3 (TIPS-3): Design, baseline characteristics and challenges in conduct. Am Heart J. 2018 Dec; 206: 72-79.
2) Kaatz S, Ahmad D, Spyropoulos AC, Schulman S, Subcommittee on Control of Anticoagulation. Definition of clinically relevant non-major bleeding in studies of anticoagulants in atrial fibrillation and venous thromboembolic disease in non-surgical patients: communication from the SSC of the ISTH. J Thromb Haemost. 2015 Nov;13 (11):2119-26.