

## Study Protocol



# Effectiveness of Polypill for Prevention of Cardiovascular Disease (PolyPars): Protocol of a Randomized Controlled Trial

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## Abstract

**Background:** Cardiovascular diseases (CVDs) are the leading cause of death in Iran. A fixed-dose combination therapy (polypill) was proposed as a cost-effective strategy for CVD prevention, especially in lower-resource settings. We conducted the PolyPars trial to assess the effectiveness and safety of polypill for prevention of CVD.

**Methods:** The PolyPars trial is a pragmatic cluster randomized controlled trial nested within the Pars Cohort Study. Participants were randomized to an intervention arm and a control arm. Participants in the control arm received minimal non-pharmacological care, while those in the intervention arm received polypill in addition to minimal care. The polypill comprises hydrochlorothiazide 12.5 mg, aspirin 81 mg, atorvastatin 20 mg, and either enalapril 5 mg or valsartan 40 mg. The primary outcome of the study is defined as the first occurrence of acute coronary syndrome (non-fatal myocardial infarction and unstable angina), fatal myocardial infarction, sudden cardiac death, new-onset heart failure, coronary artery revascularization procedures, transient ischemic attack, cerebrovascular accidents (fatal or non-fatal), and hospitalization due to any of the mentioned conditions. The secondary outcomes of the study include adverse events, compliance, non-cardiovascular mortality, changes in blood pressure, fasting blood sugar, and lipids after five years of follow-up.

**Results:** From December 2014 to December 2015, 4415 participants (91 clusters) were recruited. Of those, 2200 were in the polypill arm and 2215 in the minimal care arm. The study is ongoing. This trial was registered with ClinicalTrials.gov number NCT03459560.

**Conclusion:** Polypill may be effective for primary prevention of CVDs in developing countries.

**Keywords:** Cardiovascular prevention, Non-communicable disease risk factors, Polypill

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## Introduction

Cardiovascular diseases (CVDs) are major causes of mortality and morbidity worldwide with estimated 17.92 million deaths and 422.7 million prevalent cases in 2015<sup>1</sup> and a 16% increase in disability-adjusted life years during the last decade.<sup>2</sup> Global deaths due to CVDs increased by 41% from 1990 to 2013 in spite of a 39% decrease in age-specific death rates. The increase was driven by aging of populations and population growth.<sup>3</sup> In Iran, CVD

causes over 50% of non-communicable disease mortality in middle and old age adults.<sup>4,5</sup>

Diagnosis and treatment of CVD are expensive and may not be available, especially in low-resource settings. When available, the cost of clinical care, hospitalization and rehabilitation is huge and imposes a real burden on health care systems and governments. Prevention of CVD is possible by reducing the prevalence of risk factors (hypertension, dyslipidemia, low physical activity and

smoking) and could have greater impact on controlling the burden of CVD compared to the effects of therapeutic strategies, especially in low and middle-income countries (LMICs).<sup>5-7</sup> In spite of public health attempts and media efforts, widespread healthy lifestyle improvement to prevent CVD is quite difficult to maintain, especially in LMIC.<sup>6</sup> In addition to lifestyle improvement, the effectiveness of antiplatelet, lipid-lowering and blood pressure-lowering agents has been clearly shown by several trials<sup>8,9</sup> but lack of access and pill burden decrease adherence to preventive medications and contribute to the shortfall in preventive drug coverage<sup>10-12</sup>

Polypill, first proposed by Wald and Law in 2003 as a fixed-dose combination therapy, was estimated to increase adherence and to reduce CVD by more than 80%.<sup>13,14</sup> Following a pilot feasibility study,<sup>15</sup> we recently published the results of the first large-scale cluster randomized controlled trial powered for clinical outcomes evaluating the effectiveness of a population-level polypill strategy for primary and secondary prevention of CVD in predominantly rural Turkmen residents in northeastern Iran.<sup>16,17</sup> The median adherence rate was 80%; compared with usual care, the polypill strategy was associated with a 34% (95% confidence interval: 20%–45%) relative risk reduction of major CVD events over five years, with similar rate of adverse events between the two groups. We concluded that the polypill approach is safe and highly effective, with the potential to significantly reduce the population burden of CVD, particularly in low- and middle-income countries.<sup>16,17</sup> However, in the current study, we aim to explore the efficacy and safety of polypill in a completely different setting from our previous study and investigate whether the results are replicable. In the current study, we aim to investigate the effectiveness of polypill in primary and secondary prevention of CVD in predominantly Persian residents of Valashahr in southern Iran where the prevalence of CVDs is higher. We designed the PolyPars trial nested in the already established Pars Cohort Study (PCS) in southern Iran.<sup>18</sup> PolyPars is a pragmatic cluster randomized controlled trial with a parallel exploratory design.

## Materials and Methods

### Overview

The PCS was funded through the joint collaboration of Digestive Diseases Research Institute in Tehran University of Medical Sciences (TUMS) and the Non-Communicable Diseases Research Center in Shiraz University of Medical Sciences (SUMS). The study protocol was approved by the Ethics Committees of both universities. The study was launched in 2012 and recruitment was completed in 2014. The details of the PCS and its protocol have been already published.<sup>18</sup> In short, this cohort study started with the purpose of finding the most important risk factors of non-communicable diseases (NCDs) that lead to >80%

of deaths and disabilities in Valashahr (Baladeh) district in south of Fars province in Iran. All of the 9721 inhabitants in the district aged 40 to 75 years were invited and 9264 inhabitants accepted to participate in this study, with a 95% participation rate. After three years of follow-up, we found out that CVD is the etiology of more than 50% of deaths in the PCS. We decided to explore the most efficient interventions in order to control the risk factors and prevent CVDs in this area. The polypill Study (PolyPars) is a two-arm pragmatic cluster randomized controlled trial, which is nested within the PCS with the aim of assessing the effectiveness of both lifestyle interventions and pharmacological interventions as part of the primary prevention of CVDs and other NCDs. Participants in the control arm receive lifestyle modification advice, defined as minimal care, and those in the intervention arm receive a fixed-dose combination therapy (polypill) in addition to minimal care. All participants in the PCS older than 50 years were invited to take part in PolyPars. After the initial enrollment by the PolyPars team, the eligibility of the participants was evaluated based on strict criteria. After the definition of eligible participants, villages as the units of randomization were randomized into intervention and control arms. Participants residing in villages randomized into the intervention arm were invited once more for prescription of polypills. The outcomes of the study will be compared between the two aforementioned arms. Routine follow-up will be made by outcome assessors in the PCS who are blind to allocation of villages into the two arms. Finally, the analysts will also be blind to randomization of villages.

### Study Setting and Participants

The PCS center (PCSC) located in Valashahr city (Baladeh) was the platform of PolyPars study in both recruitment and follow-up phases. This center covers 91 villages (clusters). The villages are the units of randomization. These villages are close together and the furthest hamlet is only 40 km away from the PCSC. The target population were participants aged 50 years and above. All inhabitants aged 50 years and above at the time of enrollment for PolyPars study were invited to the PCSC by phone calls. A total of 5430 inhabitants were invited. Among them, 426 inhabitants did not refer due to various reasons (Table 1). Participants who accepted the invitation and came to the PCSC at their appointment time were briefed about the trial and if they accepted to be enrolled in the trial, a written informed consent was obtained by the PolyPars team. Participants retain the right to voluntarily withdraw from the trial at any time they wish.

### Data Collection and Management

The PolyPars team consists of a general physician (administrator), nurses, nutritionists, and laboratory assistants who performed the interview and examinations,

**Table 1.** Reasons for not Referring

| Reason                                   | Number |
|--|--------|
| Emigration                               | 201    |
| Death                                    | 43     |
| Immobility                               | 25     |
| Not referring at the time of appointment | 108    |
| Unsuccessful contact                     | 11     |
| Hospitalization                          | 12     |
| Unwillingness to participate             | 32     |
| Total                                    | 432    |

and obtained the biological samples. They recorded demographic characteristics (Table 2), medication history, past medical history, and family history of NCDs and their risk factors. Weight, height, waist and hip circumferences were measured. Blood pressure was checked twice in sitting position five minutes apart, and once in standing position. Ten cc of blood was obtained from each participant. Measurements of fasting blood glucose, lipid profile, liver and kidney function tests and urinalysis were done for all enrolled participants, after ensuring fasting for at least 8 hours. A report of lab results was given to participants a few days later. Data collected during the interview and physical examination in addition to the lab

results were entered into a smart electronic database that did not allow entry of missing information and outliers. Biological specimens were stored at -70 degrees Celsius in freezers for future ancillary genetic and molecular studies. The general physician, as the administrator of the study, actively monitored the entire process of data collection and finally, assessed the eligibility of participants based on the enrollment questionnaire and blood test results.

Data collected in this study will be extracted by staff with the participants' identifiers removed and a unique identification number (ID) provided. Paper documents containing participants' IDs and identifying information are kept in a locked cabinet in the PCS center. All electronic data collected during this study will be stored in password-protected computers. Only research team members will have access to de-identified data and only de-identified data will be used for data analysis.

### Eligibility Criteria

The exclusion criteria consisted of three broad categories: debilitating diseases causing inability to comply, contraindications for any of the components of polypill, or not consenting to participation in the study. A total of 589 participants were excluded based on the exclusion criteria (Table 3.) Patients who had high blood pressure or had disorders in their lab tests were visited by the physician

**Table 2.** Baseline Demographic Characteristics of Referring Versus Non-referring Invitees to Participate in the Study

|                     | Referring    | Non-referring | All          | P Value |
|---------------------|--------------|---------------|--------------|---------|
| All                 | 5004         | 426           | 5430         |         |
| Sex                 |              |               |              |         |
| Female, No. (%)     | 2762 (55.2%) | 221 (51.9%)   | 2983 (54.9%) | 0.186   |
| Male, No. (%)       | 2242 (44.8%) | 205 (48.1%)   | 2447 (45.1%) |         |
| Age years mean (SD) | 57.1 (6.9)   | 57.5 (7.5)    | 57.1 (6.9)   | 0.266   |
| Ethnicity           |              |               |              |         |
| Fars                | 2840 (56.7%) | 219 (51.4%)   | 3059 (56.3%) | 0.089   |
| Turk                | 1920 (38.4%) | 186 (43.7%)   | 2106 (38.8%) |         |
| Other               | 244 (4.9%)   | 21 (4.9%)     | 265 (4.9%)   |         |
| Marital status      |              |               |              |         |
| Married             | 4393 (87.8%) | 361 (64.7%)   | 4754 (87.6%) | 0.067   |
| Non-married         | 611 (12.2%)  | 65 (15.3%)    | 676 (12.4%)  |         |
| Education           |              |               |              |         |
| Literate            | 1889 (37.7%) | 138 (32.4%)   | 2027 (37.7%) | 0.028   |
| Illiterate          | 3115 (62.3%) | 288 (67.6%)   | 3403 (62.7%) |         |
| Wealth score        |              |               |              |         |
| Quintile 1          | 1231 (24.6%) | 145 (34.0%)   | 1376 (25.3%) | < 0.001 |
| Quintile 2          | 867 (17.3%)  | 74 (17.4%)    | 941 (17.3%)  |         |
| Quintile 3          | 1126 (22.5%) | 81 (19.0%)    | 1207 (22.2%) |         |
| Quintile 4          | 851 (17.0%)  | 59 (13.9%)    | 910 (16.8%)  |         |
| Quintile 5          | 929 (18.6%)  | 67 (15.7%)    | 996 (18.4%)  |         |

SD, standard deviation.

**Table 3.** Exclusion Criteria among Recruited Participants

| Exclusion Criteria  | Female, N (%) | Male, N (%) | Both, N (%) |
|---|---------------|-------------|-------------|
| Hypersensitivity to one component of polypill   | 26 (0.94%)    | 13 (0.58%)  | 39 (0.78%)  |
| History of angioedema   | 10 (0.36%)    | 2 (0.09%)   | 12 (0.24%)  |
| History of gastrointestinal bleeding or peptic ulcer disease in the last three months | 23 (0.83%)    | 42 (1.87%)  | 65 (1.30%)  |
| History of stroke   | 29 (1.05%)    | 30 (1.34%)  | 59 (1.18%)  |
| Bleeding disorders such as hemophilia   | 0 (0%)        | 1 (0.04%)   | 1 (0.02%)   |
| Regular anticoagulant use   | 15 (0.54%)    | 9 (0.40%)   | 24 (0.48%)  |
| Advanced liver disease  | 7 (0.25%)     | 4 (0.18%)   | 11 (0.22%)  |
| Uncontrolled seizures   | 22 (0.80%)    | 12 (0.54%)  | 34 (0.68%)  |
| Asthma  | 35 (1.27%)    | 24 (1.07%)  | 59 (1.18%)  |
| History of gout   | 2 (0.07%)     | 5 (0.22%)   | 7 (0.14%)   |
| Serum creatinine >2 mg/dL   | 2 (0.07%)     | 14 (0.62%)  | 17 (0.34%)  |
| Glomerular filtration rate <30 mL/min   | 17 (0.62%)    | 13 (0.58%)  | 30 (0.60%)  |
| Hemoglobin <10 mg/dL in females and <11 mg/dL in males                                | 50 (1.81%)    | 32 (1.43%)  | 82 (1.64%)  |
| Systolic blood pressure <90 mm Hg and diastolic blood pressure <60 mm Hg              | 60 (2.17%)    | 48 (2.14%)  | 108 (2.16%) |
| Debilitating medical/mental disorders affecting compliance                            | 46 (1.67%)    | 29 (1.29%)  | 75 (1.50%)  |

of the team and referred to their family physician for appropriate therapy.

### Interventions

Lifestyle modification such as low-calorie and low-salt food, exercise, and smoking and opium cessation were explained to all eligible participants upon enrollment in the trial and during the follow-up visits. This clinical trial consisted of two arms: a minimal care arm and a polypill arm. In the minimal care arm, the PolyPars team explained the role of healthy lifestyle to participants in detail. If any participant was found to have high blood pressure or abnormal blood test, he was advised to consult with his family physician. If any of the participants received any medications for their diagnosed CVD, hypertension, hyperlipidemia, or diabetes, their medication was recorded and added to the database. The PolyPars team additionally offered illustrated pamphlets addressing lifestyle modifications and explaining their components.

In the intervention arm, in addition to minimal care, the PolyPars team prescribed polypill, which is a fixed-dose combination of four components: atorvastatin (20 mg), aspirin (81 mg), hydrochlorothiazide (12.5 mg), and enalapril (5 mg). This combination was named polypill E. In case participants had a history of coughs with angiotensin-converting enzyme (ACE) inhibitors or developed this side effect during the trial, their medication was changed to polypill V, which contains valsartan (40 mg) instead of enalapril. In patients who already used any components of polypill or other blood pressure lowering, lipid lowering, or antiplatelet drugs, we adjusted the dose of their medications additional to polypill.

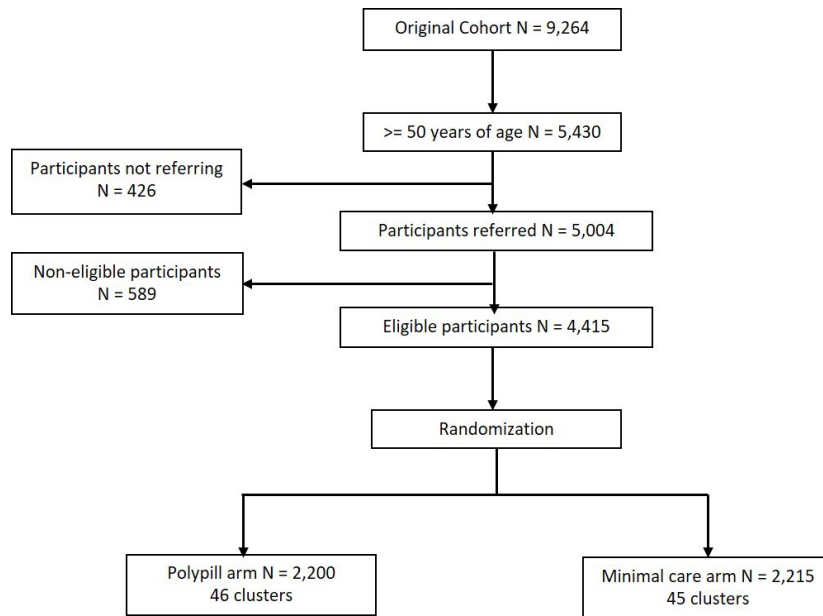
### Randomization, Allocation Concealment, and Blinding

After the baseline enrollment and excluding non-eligible participants, we randomized the villages to polypill and control arms. We used this type of randomization in order to avoid contamination. We divided the villages to six main groups based on the number of their inhabitants who were eligible and willing to participate. We used block randomization for each group of villages using a computer generated list of numbers. The random allocation sequence was produced by an independent statistician who was blinded to recruitment and intervention among participants. Participants and the PolyPars team could not be blinded, but outcome assessors and statisticians were blinded to group allocation.

After randomization, eligible participants living in villages randomized to the intervention arm were invited again to the PCSC. After full explanation of study procedures, polypill components, and its benefits and probable adverse reactions, the PolyPars team obtained written informed consent from all participants in the polypill arm once more. From December 2014 to December 2015, 4415 participants (91 clusters) were recruited. Of those, 2200 were in the polypill arm and 2215 in the minimal care arm. The study is ongoing. Figure 1 demonstrates the phases of recruiting participants.

### Exposures and Outcomes of Interest

The exposures of interest in the current study were: demographic characteristics, anthropometric indices, blood pressure, past medical history, medication history, and family history of diseases. The primary outcomes of interest were five-year occurrence of any major cardiovascular event. The outcome includes both fatal



**Figure 1.** The Profile of the Trial.

and non-fatal events. Fatal events include fatal myocardial infarction, sudden cardiac death, or death due to new-onset heart failure or stroke, either ischemic or hemorrhagic. Non-fatal events may be stable or unstable angina, non-fatal myocardial infarction, any symptoms and signs of acute coronary syndrome or non-fatal stroke, or transient ischemic attack which lead to hospitalization or needing coronary artery revascularization procedures. In all cases, all existing documents including both outpatient and inpatient records will be collected to determine the occurrence of major cardiovascular event (MCVE).

In case of a death or a CVD event, the central PCS team who are blind to the study arms visit the participant's home and the medical centers in which any major diagnostic or therapeutic procedures were done. The team collects all clinical reports, pathology reports, and hospital records, and any tumor samples that are available. For deceased participants, a verbal autopsy will be also performed.<sup>19</sup> The team in charge of ascertaining the cause of death are blind to the study arms and work independently from the personnel in the PolyPars team. In case of non-fatal events, all existing documents will be collected in a similar fashion. Two external internists independently review all available clinical documents and allocate a disease code and a date of occurrence to each outcome. The two disease codes are compared, and if they are different, a third senior internist reviews the data and makes the final decision on the code.<sup>18,19</sup> For participants with more than one event, the first event will be included in the primary outcome analysis.

Secondary outcomes of interest include the number of participants developing adverse events, non-cardiovascular causes of death, adherence to polypill based on pill count, and changes in blood pressure, fasting blood sugar, and

lipid profile during the trial. The results will be reported by subgroups including sex and age subgroups; presence or absence of pre-existing CVD, hypertension, diabetes, impaired lipid profile; and history of ever smoking or ever use of opium.

#### Follow-up

Follow-ups are scheduled for 1, 3, and 6 months after the initial enrollment in the polypill arm and every six months thereafter. For the minimal care arm, the follow-ups are arranged every six months. Follow-up visits are conducted by the PolyPars team in the PCSC and are designed to continue for five years after initial recruitment. At follow-up visits, the blisters of the polypills are monitored for pill count and new pills are prescribed for participants in the intervention arm. The occurrence of adverse effects will be explored, as well. Participants in both arms are interviewed to record new-onset symptoms and to continue participation.

#### Sample Size Estimation

As this trial is a pragmatic study nested within an existing population-based cohort, even if participants do not adhere to polypill or minimal care or do not comply with the PolyPars trial follow-ups, it will be still possible to collect primary outcome data for the majority of these participants in the context of PCS follow-up. Therefore, we allowed only for a 20% loss to follow-up rate. Given the MCVE rate of 0.0182 per year in PCS (unpublished data), we anticipated the risk of MCVE to be approximately 0.088 over 5 years. Unpublished data suggest the intra-class correlation to be around 0.005. With the available 91 clusters, and coefficient of variation of cluster sizes of 0.9, the study will have an approximately 80% power, at

5% significance, to detect a relative risk of 0.65, if 1620 participants were recruited in each arm. Considering the 20% dropout upon designing this study, we anticipated that the total required sample size would consist of 2025 participants in each arm. We finally invited and recruited all participants aged 50 years and above in the PCS, constituting 2200 in the polypill arm and 2215 in the minimal care arm. Sample size calculations were carried out using the `clustersampsi` function in Stata version 11.

### Statistical Planning

As cluster randomization was performed at the level of villages, we will use appropriate statistical methods to account for the clustering effect. The blinded results will be given to the Data Monitoring Committee (DMC). The members of DMC meet every six months and even travel to the field to evaluate the process of the study and to declare their confirmation for continuation of the study. DMC would consider the data for possible early termination of the study due to efficacy, futility, or harm. However, there is limited reason to suspect any harm (as each component is in use independently) and it is also unlikely that the effect will be so large for clear differences to be observed so early. The process will be independent from the investigators and the funders.

We will use univariate and multivariate survival analyses to compare the occurrence of outcomes between the two arms of the study. The null hypothesis (no difference) for the primary outcome would be tested using a random effects Cox proportional hazards model with time to the primary outcome and censoring those who are lost to follow-up or those who die from other causes. The primary analysis will be unadjusted. Secondary analysis will adjust for baseline covariates including age, sex, diabetes mellitus, blood pressure, and history of MCVE.

Null hypotheses for secondary outcomes would be similar to that for the primary outcome. Secondary outcomes are either binary (such as non-cardiovascular mortality), or continuous (such as systolic blood pressure), and therefore, either logistic or linear link functions within a generalized linear model with random effects will be used. Transformations will be made where appropriate to accommodate any non-normality.

All model assumptions will be checked, goodness of fit will be explored, and alternative models will be considered if necessary. All outcomes will be considered significant at the 5% level. The significance of subgroup effects will be assessed by testing interactions of covariates with the outcome of treatment. We will also investigate differences in outcomes by subgroup of adherence (low, medium, high) and will explore whether adherence is related to baseline measures.

### Patient and Public Involvement

Before the actual recruitment, we invited a number of

PCS participants over 50 years of age from various villages to the PCS center to assess the response rate, the attitude of the invitees, and the reliability and validity of all data collection procedures including interviews, physical exams, and collection of biological specimens. We incorporated the comments of the invitees, finalized our data collection instruments, and designed the trial accordingly. Upon actual recruitment, all participants older than 50 years in Valashahr were invited to the PCS center and we evaluated their willingness to take part in the study. The invitees visited the site and we fully explained the details, objectives, and outcomes of the study. Written informed consent was obtained twice. Visits were scheduled according to availability of participants. We delivered the laboratory results at the baseline of the study in written format to all participants. We will send the final written results of the study to all participants upon completion of the study.

### Dissemination

The findings of this study will be circulated at local, national, or international conferences and the manuscripts will be submitted to peer-reviewed journals. The main results of this study will also be shared with all participants and will be disseminated among researchers, health service providers, healthcare professionals, and the public through demonstrations, courses, and the internet regardless of the magnitude or direction of the effects.

### Results

Out of the 9264 participants of the original PCS, a total of 5430 participants from 50 to 75 years of age were invited. A total of 5004 participants responded while 426 invitees did not refer to the center. Our analyses show that there were not significant differences in the main general demographic characteristics between the referring and non-referring invitees. The reasons of non-referring are demonstrated in Table 1. The differences between referring and non-referring invitees are demonstrated in Table 2. There were significant differences in education and socio-economic status between referring and non-referring invitees. The referring invitees generally had higher education and were wealthier compared to non-referring invitees.

Out of the entire 5004 referring invitees, a total of 589 participants were considered to be non-eligible for participating in the trial. The reasons for non-eligibility and the number of invitees excluded based on these criteria are demonstrated in Table 3.

After excluding 589 invitees, the remaining 4415 participants were randomized: 2200 to the polypill arm and 2215 to the control arm. The baseline characteristics of these two groups are demonstrated in Table 4 and anthropometric indices, blood pressure, and biomarkers are demonstrated in Table 5.

At the time of enrollment, we asked about past medical

**Table 4.** Baseline Characteristics of Participants in the Polypill and Control Arms

|                    | Polypill     | Control       | All          |
|--------------------|--------------|---------------|--------------|
| All                | 2200         | 2215          | 4415         |
| Sex                |              |               |              |
| Female, N (%)      | 1209 (54.9%) | 1220 (55.1%)  | 2429 (55.0%) |
| Male, N (%)        | 991 (45.1%)  | 995 (44.9%)   | 1986 (45.0%) |
| Age (y), mean (SD) | 59.8 (6.7)   | 59.9 (6.8)    | 59.9 (6.7)   |
| Ethnicity          |              |               |              |
| Fars               | 1294 (58.8%) | 1180 (53.3%)  | 2474 (56.0%) |
| Turk               | 834 (37.9%)  | 888 (40.1%)   | 1722 (39.0%) |
| Other              | 72 (3.3%)    | 147 (6.6%)    | 219 (5.0%)   |
| Marital Status     |              |               |              |
| Married            | 1941 (88.2%) | 1,933 (87.3%) | 3874 (87.8%) |
| Non-married        | 259 (11.8%)  | 282 (12.7%)   | 541 (12.2%)  |
| Education          |              |               |              |
| Literate           | 881 (40.1%)  | 786 (35.5%)   | 2748 (62.2%) |
| Illiterate         | 1319 (59.9%) | 1429 (64.5%)  | 1667 (37.8%) |
| Wealth             |              |               |              |
| Quintile 1         | 531 (24.1%)  | 535 (24.2%)   | 1066 (24.1%) |
| Quintile 2         | 352 (16.0%)  | 416 (18.8%)   | 768 (17.4%)  |
| Quintile 3         | 481 (21.9%)  | 521 (23.5%)   | 1002 (22.7%) |
| Quintile 4         | 384 (17.5%)  | 354 (16.0%)   | 738 (16.7%)  |
| Quintile 5         | 452 (20.5%)  | 389 (17.6%)   | 841 (19.1%)  |

SD, standard deviation.

**Table 5.** Baseline Anthropometric Measurements, Blood Pressure Level, and Main Lab Markers in the Polypill and Control Arms

|                              | Polypill     | Control      | All          |
|------------------------------|--------------|--------------|--------------|
| All                          | 2200         | 2215         | 4415         |
| BMI, mean (SD)               | 25.9 (4.7)   | 25.7 (4.6)   | 25.8 (4.6)   |
| SBP, mean (SD)               | 123.5 (19.3) | 126.3 (20.0) | 124.9 (19.7) |
| DBP, mean (SD)               | 77.8 (11.8)  | 79.6 (12.0)  | 78.7 (12.0)  |
| Total cholesterol, mean (SD) | 201.3 (42.6) | 201.1 (42.2) | 201.2 (42.4) |
| HDL                          | 47.2 (11.5)  | 49.1 (11.4)  | 48.2 (11.5)  |
| LDL                          | 122.0 (34.5) | 119.2 (34.7) | 120.6 (34.6) |
| Triglyceride                 | 160.9 (97.0) | 164.5 (88.7) | 162.7 (92.9) |
| FBS                          | 107.7 (38.6) | 108.8 (37.4) | 108.2 (38.0) |
| Creatinine                   | 0.99 (0.22)  | 1.00 (0.31)  | 1.00 (0.27)  |
| AST                          | 19.0 (9.4)   | 18.7 (9.9)   | 18.9 (9.7)   |
| ALT                          | 17.9 (10.5)  | 18.1 (13.7)  | 18.0 (12.2)  |
| ALP                          | 247.3 (72.8) | 246.4 (73.8) | 246.8 (73.3) |
| GGT                          | 23.3 (16.5)  | 23.5 (18.1)  | 23.4 (17.3)  |
| Hemoglobin                   | 13.4 (1.5)   | 13.4 (1.5)   | 13.4 (1.5)   |
| Platelet                     | 248.9 (65.8) | 247.0 (76.9) | 247.9 (71.6) |

SD, standard deviation; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HDL, high density lipoprotein; LDL, low density lipoprotein; FBS, fasting blood sugar; AST, aspartate aminotransferase; ALT, Alanine aminotransferase; ALP, alkaline phosphatase; GGT, gamma-glutamyl transferase.

**Table 6.** Cardiovascular Disease, Risk Factors, and Medication Use in the Intervention and Control Arms

|   | Polypill, N (%) | Control, N (%) |
|---|-----------------|----------------|
| CVD self-report                             | 354 (16.1)      | 359 (16.2)     |
| Antihypertensive medication in CVD          | 269 (76.0)      | 283 (78.8)     |
| Lipid lowering medication in CVD            | 178 (50.3)      | 174 (48.5)     |
| Aspirin in CVD                              | 265 (74.9)      | 279 (77.7)     |
| Hypertension self-report                    | 680 (30.9)      | 642 (29.0)     |
| Antihypertensive medication in hypertension | 616 (90.6)      | 605 (94.3)     |
| Hyperlipidemia self-report                  | 501 (22.8)      | 491 (22.2)     |
| Lipid lowering medication in hyperlipidemia | 347 (69.3)      | 351 (71.5)     |
| Diabetes self-report                        | 279 (12.7)      | 276 (12.5)     |
| Glucose lowering medication in diabetes     | 233 (83.5)      | 219 (79.4)     |

CVD, cardiovascular disease.

history. Diseases such as CVDs including ischemic heart disease and cerebrovascular accidents and diabetes, and risk factors such as hypertension and hyperlipidemia were inquired based on past diagnosis made by a physician. Table 6 demonstrates the number and percentage of patients suffering from these diseases and the proportion of patients who receive appropriate medication.

## Discussion

The PolyIran trial recently published by our team provided substantial evidence for effectiveness of polypill in the prevention of CVD with particular emphasis for low- and middle-income countries where 80% of the global CVD burden resides and where larger preventive treatment gaps exist.<sup>16,20</sup> Availability of low-cost polypills, including aspirin for people under age 75 with risk factors or established CVD, can help nations to achieve the United Nations Sustainable Development Goal (SDG) to reduce premature mortality due to CVD by a third in low- and middle-income countries until 2030.<sup>21</sup> This, in turn, requires substantial progress in overcoming regulatory and system-level barriers and developing effective implementation strategies across diverse settings.

It is also very important to test the efficacy of polypill in different populations and ethnicities with different patterns of genetic and environmental risk factors and dietary patterns.<sup>20,22,23</sup> In the PolyPars trial, we investigate the efficacy of polypill in southern Iran in a population of different ethnicities with different patterns of diet and environmental risk factors.<sup>18</sup> When deciding to use polypill as a national strategy for prevention of CVDs, the results of the PolyPars study will help the policy maker for better decision making. The PolyPars study has several strengths. All participants are annually followed-up by PCS personnel through phone calls. Therefore, we used the existing infrastructure of the PCS to minimize follow-up losses. The primary endpoints, CVD events and

deaths, are autonomously evaluated over the cohort study. Enrolling individuals with and without established CVD permits us to compare the effect of polypill in primary and secondary prevention. In this study, the participants and PolyIran team are not blind to the allocated interventions. Placebo is not used in this study. Therefore, we can predict polypill adherence in general population more convincingly than placebo controlled trials. We plan to continue the study for the coming five years in this multi-ethnicity population, which will help us to generalize the results of this study to all Iranians. One major limitation of this study is the fact that most of the participants of this trial are illiterate, inhabit a rural area, and have low socio-economic status.

#### Authors' Contribution

FM, SGS, HP, and RM contributed to the conception and design of the work. All authors contributed to the acquisition, analysis, or interpretation of data for the work. FM, SGS, and RM drafted the manuscript. AG, ZM, HP, MM, MRF, MM, AA, RM, ShSB, VM, FA, and SM critically revised the manuscript. All authors gave final approval and all authors agree to be accountable for all aspects of work ensuring integrity and accuracy.

#### Conflict of Interest Disclosures

The author(s) declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

#### Ethical Statement

The study protocol was approved by the Ethics Committees of both Tehran and Shiraz Universities of Medical Sciences to conform to the ethical guidelines of the Declaration of Helsinki and the International Conference for Harmonization Guidelines for Good Clinical Practice. The protocol was registered at ClinicalTrials.gov (ClinicalTrials.gov ID: NCT03459560).

Individual written informed consent was obtained from participants in the study twice: once at the time of enrollment from all participants and once after randomization of participants into the intervention arm.

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