

## ORIGINAL ARTICLE

# Polypill with or without Aspirin in Persons without Cardiovascular Disease

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## ABSTRACT

**BACKGROUND**

A polypill comprising statins, multiple blood-pressure–lowering drugs, and aspirin has been proposed to reduce the risk of cardiovascular disease.

**METHODS**

Using a 2-by-2-by-2 factorial design, we randomly assigned participants without cardiovascular disease who had an elevated INTERHEART Risk Score to receive a polypill (containing 40 mg of simvastatin, 100 mg of atenolol, 25 mg of hydrochlorothiazide, and 10 mg of ramipril) or placebo daily, aspirin (75 mg) or placebo daily, and vitamin D or placebo monthly. We report here the outcomes for the polypill alone as compared with matching placebo, for aspirin alone as compared with matching placebo, and for the polypill plus aspirin as compared with double placebo. For the polypill-alone and polypill-plus-aspirin comparisons, the primary outcome was death from cardiovascular causes, myocardial infarction, stroke, resuscitated cardiac arrest, heart failure, or revascularization. For the aspirin comparison, the primary outcome was death from cardiovascular causes, myocardial infarction, or stroke. Safety was also assessed.

**RESULTS**

A total of 5713 participants underwent randomization, and the mean follow-up was 4.6 years. The low-density lipoprotein cholesterol level was lower by approximately 19 mg per deciliter and systolic blood pressure was lower by approximately 5.8 mm Hg with the polypill and with combination therapy than with placebo. The primary outcome for the polypill comparison occurred in 126 participants (4.4%) in the polypill group and in 157 (5.5%) in the placebo group (hazard ratio, 0.79; 95% confidence interval [CI], 0.63 to 1.00). The primary outcome for the aspirin comparison occurred in 116 participants (4.1%) in the aspirin group and in 134 (4.7%) in the placebo group (hazard ratio, 0.86; 95% CI, 0.67 to 1.10). The primary outcome for the polypill-plus-aspirin comparison occurred in 59 participants (4.1%) in the combined-treatment group and in 83 (5.8%) in the double-placebo group (hazard ratio, 0.69; CI, 0.50 to 0.97). The incidence of hypotension or dizziness was higher in groups that received the polypill than in their respective placebo groups.

**CONCLUSIONS**

Combined treatment with a polypill plus aspirin led to a lower incidence of cardiovascular events than did placebo among participants without cardiovascular disease who were at intermediate cardiovascular risk. (Funded by the Wellcome Trust and others; TIPS-3 ClinicalTrials.gov number, NCT01646437.)

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\*A complete list of investigators in TIPS-3 (the International Polycap Study 3) is provided in the Supplementary Appendix, available at NEJM.org.

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CARDIOVASCULAR DISEASES ACCOUNT FOR approximately 18 million deaths each year worldwide, with more than 80% of the deaths occurring in low-income and middle-income countries.<sup>1,2</sup> Elevated blood pressure and an elevated level of low-density lipoprotein (LDL) cholesterol are among the most important modifiable risk factors for cardiovascular disease.<sup>3,4</sup> The associations of these risk factors with myocardial infarction and stroke are graded, and so their simultaneous reductions, regardless of initial levels, should, theoretically, lead to substantial reductions in the incidence of cardiovascular disease.<sup>5-7</sup> These concepts provide part of the rationale for the use of “polypills,” which combine lipid-lowering and blood-pressure-lowering medications, in populations at increased risk. Aspirin is of proven value in patients with established cardiovascular disease,<sup>8</sup> but its role either alone or as part of a polypill for the primary prevention of cardiovascular disease is unclear.<sup>9</sup>

Therefore, we designed a trial to test separately whether treatment with a polypill consisting of a statin and multiple blood-pressure-lowering drugs, aspirin alone, or their combination would reduce the incidence of cardiovascular events among persons without cardiovascular disease. Here we describe the results of TIPS-3 (the International Polycap Study 3), in which we evaluated the efficacy and safety of the polypill as compared with matching placebo, of aspirin as compared with matching placebo, and of the combination of the polypill plus aspirin as compared with double placebo.<sup>10</sup>

## METHODS

### TRIAL DESIGN AND ORGANIZATION

TIPS-3 was a double-blind, randomized, placebo-controlled trial with a 2-by-2-by-2 factorial design.<sup>10</sup> In the first randomized comparison, we tested the effect of treatment with a daily polypill comprising 40 mg of simvastatin, 100 mg of atenolol, 25 mg of hydrochlorothiazide, and 10 mg of ramipril (Polycap, Cadila Pharmaceuticals), as compared with placebo, on the incidence of cardiovascular outcomes. In the second randomized comparison, we tested the effect of treatment with enteric-coated aspirin at a dose of 75 mg per day, as compared with placebo, on the incidence of cardiovascular outcomes (primary outcome) and the composite of cardiovascular out-

comes and cancer (secondary outcome). We also assessed the effects of the polypill plus aspirin as compared with double placebo. In the third randomized comparison (results not reported here), we tested the effect of treatment with vitamin D at a monthly dose of 60,000 IU, as compared with placebo, on the incidence of fractures and falls.

The trial was conducted at 86 centers in nine countries. The ethics committee at each center and the regulatory authorities in each country approved the protocol (available with the full text of this article at NEJM.org). The trial was coordinated by the Population Health Research Institute, Hamilton Health Sciences and McMaster University, in Hamilton, Ontario, Canada, with national coordinating centers in each country. Funding was provided by the Wellcome Trust and others; Cadila Pharmaceuticals provided the trial drugs and placebos as well as additional support. The trial funders had no role in the design of the trial, its conduct or supervision, in the analysis or interpretation of the data, or in the writing of the manuscript or the decision to submit it for publication. The members of the steering committee (see the Supplementary Appendix, available at NEJM.org) vouch for the completeness and accuracy of the data and for the fidelity of the trial to the protocol.

### TRIAL POPULATION

Men 50 years of age or older and women 55 years of age or older who did not have known cardiovascular disease but who had an elevated INTERHEART Risk Score<sup>11,12</sup> indicating intermediate or high cardiovascular risk were eligible for inclusion in the trial. The scale for the INTERHEART Risk Score ranges from 0 to 48, with higher scores indicating greater cardiovascular risk. Detailed trial inclusion and exclusion criteria are described in Section S2 in the Supplementary Appendix. All the participants provided written informed consent.

### PROCEDURES

Eligible participants entered a run-in phase lasting 3 to 4 weeks, during which they received low-dose polypill (half doses of blood-pressure-lowering medications plus 40 mg of simvastatin) and low-dose aspirin (75 mg) daily. Participants who had at least 80% adherence to these medication regimens, who did not have adverse events, and who agreed to undergo randomization were

assigned to receive a full-dose polypill or matching placebo, aspirin or matching placebo, and vitamin D or matching placebo. Randomization was performed with the use of an automated central randomization system, with stratification according to center. Follow-up visits occurred at 6 weeks; at 3, 6, 9 and 12 months; and every 6 months thereafter until the end of the trial. A low-dose polypill (or matching placebo) or a polypill with full doses of each component except ramipril (or matching placebo) were available for participants who had dizziness, hypotension, or cough. Blood pressure was recorded at each visit. Fasting blood samples were obtained before the run-in phase and at 6, 12, and 24 months for the local analysis of lipid levels; in addition, central analysis of lipid levels was carried out in a subgroup of participants (Section S3). All the participants received advice on healthy behaviors.

#### OUTCOMES

The primary outcome for the evaluations of the polypill and the polypill plus aspirin as compared with their respective placebos was a composite of major cardiovascular events, which included death from cardiovascular causes, stroke, and myocardial infarction, plus heart failure, resuscitated cardiac arrest, and arterial revascularization. Secondary outcomes were major cardiovascular events and the composite of the primary outcome plus angina with evidence of ischemia. For the evaluation of aspirin as compared with placebo, the primary composite outcome was death from cardiovascular causes, myocardial infarction, or stroke. Additional prespecified outcomes included death from any cause and first and recurrent (i.e., all) cardiovascular events; for the evaluation of aspirin as compared with placebo, cancer was an additional prespecified outcome. Definitions of the outcomes are provided in Section S4.

#### STATISTICAL ANALYSIS

Assuming a cardiovascular event rate of 1.2% per year in the placebo group, with the enrollment of at least 5000 participants over a period of 2 years and a mean follow-up of 5 years, we calculated that the trial would have more than 80% power to detect a 35% lower relative risk of cardiovascular events with the polypill as compared with placebo. We had intended to extend enrollment

to 7000 participants in order to enhance the power of the trial, if resources and circumstances had permitted. However, several administrative and regulatory hurdles limited trial recruitment (Section S5).

The primary analysis for each treatment comparison was based on all the participants who had undergone randomization. If no interactions were observed between the main effects of the different treatments being evaluated (Section S6), then each individual comparison was to be performed as described in this article. Survival curves for the primary and secondary outcomes were computed with the use of the Kaplan–Meier method. The primary analyses were based on the time to an unrefuted primary-outcome event (after central adjudication) with the use of Cox proportional-hazards models, stratified according to the other groups in the factorial design. The proportional-hazards assumption was tested for each primary analysis (Section S6). Sensitivity analyses that were limited to events that occurred within 30 days after the stopping of the trial regimen for nonmedical reasons (Section S5) and total-event (first and recurrent events) analyses with the use of proportional-means models<sup>13,14</sup> were also prespecified in the statistical analysis plan before unblinding. Hazard ratios with 95% confidence intervals are presented. The widths of the confidence intervals have not been adjusted for multiplicity, and therefore the intervals should not be used to infer definitive treatment effects. Treatment effects were also assessed in prespecified subgroups.

## RESULTS

#### TRIAL PARTICIPANTS

Of 7793 screened persons, 7534 were eligible to participate in the run-in phase. Of these, 1821 persons (24.2%) were not included in the trial; therefore, 5713 participants underwent randomization between July 30, 2012, and August 12, 2017 (Figs. S1 through S3). The most common reasons that participants from the run-in phase did not undergo randomization were side effects attributed to the polypill or aspirin (in 715 participants), nonadherence to the regimen (in 560), and the participant's decision to not undergo randomization (in 458) (Table S1).

The characteristics of the participants at baseline are shown in Table 1. Most participants were

recruited in India (47.9%) and the Philippines (29.3%). The mean age of the participants was 63.9 years, and 52.9% were female. Hypertension or elevated blood pressure was reported in 83.8% of the participants, and diabetes or elevated glucose level in 36.7%. The mean systolic blood pressure was 144.5 mm Hg, the mean heart rate was

77.0 beats per minute, and the mean LDL cholesterol level was 120.7 mg per deciliter (3.1 mmol per liter).

#### FOLLOW-UP AND ADHERENCE TO TRIAL REGIMENS

Of the 5713 participants who underwent randomization, 57 were withdrawn early for regula-

**Table 1. Baseline Characteristics of the Participants Randomly Assigned to Receive Double Placebo, Aspirin Alone, Polypill Alone, or Polypill plus Aspirin.\***

Characteristic	Double Placebo (N=1421)	Aspirin Alone (N=1431)	Polypill Alone (N=1432)	Polypill plus Aspirin (N=1429)
Age — yr	64.1±6.8	63.7±6.7	64.1±6.4	63.8±6.5
Female sex — no. (%)	757 (53.3)	746 (52.1)	777 (54.3)	745 (52.1)
Geographic distribution — no. (%)				
India or Bangladesh	755 (53.1)	760 (53.1)	760 (53.1)	759 (53.1)
Philippines, Malaysia, or Indonesia	479 (33.7)	477 (33.3)	478 (33.4)	479 (33.5)
Colombia	121 (8.5)	122 (8.5)	125 (8.7)	121 (8.5)
Canada	30 (2.1)	35 (2.4)	33 (2.3)	33 (2.3)
Tanzania	10 (0.7)	10 (0.7)	10 (0.7)	9 (0.6)
Tunisia	26 (1.8)	27 (1.9)	26 (1.8)	28 (2.0)
Cardiovascular risk factor — no. (%)				
Reported hypertension or systolic blood pressure >140 mm Hg	1179 (83.0)	1220 (85.3)	1199 (83.7)	1192 (83.4)
Reported diabetes or glucose level >126 mg/dl (7.0 mmol/liter)	527 (37.1)	503 (35.2)	543 (37.9)	522 (36.5)
Impaired fasting glucose ≥110–126 mg/dl (6.1–7.0 mmol/liter)	97 (6.8)	101 (7.1)	109 (7.6)	98 (6.9)
Current smoking	115 (8.1)	138 (9.6)	123 (8.6)	136 (9.5)
INTERHEART Risk Score†	17.9±4.8	17.8±4.7	18.0±4.8	17.9±4.7
Physiological variables				
Heart rate — beats/min	77.1±10.9	77.3±10.5	77.0±10.5	76.6±10.5
Blood pressure — mm Hg				
Systolic	144.4±17.2	144.7±16.8	144.7±16.9	144.3±16.6
Diastolic	83.6±9.6	83.7±9.9	84.2±9.9	84.1±9.4
Cholesterol — mg/dl				
Total	196.4±46.9	196.1±45.1	196.7±45.6	195.5±44.9
LDL	120.7±41.9	120.8±40.1	121.2±40.7	120.0±40.2
HDL	48.2±13.5	47.1±11.9	47.7±13.0	47.9±13.6
Triglycerides — mg/dl	143.2±70.8	148.7±82.8	146.4±70.6	144.7±72.3
Fasting plasma glucose — mg/dl	113.5±43.0	114.4±46.6	114.9±45.5	114.5±44.9
Creatinine — mg/dl	0.9±0.3	0.9±0.3	0.9±0.3	0.9±0.3
Body-mass index‡	25.6±4.6	25.7±4.8	26.1±4.9	25.8±4.6
Waist-to-hip ratio				
Among women	0.91±0.07	0.91±0.07	0.91±0.07	0.91±0.08
Among men	0.96±0.07	0.96±0.06	0.96±0.06	0.96±0.07

**Table 1. (Continued.)**

Characteristic	Double Placebo (N=1421)	Aspirin Alone (N=1431)	Polypill Alone (N=1432)	Polypill plus Aspirin (N=1429)
Medication use — no. (%)				
Antihypertensive drug	155 (10.9)	156 (10.9)	161 (11.2)	157 (11.0)
Calcium-channel blocker	137 (9.6)	141 (9.9)	153 (10.7)	138 (9.7)
Aspirin or clopidogrel	2 (0.1)	1 (0.1)	0	2 (0.1)
Oral anticoagulant	4 (0.3)	2 (0.1)	2 (0.1)	8 (0.6)
Insulin	35 (2.5)	29 (2.0)	24 (1.7)	29 (2.0)
Oral hypoglycemic agent	302 (21.3)	292 (20.4)	310 (21.6)	314 (22.0)
Statin	0	0	1 (0.1)	0
Other lipid-lowering agent	1 (0.1)	0	0	2 (0.1)

\* Plus-minus values are means  $\pm$ SD. Percentages may not total 100 because of rounding. To convert the values for cholesterol to millimoles per liter, multiply by 0.0259. To convert the values for triglycerides to millimoles per liter, multiply by 0.01129. To convert the values for glucose to millimoles per liter, multiply by 0.05551. To convert the values for creatinine to micromoles per liter, multiply by 88.4. HDL denotes high-density lipoprotein, and LDL low-density lipoprotein.

† The scale for the INTERHEART Risk Score ranges from 0 to 48, with higher scores indicating greater cardiovascular risk.

‡ The body-mass index is the weight in kilograms divided by the square of the height in meters.

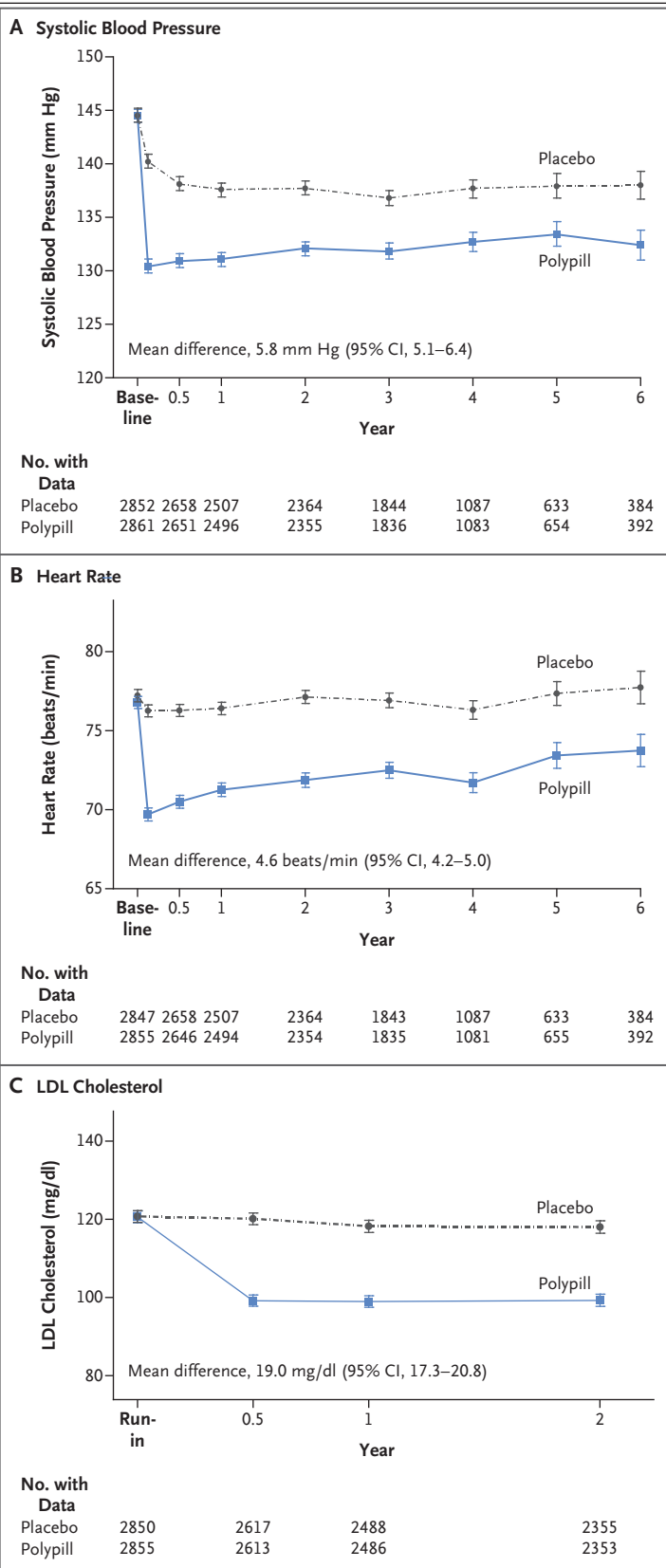
tory and administrative reasons (as described in Section S5 and Figs. S1 through S3). Follow-up events that occurred before the withdrawal of these participants are included in the analyses. For all the other participants, follow-up included events that were known to have occurred by June 30, 2020. The mean follow-up in the overall trial was 4.6 years (median, 4.4 years). At the end of the scheduled follow-up, vital status was available for 5667 of the 5713 participants (99.2%) who had undergone randomization.

For the comparison of the polypill with placebo, 81.1% of the participants in the polypill group and 81.3% of those in the placebo group were adhering to the trial regimen at 24 months; at 48 months, adherence was 67.7% and 69.4%, respectively. For the comparison of aspirin with placebo, 82.0% of the participants in the aspirin group and 82.1% of those in the placebo group were adhering to the trial regimen at 24 months; at 48 months, adherence was 73.0% and 71.0%, respectively. The overall incidence of discontinuation of the trial regimen was 42.2% for the polypill comparison and 39.7% for the aspirin comparison, both of which were higher than the 20% that was anticipated in the trial protocol. Major factors in the discontinuation of trial regimens included administrative, regulatory, and drug-delivery barriers and delays as well as restrictions related to the coronavirus disease 2019

(Covid-19) pandemic. Circumstances contributing to nonadherence and additional information regarding adherence as well as open-label drug use are presented in Sections S5 and S7 and Tables S2 through S11.

#### BLOOD PRESSURE, HEART RATE, AND LIPID LEVELS

During the trial, the mean systolic blood pressure was 5.8 mm Hg lower in the polypill group than in the placebo group (Fig. 1). This difference was 9.8 mm Hg at 6 weeks and 6.5 mm Hg at 12 months. The mean diastolic blood pressure was 3.2 mm Hg lower in the polypill group than in the placebo group. The mean heart rate was 4.6 beats per minute lower in the polypill group than in the placebo group during the trial; the difference of 6.6 beats per minute at 6 weeks diminished to 5.1 beats per minute at 12 months. The mean LDL cholesterol level was 19.0 mg per deciliter (0.50 mmol per liter) lower in the polypill group than in the placebo group; the between-group difference was 19.2 mg (0.50 mmol per liter) at 12 months and 18.8 mg per deciliter (0.49 mmol per liter) at 24 months. On the basis of central laboratory lipid measurements, the mean between-group difference was 16.2 mg per deciliter (0.42 mmol per liter) at a mean follow-up of 50 months (Table S12). The reductions in blood pressure, the heart rate, and the LDL cholesterol level were similar for the comparison of



**Figure 1.** Effects of the Polypill, as Compared with Placebo, on Systolic Blood Pressure, Heart Rate, and the Low-Density Lipoprotein (LDL) Cholesterol Level. I bars indicate 95% confidence intervals (CIs).

combined therapy (polypill plus aspirin) with double placebo.

**OUTCOMES FOR THE POLYPILL AS COMPARED WITH PLACEBO**

The primary outcome for the polypill comparison (major cardiovascular events plus heart failure, resuscitated cardiac arrest, and arterial revascularization) occurred in 126 participants (4.4%) in the polypill group, as compared with 157 (5.5%) in the placebo group (hazard ratio, 0.79; 95% confidence interval [CI], 0.63 to 1.00) (Fig. 2 and Table 2). Death from cardiovascular causes, myocardial infarction, or stroke (secondary outcome) occurred in 111 participants (3.9%) in the polypill group and in 139 participants (4.9%) in the placebo group (hazard ratio, 0.79; 95% CI, 0.61 to 1.01). The total number of primary-outcome events (including first and recurrent events) was 138 in the polypill group and 179 in the placebo group (hazard ratio, 0.76; 95% CI, 0.60 to 0.97). No interactions were observed between the effects of the different treatments being evaluated, and the proportional-hazards assumption was confirmed for each primary analysis (Section S6).

In the prespecified sensitivity analysis that excluded events that occurred more than 30 days after the trial regimen was stopped for non-medical reasons, 95 participants (3.3%) in the polypill group had a primary-outcome event, as compared with 126 (4.4%) in the placebo group (hazard ratio, 0.74; 95% CI, 0.57 to 0.97), with similar numbers of events in the two randomized groups (31 and 31, respectively) occurring after the period of censoring (Table S13). There was no evidence of heterogeneity of treatment effect across the prespecified subgroups (Fig. S4).

More participants in the polypill group than in the placebo group stopped the trial regimen because of dizziness (28 vs. 17 participants), hypotension (51 vs. 14), or cough (31 vs. 17); however, the numbers of participants who discontinued the polypill or placebo because of muscle pain (9 and 11 participants, respectively) and weakness (5 and 4, respectively) were simi-

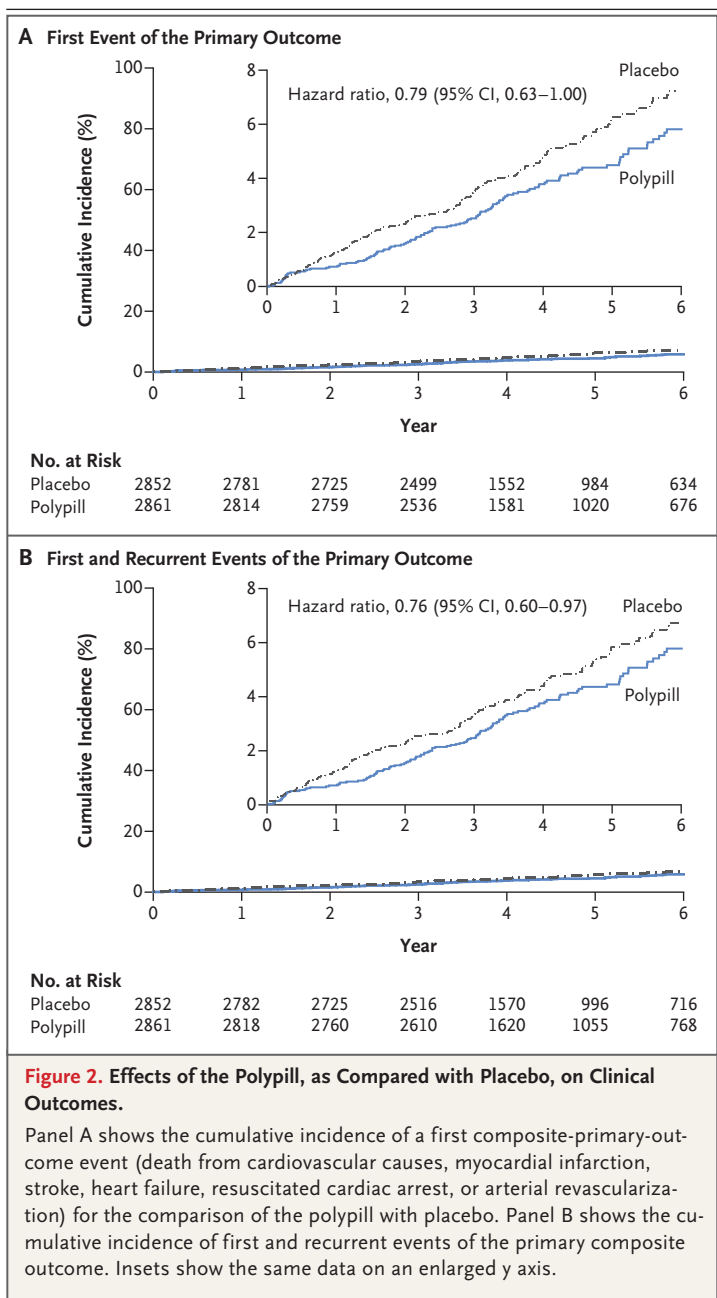
lar in the two groups (Table S6). The incidence of permanent discontinuation of the trial regimen because of side effects was 5.4% in the polypill group and 3.9% in the placebo group (Table S7). Serious adverse events and adverse events that led to hospitalization are listed in Tables S14 and S15, respectively.

#### OUTCOMES FOR ASPIRIN AS COMPARED WITH PLACEBO

The primary outcome for the aspirin comparison (death from cardiovascular causes, myocardial infarction, or stroke) occurred in 116 participants (4.1%) in the aspirin group and in 134 participants (4.7%) in the placebo group (hazard ratio, 0.86; 95% CI, 0.67 to 1.10) (Fig. 3 and Table 3). Death from cardiovascular causes, myocardial infarction, stroke, or cancer (secondary outcome) occurred in 153 participants (5.3%) in the aspirin group and in 177 participants (6.2%) in the placebo group (hazard ratio, 0.86; 95% CI, 0.69 to 1.07). The total number of primary-outcome events (including first and recurrent events) was 124 in the aspirin group and 144 in the placebo group (hazard ratio, 0.86; 95% CI, 0.67 to 1.11). New cancer occurred in 38 participants (1.3%) in the aspirin group and in 46 (1.6%) in the placebo group (hazard ratio, 0.83; 95% CI, 0.54 to 1.27). The distribution of cancers according to body site is provided in Table S16.

In the prespecified sensitivity analysis that excluded events that occurred more than 30 days after the trial regimen was stopped for nonmedical reasons, primary-outcome events occurred in 83 participants (2.9%) in the aspirin group and in 100 participants (3.5%) in the placebo group (hazard ratio, 0.83; 95% CI, 0.62 to 1.10) (Table S17). There was no evidence of heterogeneity of treatment effect in subgroups defined according to sex, diabetes or hypertension status, lipid or blood-pressure levels, age (in three subgroups), INTERHEART Risk Score, or geographic region either for the primary outcome (Fig. S5) or for the primary outcome plus cancer (Fig. S6).

In the aspirin group and the placebo group, a similar number of participants had major bleeding (21 and 19 participants, respectively), minor bleeding (17 and 14, respectively), and gastrointestinal bleeding (12 and 10); a similar number of participants in the aspirin group and the placebo group had dyspepsia (5 and 4 participants, respectively) or peptic ulcer (5 and 5, re-



spectively) that led to discontinuation of the trial regimen (Tables S8, S9, and S18). Serious adverse events and adverse events that led to hospitalization are listed in Tables S19 and S20, respectively.

#### OUTCOMES WITH POLYPILL PLUS ASPIRIN AS COMPARED WITH DOUBLE PLACEBO

The primary outcome for this comparison (major cardiovascular events plus heart failure, resusci-

**Table 2. Clinical Outcomes with the Polypill or Placebo.**

Outcomes	Polypill (N=2861)	Placebo (N=2852)	Hazard Ratio (95% CI)*
<b>Primary outcome</b>			
Death from cardiovascular causes, myocardial infarction, stroke, heart failure, resuscitated cardiac arrest, or arterial revascularization — no. (%)	126 (4.4)	157 (5.5)	0.79 (0.63–1.00)
<b>Secondary outcomes</b>			
Death from cardiovascular causes, myocardial infarction, or stroke — no. (%)	111 (3.9)	139 (4.9)	0.79 (0.61–1.01)
Death from cardiovascular causes, myocardial infarction, stroke, heart failure, resuscitated cardiac arrest, arterial revascularization, or angina with evidence of ischemia — no. (%)	132 (4.6)	164 (5.8)	0.79 (0.63–1.00)
<b>Components of the primary and secondary outcomes</b>			
Death from cardiovascular causes — no. (%)†	84 (2.9)	101 (3.5)	0.82 (0.61–1.09)
Myocardial infarction — no. (%)	17 (0.6)	26 (0.9)	0.66 (0.36–1.22)
Stroke — no. (%)	26 (0.9)	36 (1.3)	0.71 (0.43–1.18)
Heart failure — no. (%)	12 (0.4)	10 (0.4)	1.19 (0.51–2.74)
Resuscitated cardiac arrest — no. (%)	1 (<0.1)	0	—
Arterial revascularization — no. (%)	12 (0.4)	25 (0.9)	0.48 (0.24–0.95)
Angina with evidence of ischemia — no. (%)	17 (0.6)	22 (0.8)	0.77 (0.41–1.44)
<b>Other efficacy outcomes</b>			
Death from any cause — no. (%)	149 (5.2)	163 (5.7)	0.90 (0.72–1.13)
First and recurrent events of the primary outcome			
No. of participants with ≥1 event	126	157	—
No. of participants with ≥2 events	12	22	—
Total no. of events	138	179	0.76 (0.60–0.97)‡

\* The widths of the confidence intervals have not been adjusted for multiplicity, so the intervals should not be used to infer definitive treatment effects.

† Death from cardiovascular causes included confirmed death from cardiovascular causes (in 57 participants in the polypill group and in 80 in the placebo group) and death from an unknown cause, which was categorized according to the protocol definition as presumed death from cardiovascular causes (in 27 and 21 participants, respectively).

‡ The analysis was conducted with the use of a proportional-means model.

tated cardiac arrest, or arterial revascularization) occurred in 59 participants (4.1%) in the polypill-plus-aspirin group, as compared with 83 (5.8%) in the double-placebo group (hazard ratio, 0.69; 95% CI, 0.50 to 0.97) (Fig. 4 and Table 4). There was a similar effect on death from cardiovascular causes, myocardial infarction, or stroke (secondary outcome; 52 participants [3.6%] in the polypill-plus-aspirin group vs. 75 [5.3%] in the double-placebo group; hazard ratio, 0.68; 95% CI, 0.47 to 0.96). The total number of primary-outcome events (including first and recurrent events) was 64 in the polypill-plus-aspirin group and 93 in the double-placebo group (hazard ratio, 0.68; 95% CI, 0.48 to 0.96).

In the prespecified sensitivity analysis that excluded events that occurred more than 30 days

after the trial regimen was stopped for non-medical reasons, primary-outcome events occurred in 40 participants (2.8%) in the polypill-plus-aspirin group and in 64 participants (4.5%) in the double-placebo group (hazard ratio, 0.61; 95% CI, 0.41 to 0.91) (Table S21). The results were consistent across subgroups defined according to diabetes status, initial LDL cholesterol level, systolic blood pressure, and geographic region (Fig. S7).

The number of participants who discontinued the trial medications or placebo because of side effects was similar in the polypill-plus-aspirin group and the double-placebo group (5 and 7, respectively because of muscle symptoms; 3 and 1 because of gastrointestinal bleeding; 3 and 3 because of dyspepsia; 19 and 22 because of gastri-

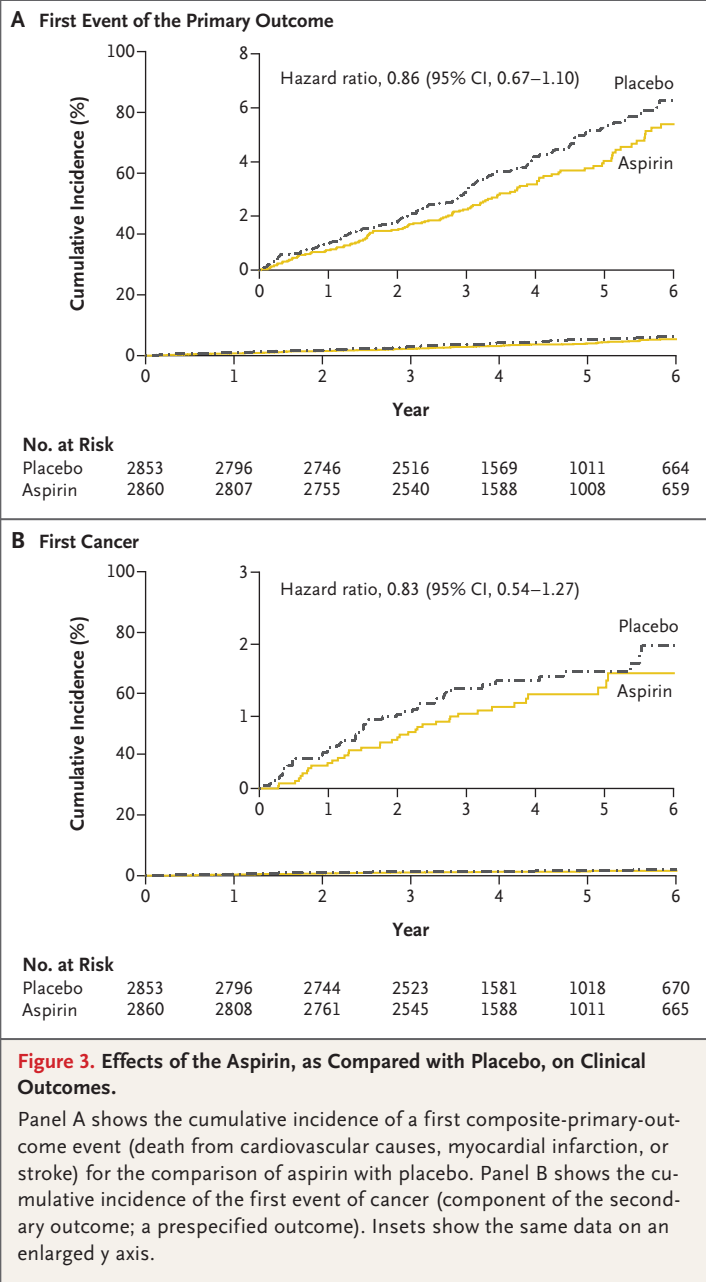


tis; and 3 and 3 because of peptic ulcer). More participants in the polypill-plus-aspirin group than in the double-placebo group discontinued the trial regimen because of dizziness or hypotension (45 vs. 22 participants). Major bleeding was reported in 9 participants in the polypill-plus-aspirin group and in 12 participants in the double-placebo group. Details of the safety outcomes and discontinuations of the trial regimen are provided in Tables S10, S11, and S22 through S26.

## DISCUSSION

In TIPS-3, the combination of a polypill (consisting of simvastatin and three blood-pressure-lowering drugs) plus aspirin administered for a mean of 4.6 years in a primary-prevention population at intermediate risk led to a 31% lower relative risk of cardiovascular events (absolute risk difference, 1.7 percentage points) in an intention-to-treat analysis. The benefit was similar in an analysis that included both first and recurrent events and in an analysis that excluded events that occurred more than 30 days after the trial regimen was stopped for nonmedical reasons. Both interventions appear to have contributed to the overall benefit of the combination, with a larger portion of the benefit attributable to the polypill.

The reduction in the LDL cholesterol level with the polypill was half the value that we had anticipated on the basis of previous trials of simvastatin at a dose of 40 mg per day,<sup>15</sup> of the TIPS-1 and TIPS-2 (the Indian Polycap Study 1 and 2) pilot studies,<sup>16,17</sup> or of trials of the newer statins (atorvastatin or rosuvastatin).<sup>18,19</sup> The degree of blood-pressure lowering was also less by approximately one third, as compared with the findings of previous short-term trials.<sup>20</sup> However, the reduction in systolic blood pressure that was observed in TIPS-3 (with full doses of three blood-pressure-lowering drugs) was similar to that seen in the Heart Outcomes Prevention Evaluation (HOPE)-3 trial, which used two blood-pressure-lowering drugs at half doses,<sup>21</sup> and was larger than that observed in the long-term PolyIran trial, in which no difference in diastolic blood pressure was observed at the end of the trial.<sup>22</sup> An attenuation of both a short-term reduction in the LDL cholesterol level and a short-term reduction in blood pressure during long-term follow-up has been observed in previ-



ous trials.<sup>21-23</sup> The observed benefits on cardiovascular events were consistent with what would be expected from the modest reduction in the LDL cholesterol level and blood pressure, with added benefits from aspirin.

The smaller-than-expected reductions in risk factors in this trial may have contributed to the fact that the observed clinical benefit was smaller than the 40 to 45% lower relative risk that we had expected on the basis of risk-factor changes

<b>Table 3. Clinical Outcomes with Aspirin or Placebo.</b>			
<b>Outcome</b>	<b>Aspirin (N=2860)</b>	<b>Placebo (N=2853)</b>	<b>Hazard Ratio (95% CI)*</b>
<b>Primary outcome</b>			
Death from cardiovascular causes, myocardial infarction, or stroke — no. (%)	116 (4.1)	134 (4.7)	0.86 (0.67–1.10)
<b>Secondary Outcome</b>			
Death from cardiovascular causes, myocardial infarction, stroke, or cancer — no. (%)	153 (5.3)	177 (6.2)	0.86 (0.69–1.07)
<b>Components of the primary and secondary outcomes</b>			
Death from cardiovascular causes — no. (%) †	85 (3.0)	100 (3.5)	0.85 (0.64–1.14)
Myocardial infarction — no. (%)	22 (0.8)	21 (0.7)	1.04 (0.57–1.89)
Stroke — no. (%)	23 (0.8)	39 (1.4)	0.58 (0.35–0.98)
Cancer — no. (%)	38 (1.3)	46 (1.6)	0.83 (0.54–1.27)
<b>Other efficacy outcomes</b>			
Death from any cause — no. (%)	145 (5.1)	167 (5.9)	0.87 (0.70–1.09)
<b>First and recurrent events of the primary outcome</b>			
No. of participants with ≥1 event	116	134	—
No. of participants with ≥2 events	8	10	—
Total no. of events	124	144	0.86 (0.67–1.11) ‡
<b>First and recurrent events of the secondary outcome</b>			
No. of participants with ≥1 event	153	177	—
No. of participants with ≥2 events	12	17	—
Total no. of events	165	194	0.85 (0.68–1.06) ‡

\* The widths of the confidence intervals have not been adjusted for multiplicity, so the intervals should not be used to infer definitive treatment effects.

† Death from cardiovascular causes included confirmed death from cardiovascular causes (in 68 participants in the aspirin group and in 69 in the placebo group) and death from an unknown cause, which was categorized according to the protocol definition as presumed death from cardiovascular causes (in 17 and 31 participants, respectively).

‡ The analysis was conducted with the use of a proportional-means model.

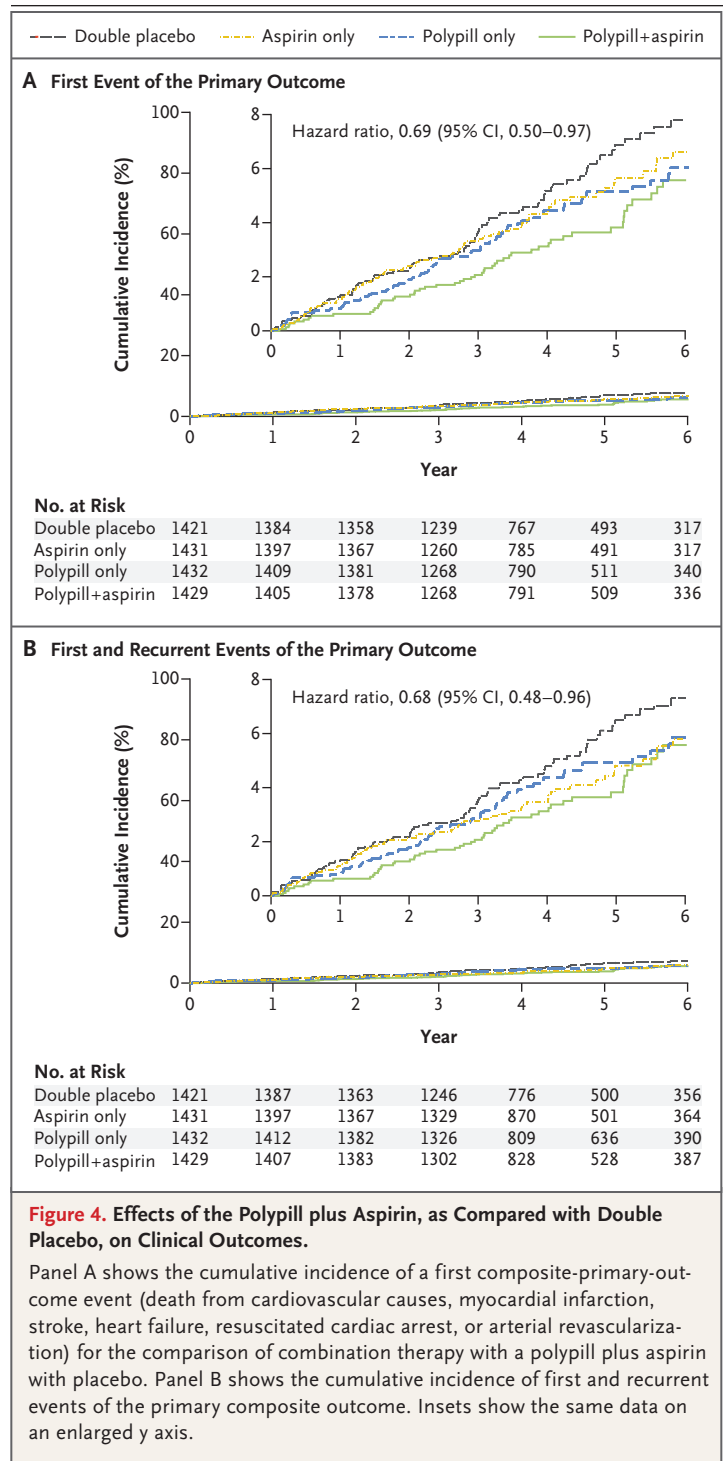
that had been observed in our pilot studies. However, our results are consistent with the 29% lower relative risk (absolute risk difference, 1.4 percentage points) of cardiovascular events among participants receiving a statin plus two blood-pressure-lowering drugs in the HOPE-3 trial<sup>23</sup> and the 34% lower relative risk (absolute risk difference, 2.9 percentage points) that was seen in the PolyIran trial, which used a polypill that included a statin, two blood-pressure-lowering drugs, and aspirin.<sup>22</sup> Exploratory analyses (data not shown) suggested that the group of centers that had the greatest differences in risk factors had the greatest differences in the incidence of cardiovascular events with the polypill plus aspirin. Therefore, future formulations of a polypill that can result in greater differences in risk factors may be expected to lead to greater benefits than were observed in the current trial.

It is likely that the lower relative risk that was associated with combined treatment with the polypill plus aspirin than with double placebo that was observed in the intention-to-treat analysis in our trial is an underestimate of the true effects of treatment because of the high incidence of discontinuation of the trial regimen, which was mostly for reasons unrelated to side effects. During the trial, complexities in the processes of drug distribution resulted in drug-supply delays to many sites (Section S5). These delays not only limited the initial access to the trial medications and placebos for participants but often impeded resupply, leading to discontinuation after the initiation of the regimen. In addition, the Covid-19 pandemic restricted site operations in virtually all countries beginning in March 2020. This situation restricted the ability of the participants to physically return to sites,

to obtain trial medications and placebo, and to complete the end-of-trial visits. As a consequence, the overall trial follow-up was somewhat shorter than we had planned. TIPS-3 had a median of 4.4 years of follow-up, as compared with the planned 5 years, whereas the median follow-up in the HOPE-3 trial was 5.6 years<sup>23</sup> and in the PolyIran trial all the participants were followed for 5 years.<sup>22</sup>

The magnitude of risk reduction that we observed was substantially lower than the 80% lower relative risks of stroke and myocardial infarction that were hypothesized by Wald and Law in their advocacy for the polypill concept in 2003.<sup>7</sup> Wald and Law assumed that polypill treatment would reduce blood pressure and the LDL cholesterol level to a much larger extent than the effects observed in TIPS-3 and in most other long-term trials.<sup>15,19,21,24</sup> They also assumed that aspirin therapy would reduce the risk of cardiovascular events by 30% and that lowering the homocysteine level (with vitamin B<sub>12</sub>, vitamin B<sub>6</sub>, and folate therapy) would further reduce cardiovascular risk. The effects of lowering the homocysteine level with regard to reducing cardiovascular risk are unclear,<sup>25,26</sup> so we chose not to include this component in the polypill we tested. The benefits we observed are nonetheless likely to be of clinical and population-wide importance, especially if the polypill is inexpensive. A similar formulation of the Polycap in India costs approximately \$15 U.S. dollars per month. We have not yet completed a formal economic analysis. The polypill was given in addition to regular advice on lifestyle modification; such an approach could be part of a comprehensive strategy for the prevention of cardiovascular diseases in the community.<sup>27</sup>

There was a higher incidence of hypotension, dizziness, and cough, but no excess of bleeding, with the use of the polypill plus aspirin than with double placebo. In considering the relatively low incidence of adverse events, it is important to note that the trial had an active run-in phase during which participants received a low-dose polypill plus aspirin. Of the 7534 participants who entered the run-in phase, 715 (9.5%) did not undergo randomization because of side effects. An additional 560 participants (7.4%) did not undergo randomization because they had less than 80% adherence to the trial-drug regimen — a figure that was not related primarily to



drug-distribution issues. Therefore, TIPS-3 may underestimate the number of persons who would stop treatment for side effects or poor adherence if a polypill including aspirin were

**Table 4. Clinical Outcomes with Polypill plus Aspirin or Double Placebo.**

Outcome	Polypill plus Aspirin (N=1429)	Double Placebo (N=1421)	Hazard Ratio (95% CI)*
<b>Primary outcome</b>			
Death from cardiovascular causes, myocardial infarction, stroke, heart failure, resuscitated cardiac arrest, or arterial revascularization — no. (%)	59 (4.1)	83 (5.8)	0.69 (0.50–0.97)
<b>Secondary outcomes</b>			
Death from cardiovascular causes, myocardial infarction, or stroke — no. (%)	52 (3.6)	75 (5.3)	0.68 (0.47–0.96)
Death from cardiovascular causes, myocardial infarction, stroke, heart failure, resuscitated cardiac arrest, arterial revascularization, or angina with evidence of ischemia — no. (%)	61 (4.3)	86 (6.1)	0.69 (0.50–0.96)
<b>Components of the primary and secondary outcomes</b>			
Death from cardiovascular causes — no. (%)†	38 (2.7)	54 (3.8)	0.69 (0.46–1.05)
Myocardial infarction — no. (%)	10 (0.7)	14 (1.0)	0.69 (0.31–1.56)
Stroke — no. (%)	10 (0.7)	23 (1.6)	0.42 (0.20–0.89)
Heart failure — no. (%)	7 (0.5)	3 (0.2)	2.30 (0.60–8.90)
Resuscitated cardiac arrest — no. (%)	0	0	—
Arterial revascularization — no. (%)	5 (0.3)	12 (0.8)	0.40 (0.14–1.14)
Angina with evidence of ischemia — no. (%)	6 (0.4)	10 (0.7)	0.59 (0.22–1.63)
<b>Other outcomes</b>			
Death from any cause — no. (%)	75 (5.2)	93 (6.5)	0.80 (0.59–1.08)
Cancer — no. (%)	19 (1.3)	24 (1.7)	0.78 (0.43–1.42)
Primary-outcome event or cancer — no. (%)	76 (5.3)	106 (7.5)	0.70 (0.52–0.94)
<b>First and recurrent events of the primary outcome</b>			
No. of participants with ≥1 event	59	83	
No. of participants with ≥2 events	5	10	
Total no. of events	64	93	0.68 (0.48–0.96)‡

\* The widths of the confidence intervals have not been adjusted for multiplicity, so the intervals should not be used to infer definitive treatment effects.

† Death from cardiovascular causes included confirmed death from cardiovascular causes (in 24 participants in the polypill-plus-aspirin group and in 36 in the double-placebo group) and death from an unknown cause, which was categorized according to the protocol definition as presumed death from cardiovascular causes (in 14 and 18 participants, respectively).

‡ The analysis was conducted with the use of a proportional-means model.

used widely among eligible persons in the general population.

In this large, randomized trial, we found that combination treatment with a polypill (consisting of a statin plus three blood-pressure-lowering drugs) plus aspirin led to a lower incidence of cardiovascular events than did placebo among participants without established cardiovascular disease who were at intermediate cardiovascular risk.

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## APPENDIX

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