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Polypill Strategy in Secondary Cardiovascular Prevention

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ABSTRACT

BACKGROUND

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

METHODS

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

RESULTS

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

CONCLUSIONS

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

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

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

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

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

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

METHODS

TRIAL DESIGN AND OVERSIGHT

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

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

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

PATIENTS

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

TRIAL TREATMENTS AND PROCEDURES

Patients were randomly assigned to a polypill strategy or usual care (with a care program determined on the basis of current European Society of Cardiology guidelines) by means of a centralized online system. Randomization was stratified according to trial center. The polypill contained any of three formulations of Polypill AAR40 — a single pill containing aspirin (100 mg), ramipril (2.5, 5, or 10 mg), and atorvastatin (40 mg). If the investigator decided to reduce the atorvastatin dose on the basis

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of the patient's history or the results of blood tests, the patient could be switched to Polypill AAR20 (same as AAR40 but with a reduced dose of atorvastatin [20 mg]). Among the patients who had not received ramipril, treatment was started at a dose of 2.5 mg; among those who were already taking an angiotensin-converting–enzyme (ACE) inhibitor, treatment was started at a bioequivalent dose of ramipril. The dose was increased to a goal of 10 mg (if the patient had no unacceptable side effects) at 3-week intervals. Details regarding the two treatment groups are provided in the protocol, available at NEJM.org.

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

EFFICACY AND SAFETY OUTCOMES

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

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

STATISTICAL ANALYSIS

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

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

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

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

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For secondary outcomes aside from the key secondary outcome, the 95% confidence intervals were not adjusted for multiple testing and should not be used to infer definitive treatment effects. Ordinal logistic regression was used to calculate common odds ratios comparing adherence categories. Mean differences in scores for treatment satisfaction and changes in risk factors from baseline were compared with the use of two-sample t-tests and analysis of covariance, respectively. The numbers of safety outcomes were summarized according to treatment group and compared with the use of chi-square tests. All analyses were performed with the use of Stata software, version 17.0 (StataCorp).

RESULTS

PATIENTS

From August 2016 through December 2019, a total of 4003 patients underwent screening; of these patients, 1504 (37%) were either not eligible or declined to participate in the trial. A total of 2499 patients underwent randomization (1258 to the polypill group and 1241 to the usual-care group). The median time between the index myocardial infarction and randomization was 8 days (interquartile range [IQR], 3 to 37). Follow-up data were missing for 21 patients in the polypill group and 12 in the usual-care group, so the intention-to-treat population consisted of 2466 patients (1237 in the polypill group and 1229 in the usual-care group) (Fig. S1). Of these patients, withdrawal during follow-up was reported in 174 patients in the polypill group and 166 in the usual-care group; data for these patients were censored at time of withdrawal (Table S3).

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

TREATMENT EFFECTS

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

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

The mean systolic and diastolic blood pressure levels at 24 months were 135.2 mm Hg and 74.8 mm Hg, respectively, in the polypill group and 135.5 mm Hg and 74.9 mm Hg, respectively, in the usual-care group (Table S11). No substantial differences were found in LDL cholesterol levels over time between the groups, with a mean value at 24 months of 67.7 mg per deciliter in the polypill group and 67.2 mg per deciliter in the usual-care group. The distribution of LDL cholesterol levels and systolic and diastolic blood pressures among patients in the two groups at each follow-up visit is provided in Figure S2.

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

PRIMARY OUTCOME

The median follow-up duration was 3.0 years (IQR, 2.0 to 3.9). A primary-outcome event (cardiovascular death, nonfatal type 1 myocardial infarction, nonfatal ischemic stroke, or urgent revascularization) occurred in 118 of 1237 patients (9.5%) in the polypill group and in 156 of 1229 (12.7%) in the usual-care group (hazard ratio, 0.76; 95% CI, 0.60 to 0.96; P<0.001 for

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

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

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

noninferiority; P=0.02 for superiority) (Fig. 1A and Table 3). A key secondary-outcome event (a composite of cardiovascular death, type 1 myocardial infarction, or ischemic stroke) occurred in 101 patients (8.2%) in the polypill group and in 144 (11.7%) in the usual-care group (hazard ratio, 0.70; 95% CI, 0.54 to 0.90; P=0.005) (Fig. 1B).

All components of the primary outcome contributed to the observed treatment effect (Fig. S3).

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

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

* Treatment adherence was measured with the use of the eight-item Morisky Medication Adherence Scale, which ranges from 0 to 8, as follows: low adherence, <6; medium adherence, 6 to <8; and high adherence, 8.

† The risk ratio was calculated as the probability of high treatment adherence as compared with low or medium adherence in the polypill group as compared with the usual-care group. The 95% confidence intervals were not adjusted for multiple testing and should not be used to infer definitive treatment effects.

Cardiovascular death occurred in 48 patients (3.9%) in the polypill group and in 71 (5.8%) in the usual-care group (hazard ratio, 0.67; 95% CI, 0.47 to 0.97). The frequency of death from any cause was similar in the two groups (hazard ratio, 0.97; 95% CI, 0.75 to 1.25) (Table S13). Treatment effects with respect to the primary outcome in prespecified subgroups (according to country, age, sex, and the presence or absence of diabetes, chronic kidney disease, and previous vascular event) are shown in Figure 2. Results of the per-protocol analyses were consistent with those of the primary analyses (Table S14). Sensitivity analyses with respect to the primary and secondary outcomes after adjustment for sex, age (<75 years or ≥75 years), and the presence or absence of diabetes, chronic kidney disease, and previous vascular events also remained consistent (Table S15). Analyses that were stratified according to trial center are shown in Table S16. The results of sensitivity analyses were consistent with those of the primary analysis; in these analyses, death from noncardiovascular causes was considered as a competing risk for the primary outcome, for the key secondary outcome, and for cardiovascular death; death from any cause was considered as a competing risk for type 1 myocardial infarction, ischemic stroke, and urgent revascularization (Table S17).

ADVERSE EVENTS

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

DISCUSSION

In the SECURE trial, a treatment strategy for secondary prevention with a polypill containing aspirin, ramipril, and atorvastatin in older patients with recent myocardial infarction resulted in a lower risk of major adverse cardiovascular events than a usual-care strategy of administration of medications on the basis of current European Society of Cardiology guidelines. The results were consistent regardless of country, age, sex, or the presence or absence of diabetes,

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chronic kidney disease, or previous revascularization. The trial results are broadly applicable to the general population, especially considering that the average age at the time of a first myocardial infarction is now 65.6 years for men and 72.0 years for women,[21] along with the high prevalence of diabetes mellitus, chronic kidney disease, and previous coronary artery disease in these patients.[13,21] Table S19 provides detailed information on the representativeness of the patients who were included in the trial.

The risk reductions that were observed in the polypill group may be explained partly by increased adherence.[22] In a trial involving patients with recent myocardial infarction, investigators assessed pharmacy claims to investigate the relationship between adherence to the prescribed drugs and the risk of major adverse cardiovascular events. They found that cardiovascular risk was 27% lower among the patients with a high degree of adherence than among those with a low degree of adherence.[8] In another similar trial with a 2-year follow-up, investigators found that patients who received a polypill containing aspirin, ramipril, and atorvastatin for secondary prevention had a 27% lower frequency of recurrent cardiovascular events than those who received other treatments for lowering lipid levels and blood pressure.[23] These results are consistent with those of our trial and support the hypothesis that the use of a polypill strategy as secondary prevention in older patients reduces the risk of recurrent cardiovascular events, at least partly through increased adherence.

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

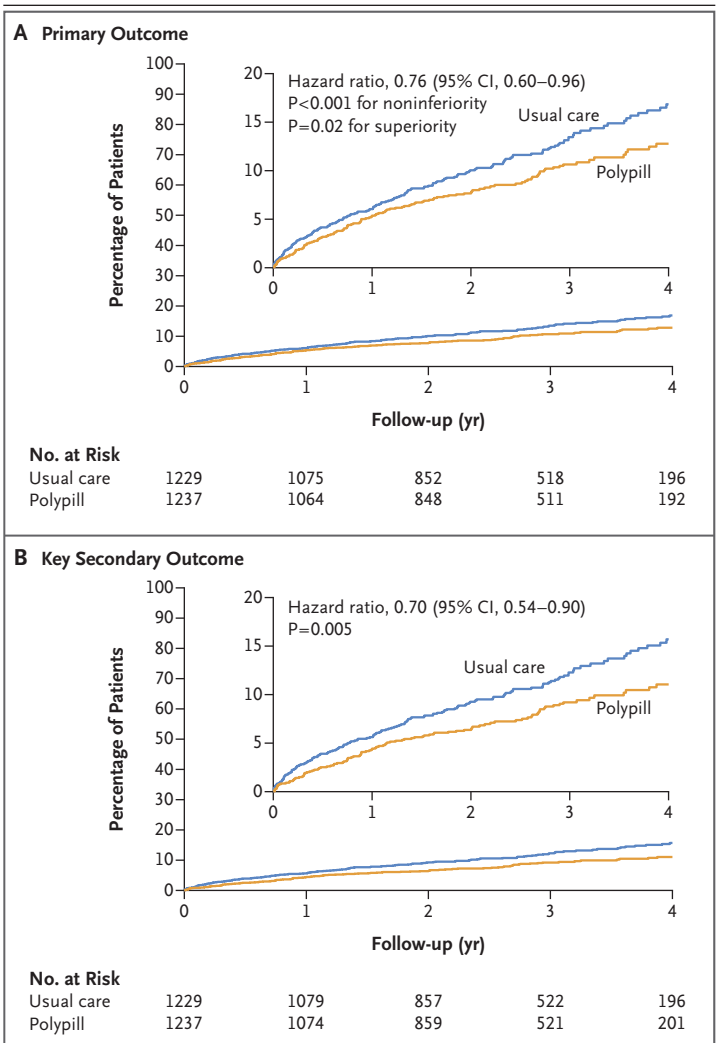

Figure 1. Primary and Key Secondary Outcome at a Median of 36 Months. Panel A shows the cumulative incidence of a primary-outcome event (death from cardiovascular causes, nonfatal type 1 myocardial infarction, nonfatal ischemic stroke, or urgent revascularization) in the polypill group and the usual-care group. Panel B shows the cumulative incidence of a key secondary-outcome event (cardiovascular death, nonfatal type 1 myocardial infarction, or nonfatal ischemic stroke). The insets show the same data on an expanded y axis.

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

The incidence of death from any cause was similar in the two groups. Although there was no substantial between-group difference in the incidence of death from noncardiovascular causes,

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Table 3. Primary and Secondary Outcomes.

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

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

more cases were observed in the polypill group than in the usual-care group, driven mainly by cancer deaths (21 in the polypill group vs. 11 in the usual-care group). This finding may be explained by competing risks between cardiovascular and cancer mortality[27] — in other words, fewer cardiovascular deaths in the polypill group left more patients vulnerable to die from noncardiovascular causes (e.g., cancer), particularly in consideration of the average age of the patients and the fact that 55% were current or previous smokers. Adverse events were similar in the two groups.

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

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

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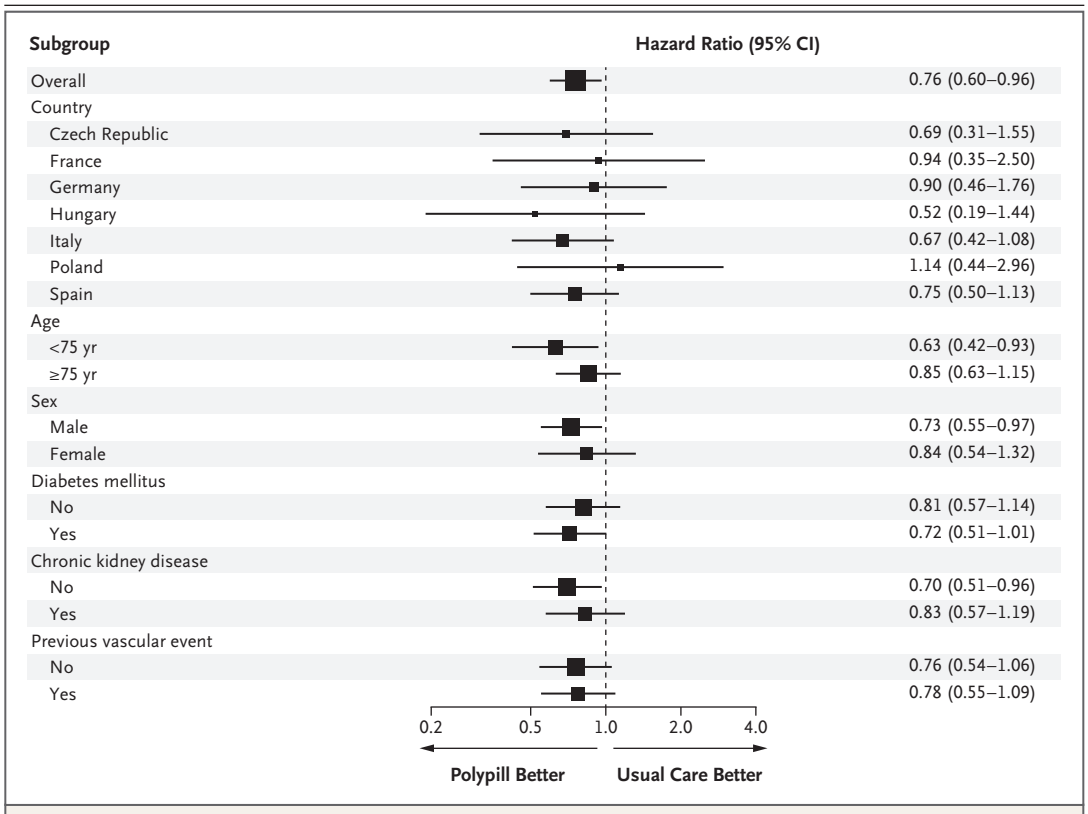

Figure 2. Primary Composite Outcome, According to Subgroup.

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

egy to improve accessibility and adherence to treatment, thus decreasing the risk of recurrent disease and cardiovascular death.

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

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

APPENDIX

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