

Effectiveness of polypill for primary and secondary prevention of cardiovascular diseases (PolyIran)

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A pragmatic cluster randomized controlled trial of the effectiveness of polypill for primary and secondary prevention of cardiovascular diseases: results from the PolyIran study

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Abstract

Background: Cardiovascular diseases (CVDs) continues to be the leading cause of death worldwide. A fixed-dose combination therapy (“polypill” strategy) was proposed as a cost-saving method for CVD prevention, especially in lower resource settings. We conducted the PolyIran Study to assess the effectiveness and safety of a four-component polypill including aspirin, atorvastatin, hydrochlorothiazide and either enalapril or valsartan, for primary and secondary prevention of CVD.

Methods: The PolyIran study is a two-arm pragmatic cluster randomized trial nested within the Golestan Cohort Study (GCS). The sampling frame for the PolyIran study was rural GCS participants aged 50 years or older. Considering villages as clusters, and using a cluster randomization, the study participants were allocated to a package of non-pharmacological preventive interventions either alone (minimal care arm) or together with a once daily polypill (polypill arm). All participants were followed for 60 months and the primary outcome was occurrence of major cardiovascular events (MCVE). The risk of MCVE between the two arms was compared using Cox regression models, with shared frailty models.

Findings: Overall, 6841 individuals were enrolled in the study, including 3,417 (in 116 clusters) in the minimal care arm and 3,421 (in 120 clusters) in the polypill arm. Median (interquartile range) adherence to polypill tablets was 80.5% (48.5-92.2). During the follow up, 202 and 301 participants in the polypill arm and minimal care arm respectively had one or more MCVE, representing a 34% reduction (adjusted hazard ratio [HR]=0.66; 95% confidence interval [CI]: 0.55-0.80) in risk of MCVE in the polypill arm. The risk of MCVE in participants with high adherence was significantly lower when compared with the minimal care arm (adjusted HR=0.43; 95%CI: 0.33-0.55). The effect of polypill was stronger in participants without pre-existing CVD (primary prevention group) (HR=0.61, 95% CI: 0.49-0.75) than those with history of CVD (secondary prevention group) (HR=0.80, 95% CI: 0.57-1.12) (p-value for interaction=0.19). Overall, the frequency of adverse events was comparable between the two arms.

Interpretation: The PolyIran study is the first large scale pragmatic trial with long term follow up demonstrating the effectiveness of a fixed-dose combination therapy in primary and secondary prevention of CVDs. Our results showed high medication adherence and the risk of adverse events was similar between the two arms. The polypill strategy may be

considered as an additional effective component in controlling CVDs, especially in low resources settings.

Key words: Cardiovascular Diseases, Primary Prevention, Secondary Prevention, Fix dose combination Drug Therapy

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Trial registration: The protocol of the PolyIran study was registered with clinicaltrials.gov, number NCT01271985.

Introduction:

Cardiovascular diseases (CVDs) are the main cause of death and a major cause of health loss worldwide with estimated 422.7 million prevalent cases and 17.92 million deaths in 2015¹ and a 16% increase in disability-adjusted life years (DALYs) during the last decade.² The highest age standardized prevalence of CVDs was found in West Africa, Morocco, Iran, Oman, Zambia, Mozambique, and Madagascar.¹ The age standardized disability-adjusted life years (DALYs) rates of CVD was considerably higher in the Eastern Mediterranean Region (EMR) than in other regions,³ suggesting greater burden of CVD in low-resources settings.

Data from the GBD project suggest that according to current trends, the United Nation Sustainable Development Goal (SDG) to reduce premature mortality due to CVD by a third in 2030 will not be possible for majority of low- and middle-income countries (LMICs).⁴⁻⁶ Ischemic heart disease (IHD) and stroke are the primary causes of death among middle aged and older Iranian adults and occur at a relatively younger age in Iran compared to high-income countries.^{7,8} The Golestan Cohort Study (GCS)⁹ is the largest prospective study in central and Western Asia and was primarily intended to study the etiology of very prevalent esophageal cancer in Northeastern Iran. However, it revealed that 63.3% of all deaths occurred prematurely with IHD accounting for 33.9% of all premature deaths, followed by stroke (14.0%). The results of the GCS also suggested that 30% and 64% of all CVD-related deaths were occurred in participants below 60 and 70 years old, respectively.⁷

The strategy of a fixed-dose combination therapy (“polypill”) administered to asymptomatic adults was proposed to increase adherence^{10,11} and it was believed that it could reduce CVD by more than 80%.¹² It is also cost-saving when compared to usual care.¹³ Different formulations of polypill were used in several studies worldwide.¹⁴⁻²¹ The results of a pilot study from Iran suggested that a polypill consisted of aspirin 81 mg, enalapril 2.5 mg, atorvastatin 20 mg and hydrochlorothiazide 12.5 mg was well tolerated and participants' compliance to the polypill was satisfactory, with modest reductions in blood pressure and lipid levels.²² It also confirmed the feasibility of a fully powered trial to investigate the impact of the polypill on major cardiovascular events (MCVE). Therefore, the PolyIran study was designed to assess the effectiveness of a four-component polypill including aspirin (80 mg), atorvastatin, (20 mg), hydrochlorothiazide (12.5 mg) and either enalapril (5 mg) or valsartan (40 mg), together with advice on lifestyle modification for primary and secondary prevention of CVD compared with advice on lifestyle modification alone.

Methods:

Study setting and sampling frame:

The PolyIran study is a two-arm pragmatic cluster randomized trial nested within the Golestan cohort study (GCS),⁹ a cohort study with 50,045 participants aged 40-75 years from Golestan province in northern Iran. Twenty percent of the GCS participants were enrolled from Gonbad city and 80% from rural areas covering the villages in Gonbad, Aq-Qala and Kalaleh districts. The main aim of the GCS was to investigate esophageal cancer risk factors in this high-risk area. The sampling frame for the PolyIran study included the 28,660 GCS participants from rural areas (villages) aged 50 years and above in 2011 (the beginning of the study).

Sample size justification:

Given the MCVE rate of 0.0171 per year in the GCS (unpublished data), we anticipated the risk of an event to be approximately 0.077 over 5 years. With the available 262 clusters, with an average size of 28 individuals (22 after drop out), and using the upper estimate of the intra-cluster correlation (ICC) of 0.038, coefficient of variation of cluster size of 0.9, considering 80% power, at 5% significance, a clinically important effect size of 0.65 and 20% loss to follow up, a total sample size of 7224 participants (3612 per arm) was calculated for the PolyIran study.

Treatment arms, study population, and randomization:

The study methods and design were described previously.²³ Briefly, from the PolyIran sampling frame, 13,875 individuals were selected using a simple stratified random selection procedure weighted according to the number of eligible inhabitants in each village. These random samples from each village constituted the clusters (262 clusters). Villages (i.e. clusters) were then randomly allocated to a package of non-pharmacological preventive interventions either alone (minimal care arm; 6,883 individuals, 132 clusters) or together with a once daily polypill tablet (polypill arm; 6,992 individuals, 130 clusters). Accordingly, all participants within a cluster were randomized to receive the same intervention. Cluster randomization was used in this study to avoid issues of contamination that would be likely to arise due to sharing of medicines.

Villages (clusters) that were hard to access were excluded from the PolyIran study. Table 1 shows eligibility criteria at individual level.

For the first 48 clusters enrolled in the study, the enrollment team was aware of the allocation of clusters, which resulted an imbalance in covariates and the proportion of ineligible participants between the polypill and minimal care arms. An interim analysis at this point demonstrated that the proportion of subjects who met the exclusion criteria differed between the polypill and minimal care arms, presumably due to preferential behavior of the enrolling physician applying the exclusion criteria more stringently to the polypill arm. After that point, there was full allocation concealment. Polypill tablets were since then provided by the Behvarz a few days after enrolment of the participants and the allocation of the clusters was thus concealed from the enrolment team members. To assess the effects of allocation concealment, we categorized study participants into two subgroups: those enrolled without allocation concealment and with allocation concealment.

Of the 28,660 rural GCS participants aged 50 or older (PolyIran sampling frame), 14,785 individuals were not considered to be randomized and thus were invited to participate in the PolyIran study. In addition, 5465 participants who were initially selected for random allocation in the two arms (2759 participants in polypill arm and 2706 participants in minimal care arm) did not attend eligibility check. These total 20,250 individuals who did not receive the interventions of the PolyIran study (neither polypill nor minimal care), were considered as an additional external, non-randomized comparison in the PolyIran study. They received usual care offered by the public and private sector, and hence were defined as “the usual care group”.

Intervention:

All participants in both arms received minimal care, a package of non-pharmacological interventions including educational training about a healthy lifestyle, including healthy diet with low salt, sugar and fat content, exercise, weight control and abstinence from smoking and opium. These interventions were delivered through face-to-face interview, by a short text messages (SMS) twice monthly and a pictorial pamphlet. The contents include educational training about a healthy lifestyle, including healthy food intake with low salt, sugar and fat content, exercise, weight control and abstinence from smoking and opium. All participants in both arms had also biannual blood pressure measurement and those identified as hypertensive were referred to their local family physicians for blood pressure control.

In addition to minimal care, participants in the polypill arm who met the eligibility criteria received a polypill tablet. Two formulations of polypill tablet were used in this study (Alborz Darou Pharmaceutical Company, Tehran, Iran). Participants were first prescribed polypill 1,

(hydrochlorothiazide 12.5 mg, aspirin 81 mg, atorvastatin 20 mg and enalapril 5 mg). Those who developed cough during follow-up were switched by the study physician to polypill 2, which substitutes enalapril 5 mg with valsartan 40 mg.

The usual care group received neither polypill nor minimal care. They received only usual care offered by the public and private sector.

Follow up:

Field Follow-up visits were scheduled to occur at months 1, 2, 3, 6 and then 6 monthly in the polypill arm and at months 3, 6 and then 6 monthly in minimal care arm. At follow-up visits, all participants were offered minimal care, and in the polypill arm, tablets were dispensed and pill counts undertaken. Participants were interviewed to maintain study participation and to assess the presence of symptoms that might indicate adverse events. Participants who reported symptoms were first visited by the study physician and at the study physician's discretion were referred to their local family physicians.

Outcomes:

The primary outcome is the occurrence of MCVE during 60 months after enrollment. MCVE included hospitalization for acute coronary syndrome (non-fatal myocardial infarction and unstable angina), fatal myocardial infarction, sudden death, heart failure, coronary artery revascularization procedures, and non-fatal and fatal stroke. For participants with more than one MCVE, the first event was included in the primary outcome analysis. Secondary outcomes were the components of the MCVE considered individually, non-cardiovascular causes of death (including neoplastic, respiratory, hepatic, renal and other medical causes), adherence to the polypill (based on pill count) and changes in blood pressure and low-density lipoprotein (LDL) cholesterol during the study.

The study continued for 60 months. Participants who were lost to follow up, those who were still alive at month 60 and those who died from non-MCVE causes were censored.

Outcome ascertainment was through the GCS follow up team and personnel responsible for outcome ascertainment were therefore independent of the PolyIran team and therefore blind to allocation status. Briefly, all GCS participants were contacted by telephone annually inquiring about health status and any admission to hospital or outpatient CVD clinics. On learning of a death or possible non-fatal CVD event, all relevant medical documents were collected by one of the study staff from hospitals or patients' homes. Two separate internists then independently reviewed all documents and ascertained the outcome on the basis of standardized criteria. In case of discordance, the outcome was ascertained following review of all documents by a panel of expert cardiologists and internists.

Statistical analysis:

Analysis of primary outcomes: Analysis were done by intention to treat and all subjects who met the eligibility criteria were included. The null hypothesis (no difference) for the primary outcome were tested using a random effects Cox model with time to the primary outcome and censoring those who were lost to follow-up or who die from other causes. We used Cox regression models, with shared frailty to account for cluster randomization, to obtain hazard ratios (HR) and 95% confidence intervals (95%CI). Results of both unadjusted and adjusted models are presented. In addition, the clustering effects were also assessed using VCE option and the results were compared with those of frailty model. As described in the analysis plan, adjustments were done for age (in years), gender (male or female), history of MCVE, diabetes mellitus, and hypertension. Diabetes was defined as: self-report based on a physician diagnosis; fasting blood glucose ≥ 126 mg/dl; or use of anti-diabetes drugs. Hypertension was defined as systolic blood pressure (SBP) ≥ 140 mmHg, diastolic blood pressure (DBP) ≥ 90 mmHg, physician-confirmed diagnosis of hypertension, or use of anti-hypertensive drugs (in participants without history of CVD).

Several prespecified subgroup analyses were performed by gender, age group, preexisting CVD, preexisting hypertension, preexisting diabetes mellitus, ethnicity, history of smoking, baseline cholesterol level, and adherence to polypill. Interaction terms were introduced in the models. For these analyses, age was categorized into two groups, ≤ 65 and > 65 years. For cholesterol, the participants were categorized into ≤ 198 and > 198 mg/dL groups. Adherence to polypill was measured using pill count, during each study visit and for the entire study period. If a participant could not be accessed in a follow up visit and no further information was available, adherence for that follow-up was coded as missing. The study participants were *a priori* categorized into three groups: high adherence ($\geq 70\%$), medium adherence (50%-69%), and low adherence ($< 50\%$). As there were relatively few participants in the latter two groups (medium and low) and the participants in these two categories had similar characteristics and outcome, we merged them into a single group, and therefore the final categorization was dichotomized as high ($\geq 70\%$) and medium/low adherence ($< 70\%$).

Analysis of secondary outcomes: The risks of the components of MCVE (i.e., non-fatal myocardial infarction and unstable angina, fatal myocardial infarction, sudden death, heart failure, coronary artery revascularization procedures, non-fatal and fatal stroke), non-cardiovascular mortality as well as overall mortality were compared between polypill and minimal care arms. For time to certain occurrence of secondary outcomes (e.g., time to death), unadjusted and adjusted HRs and the 95% CI were calculated using Cox regression

analysis with frailty models. For continuous secondary outcomes (changes in blood pressure and LDL-cholesterol), data were analyzed using mixed effects linear regression models. Log transformations were considered for variables with non-normal distribution. To assess the association of adherence to polypill tablet with baseline covariates, odds ratios and 95% CIs were calculated using mixed effects logistic regression models.

Analysis of adverse events:

Data on adverse events were collected for all participants who attended the follow up visits. If a participant reported similar adverse events in more than one follow-up visit, the earliest date was taken into account. At the end of study (month 60 follow up visit), the study participants were asked about the occurrence of physician-confirmed diagnosis of selected conditions including peptic ulcer diseases and upper gastrointestinal bleeding.

Additional comparison:

The aim of additional comparison was to compare the HRs of MCVE in usual care group with those of polypill and minimal care arms. Usual care group participants were not assessed for eligibility criteria; hence it was not possible to determine eligible subjects in this group. Therefore, all eligible and ineligible participants in the polypill (n=4,233) and minimal care (n=4,177) arms were entered into the additional comparison. Since outcome ascertainment in all 20,250 would have been burdensome and expensive, a random sample of 4,305 participants was selected from the usual care group using cluster randomization method, for whom complete outcome ascertainment was performed similar to study arms.

Cox regression models were used to compare the HR of MCVE in usual care group with those of polypill and minimal care arms. As the usual care group members did not attend the eligibility check, there was no enrollment time for these participants. Therefore, we considered a fixed date (the date of enrollment of the first participant in the polypill or minimal care arms) as enrollment date for all usual care participants. As with previous analyses, Cox regression results were adjusted for clustering effects using shared frailty models.

Ethical approval and Trial registration:

The protocol of the PolyIran study was reviewed and approved by Institutional Review Board (IRB) of Digestive Diseases Research Institute and Tehran University of Medical Sciences and registered with clinicaltrials.gov (clinicaltrials.gov identifier: NCT01271985).

Results:

Main comparison

Enrollment of study participants: A total of 6841 individuals were enrolled in the study, 3,417 (in 116 clusters) in the minimal care arm and 3,421 (in 120 clusters) in the polypill arm. Further details are shown in the study flow chart (Figure 1) and in Supplementary Figure 1. Figure 2 shows the time sequence of steps and blinding status in the PolyIran study. The allocation status was concealed to the enrolment team in the first 48 clusters (1,836 participants) and the remaining 188 clusters (5,002 participants) were enrolled with allocation concealment (Table 2).

Analysis of primary outcomes: The two study arms are reasonably balanced with respect to gender, history of pre-existing cardiovascular disease, hypertension, diabetes mellitus, smoking, age group, and other potential confounders. (Table 2)

Table 3 shows the results of the primary and subgroup analyses. There were 202 MCVE during the 60 months in the polypill arms and 301 in the minimal care arm. There was a 34% reduction (adjusted HR=0.66; 95%CI: 0.55-0.80) in risk of MCVE in polypill arm when compared to minimal care arm. The corresponding Kapan-Meier curve is shown in Figure 3. The results using shared frailty models were very similar to those without frailty models, as were those using the VCE option in Stata (Supplementary Table 1). The number to treat (95% CI) to prevent one MCVE was 35 (95% CI: 24-60).

The risk of MCVE in participants with high adherence to polypill tablet was significantly lower when compared with the minimal care arm (adjusted HR=0.43; 95%CI: 0.33-0.55), corresponding to a NNT of 21 (95%CI: 17-28) to prevent one MCVE.

When stratified by age, gender, pre-existing MCVE, hypertension, diabetes mellitus, baseline cholesterol levels and smoking, there was no statistically significant difference in effect among the subgroups (Table 3). However, there was a non-significant stronger effect on primary (no prior MCVE) than secondary prevention (prior MCVE). See Table 3 and Figure 4.

Our findings suggested that a longer duration of polypill use was associated with a stronger protective effect of polypill use; the HR was considerably lower during the latter part of the follow up period (between month 37 and month 60) (HR=0.52; 95%CI:0.39-0.70) than the earlier parts of the study follow up period (Table 4).

Analysis of secondary outcomes: The median (interquartile range) of adherence was 80.5% (48.5-92.2). The adherence levels were high, medium and low in 2,144 (62.7%), 405 (11.8%) and 872 (25.5%) participants. Figure 5 shows adherence levels in polypill participants by follow up month. Relationships between different covariates with high adherence (adherence \geq 70%) to polypill tablet are presented in Table 5. The proportion of participants

with high adherence to polypill was significantly higher in men and those with pre-existing hypertension, and significantly lower in participants with preexisting CVD and smokers.

Table 6 shows the risk of components of MCVE, non-MCVE mortality as well as overall mortality in the two arms. The risk of fatal (HR=0.51; 95%CI: 0.30-0.87) and non-fatal (HR=0.74;95%CI: 0.58-0.96) IHD as well as fatal (HR=0.38;95%CI: 0.18-0.82) and non-fatal (HR=0.44;95%CI: 0.23-0.82) stroke was significantly lower in polypill arm. We found no significant differences in the risk of overall mortality, non-MCVE mortality, sudden death and heart failure between the study arms (Table 6).

Our results suggested significantly reduction in systolic blood pressure in polypill arm at month 24 (p-value=0.01) (Table 7). The changes in systolic (p-value=0.08) and diastolic (p-value=0.09) blood pressure at the end of study were slightly greater in polypill arm when compared to minimal care arm. Changes in LDL-cholesterol were significantly greater in polypill arm both at month 24 and at the end of the study (p-value<0.01) (Table 7).

Adverse events

Figure 6 shows the frequencies of adverse events in polypill and minimal care arms. Overall, the frequency of adverse events was comparable between the two arms. We found decreasing trends in the frequencies of dyspepsia, cough and dizziness during the study period. The trends for cataract/vision loss and renal colic were increasing. The frequencies of adverse events and their trends were almost similar in polypill and minimal care arms.

A total number of 21 cases of intracranial hemorrhages were ascertained during the 5 years follow up, including 10 participants (0.29%) in polypill arm and 11 participants (0.32%) in minimal care arm (p-value=0.82).

The frequencies of physician-confirmed diagnosis of peptic ulcer disease were 34 (1.13%) and 35 (1.18%) in polypill and minimal care arms, respectively (p-value=0.86). The frequencies of physician-confirmed diagnosis of upper GI bleeding were 13 (0.43%) and 9 (0.30%) in polypill and minimal care arms, respectively (p-value=0.40).

Additional comparison with usual care arm

In total, 12,715 participants were entered into the analysis of additional comparison in three groups including polypill arm (n=4,233), minimal care arm (n=4,177) and usual care group (n=4,305) (Supplementary Figure 2). During 60 months of follow-up 1,126 new MCVEs occurred among all 12,715 participants included in the additional comparison analysis, including 308, 404 and 414 in the polypill arm, minimal care arm, and usual care group, respectively. Table 8 and Figure 7 presents the results of Cox regression models. The results showed significant lower risk of MCVE in polypill arm compared to the usual care group

(adjusted HR=0.79; 95%CI: 0.68-0.92). Our results showed no difference in the risk of MCVE between minimal care arm and usual care group.

Discussion:

The main aim of the PolyIran study was to assess the effect of a polypill (a fixed-dose combination pill comprising aspirin 81 mg, atorvastatin 20 mg, hydrochlorothiazide 12.5 mg, and either enalapril 5 mg or valsartan 40 mg per day) on the risk of major cardiovascular events. To our knowledge, this is the first large-scale pragmatic trial with long term follow up to investigate the effects of a fixed-dose combination therapy on primary and secondary prevention of CVDs.

Our results showed that once daily polypill for a period of 5 years in 50-75 years-old participants reduced the risk of MCVE by 34%. The most striking difference was seen by adherence to treatment. We found a greater reduction (57%) in the risk of MCVE in participants with high adherence to polypill tablet. These significant results were consistent among men and women, younger and older individuals, and those with or without preexisting hypertension or a high blood cholesterol level. The risk of both fatal and non-fatal ischemic heart disease and both fatal and non-fatal stroke decreased significantly in the polypill arm. Adverse events were comparable between the polypill arm and the minimal care arm, suggesting that polypill tablet could reduce cardiovascular outcomes without additional adverse events.

Several similar trials were conducted on fixed-dose combination pills in different population, but most of them were focused on adherence to polypill intake and its effects on CVD risk factors not hard outcomes as in this study (major cardiovascular events) and most studies also had a shorter follow up than the 60 months of the PolyIran study.^{17,21,24,25}

The 34% reduced MCVE risk (57% reduction in those with high adherence) confirms that such a polypill strategy could help achieve the United Nation SDG to reduce premature mortality due to CVD by at least a third before 2030.⁵ A polypill strategy should therefore be in the agenda of health policy makers, especially in low- and middle-income countries.

The PolyIran study showed approximately 40% reduction in the risk of MCVE in individuals without a history of CVDs (primary prevention) and 20% in those with previous CVDs (secondary prevention); the difference not being statistically significant. Therefore, polypill strategy could be used for both primary and secondary prevention in such high-risk settings.

The rationale behind using polypill for primary or secondary prevention of CVDs is not quite the same. One of the main aims for using polypill in secondary prevention is to increase adherence to multi-drug regimens in patients with established CVD. In the PURE study,²⁶ 4-5 years after their cardiovascular events, more than 50% of patients (from 10% in high-income to >75% in low-income countries) were not taking any of the drugs recommended for secondary prevention.²⁶ Similarly low drug adherence for secondary prevention of CVDs has been recently reported in the participants of the GCS in the northeast of Iran especially among participants with less education and lower socioeconomic status.²⁷

Using polypill strategy for primary prevention of CVD may be implemented at individual or population levels^{14,28}. The individual level approach, participants are screened for risk factors of CVD and the polypill is administered to individuals whose risk score is over a threshold. But, this approach has major limitations including high screening costs and difficulties in developing prediction models for different type of risk factors and different population.²⁹ Therefore, it is recommended to consider a population-based strategy to reduce risk factor levels at population level^{28,30}. It has been suggested that population level strategies using polypill for primary prevention of CVD may have a larger impact than focusing only on high-risk individuals.³¹

In the PolyIran study, we considered the population-based primary prevention strategy and our results confirmed the effectiveness of polypill for primary prevention of CVD at population level.

Compared with the use of aspirin in secondary prevention among patients at high baseline risk of further MCV, aspirin use for primary prevention of CVDs remain controversial due to its side effects mostly bleeding.^{14,32,33} A meta-analysis of aspirin use in primary prevention showed that aspirin, even less than 100 mg/d, is associated with approximately 11% reduction in cardiovascular events in both low- and high-risk populations, although the risk of major bleeding was increased.³³ In our study, high-risk individuals for bleeding were ineligible and excluded from the trial²³ and we found no significant increase in risk of GI or intracranial bleeding in the polypill group. Based on these rationales and specific considerations, a low-cost fixed-dose combination pill (production fee: 5 US cents per pill) including known medications for prevention of CVDs^{7,10,17,27,33,34} was produced and delivered free of charge for both primary and secondary prevention groups.²³

This study showed relatively high adherence to polypill tablet (median=80.5%) which remained stable through the study period. Improving adherence is one of the major benefits of polypill strategy and was considered as the main primary outcome in most of initial

clinical trials on polypill.^{34,35} The high adherence may in part though be due to the PolyIran study being conducted within the well-established GCS with its good associated infrastructure and knowledgeable population.²³

Previous reports suggested that a 1% reduction in LDL-cholesterol gives a 1% decrease in the risk of atherosclerotic CVDs.³⁶ Moderate-dose statin use (i.e., atorvastatin 20 mg/d) typically decreases LDL-cholesterol level by 30-49%.³⁶ In our study, after 5 years, LDL-cholesterol level decreased by 35 mg/dl (30%) in the polypill arm, but the mean difference between two main arms was 19.5 mg/dl (17%). Healthy lifestyle education and likely use of LDL-cholesterol lowering drugs in the minimal care arm could have contributed to the differential 20 mg/dl reduction in LDL-cholesterol in this arm.

A meta-analysis showed that every 10 mmHg reduction in systolic blood pressure reduced the risk of major CVD events by 20% in primary and secondary prevention individuals.³⁷ In our study, the mean reduction in systolic blood pressure in the polypill arm was 5.6 mmHg but the mean difference between the polypill arm and minimal care arm was only 1.4 mmHg. These results could be due to the insufficient dosing of antihypertensive drugs. Our participants were almost healthy with normal BP, so we did not expect considerable decrease in blood pressure in our study. Likewise, in the HOPE-3 study, using candesartan and hydrochlorothiazide (16 and 12.5 mg per day, respectively), systolic blood pressure reduced by 6 mmHg in the context of primary prevention and was not associated with a lower rate of cardiovascular events, compared with placebo.³⁸

The results of additional non randomized comparisons showed significant reduction in the risk of MCVE in polypill arm when compared to the minimal care and usual care arms. It also showed that there were no significant differences in the risk of outcomes between minimal care arm and usual care group. This may partly be explained by implementation of cardiovascular diseases surveillance program in public health network in Iran during the last decade which is being conducted more rigorously during recent years as part of the national action plan for prevention and control of non-communicable diseases.³⁹ The aim of this program is to identify high-risk individuals for CVD and to perform periodical assessment and referring the high-risk individuals to physician for monitoring and controlling the conditions. These programs are almost similar to the minimal care intervention of the minimal care arm of the PolyIran study. These national preventive services were routinely provided to all individuals in our study area including the participants of the polypill arm, minimal care arm as well as usual care arm. It is possible that the benefits of the polypill in populations where there are no similar preventive services may be bigger than those observed

in this study. Therefore, this point should be taken into account during interpretation of the PolyIran results.

This study has some limitations. First, we used only one fixed-dose combination pill for all participants, including primary and secondary prevention individuals. It seems that using flexible possibilities (i.e., different dosage levels for each drug and different combinations to tailor for specific clinical settings) could improve drug adherence and efficacy.²⁷ Second, in the beginning of the study (involving 48 clusters, 2115 participants), the enrolment team was aware of the allocation of clusters. It could have affected the behaviors of the enrolling physicians, e.g. in applying the exclusion criteria more stringently to the polypill arm. Thereafter, enrolment team were blinded to cluster allocation. A subgroup analysis did not show a significant difference between participants with or without allocation concealment. Third, healthy lifestyle education (e.g., face-to-face interview and twice monthly short text messages) during the study could encourage participants in the minimal care arm to visit physicians and likely take medications, which could underestimate the size of the benefits of the polypill. Fourth, the PolyIran study was conducted only on rural population and this point may affect the generalizability of our findings and should be considered in interpretation of our results.

In conclusion, the PolyIran study, using fixed-dose combination of aspirin, atorvastatin, and two blood pressure lowering drugs was associated with a significant lower risk of major cardiovascular events in 50-75 year-old individuals. This pragmatic trial showed for the first time that using a low-cost polypill in a real-life setting could significantly reduce cardiovascular events and should now be considered an important step in applying the cardiovascular polypill strategy to eligible adults, broadly, especially in LMICs.

Figure 1. PolyIran study flow

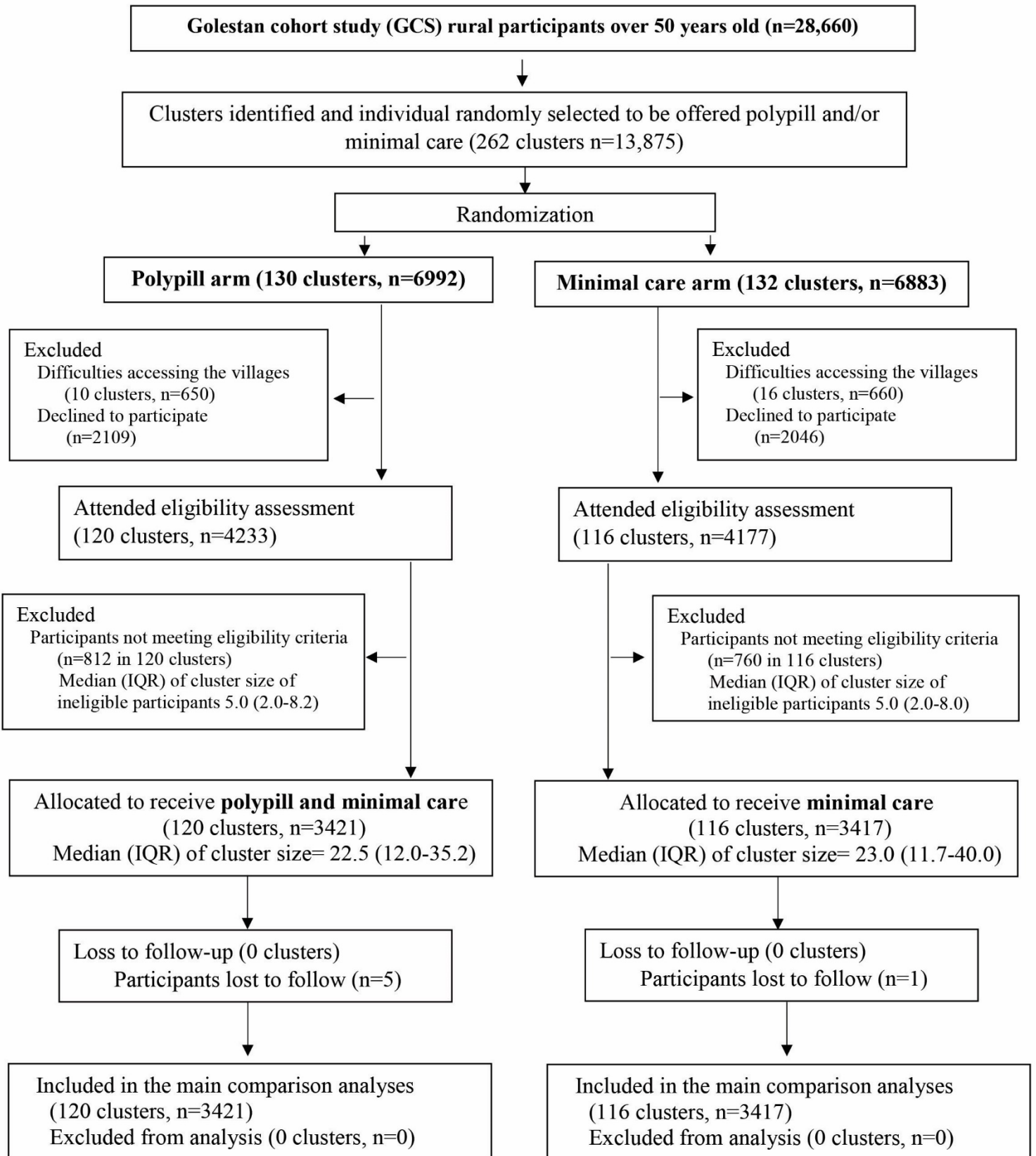
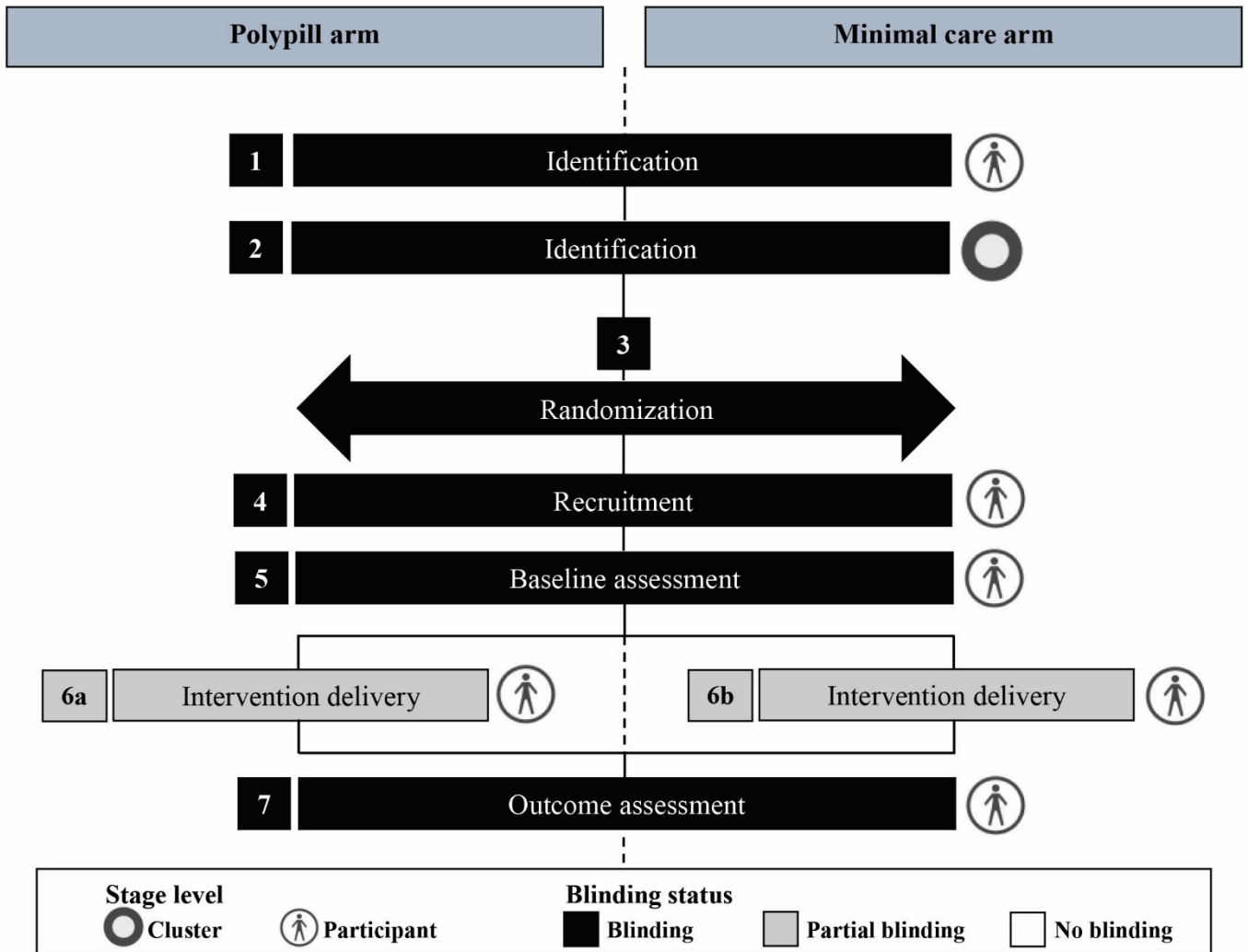


Figure 2. Timeline cluster diagram of PolyIran study



- 1 Participants identification**
Participants of Golestan Cohort Study (GCS) who lived in rural areas (villages of three districts of Golestan province) and over constituted the sampling frame for the PolyIran study. From PolyIran sampling frame, 13,875 individuals were selected using a simple stratified random selection procedure by statisticians at the University of Birmingham, UK, independent of the local study team.
- 2 Cluster identification**
PolyIran participants were randomly selected in proportion to the number of eligible inhabitants in each village. These random samples from each village constituted the PolyIran clusters (262 clusters).
- 3 Randomization**
Villages (i.e. clusters) were randomly allocated to study arms. All subjects within a cluster were randomized to receive the same intervention. Randomization was stratified by the three districts with the village as the unit of randomization. A balanced randomization algorithm was used. Balancing was implemented using block sizes of 20 and balancing over cluster size or natural log of the cluster size. Randomization was undertaken at a fixed point in time (January 2011) by statisticians at the University of Birmingham, UK, independent of the local study team.
- 4 Recruitment**
The selected individuals were invited by blinded auxiliary health workers locally called ‘Behvarz’ to attend their local health house (study site).
- 5 Baseline assessment**
Individuals who attended the study site were assessed for baseline characteristics and eligibility criteria by the trial enrolment team. For the first 20% of clusters/participants enrolled, the enrollment team was aware of the allocation status, which resulted an imbalance in covariates and the proportion of ineligible subjects between the polypill and minimal care arms. Beyond that point, subjects in the remaining clusters were enrolled with the trial enrolment team blinded to allocation status.
- 6a Intervention delivery**
Participants in polypill arm received polypill in addition with minimal care. Participants were not blinded to allocation status. For the first 20% of clusters/participants enrolled, the enrollment team was not blinded to allocation status. Beyond that point, subjects in the remaining clusters were enrolled with the trial enrolment team blinded to allocation status.
- 6b Intervention delivery**
Participants in minimal care arm received only minimal care. Participants were not blinded to allocation status. For the first 20% of clusters/participants enrolled, the enrollment team was not blinded to allocation status. Beyond that point, subjects in the remaining clusters were enrolled with the trial enrolment team blinded to allocation status.
- 7 Outcome assessment**
Outcome ascertainment was performed by GCS follow up team who were independent of PolyIran enrollment team and were blinded to allocation status.

Table 1. Eligibility criteria in PolyIran study. All subjects in the polypill arm, minimal care arm and those receiving usual care were assessed for inclusion criteria but the exclusion criteria were only applied to the minimal care and polypill arms.

Inclusion criteria

- Age over 50 years old
- Living in rural areas

Exclusion criteria

- Hypersensitivity to one of components of polypill (excluding cough due to enalapril)
- History of angioedema
- History of gastrointestinal bleeding or peptic ulcer disease within 3 months of eligibility assessment
- History of stroke
- Pregnancy or lactation
- Bleeding disorders such as haemophilia
- Regular anticoagulant use (excluding aspirin)
- Alcohol consumption more than three times a day
- Advanced liver diseases defined as history of chronic liver disease and platelet count lower than 100,000/ml at the time of eligibility assessment
- Uncontrolled seizures defined as history of any seizure episode within 2 years of eligibility assessment either on or off the anticonvulsant treatment
- Presence of any of the following in asthmatic patient:
 - a. Daily symptoms
 - b. Night-time symptoms ≥ 1 night per week
 - c. History of nasal polyposis
 - d. Symptoms attributed to rhinitis without evidence of upper respiratory tract infection
- History of gout
- Serum creatinine >2 mg/dl
- Glomerular filtration rate (GFR) <30 ml/min
- Haemoglobin <10 mg/dl in females and <11 mg/dl in males
- Systolic blood pressure <90 mmHg and diastolic blood pressure <60 mmHg
- Medical/psychiatric comorbidities potentially affecting the adherence of the participants:
 - a. Major depression disorder, dementia, schizophrenia, manic-depressive bipolar disorder and other disorders with presentation of psychosis
 - b. Cognitive impairments
 - c. Blindness
 - d. Inability to do diurnal activities independently, e.g. wheelchair-bound patients
 - e. Disorientation with the study and its goals
- Unavailability of the subjects

Table 2. Baseline Characteristics of participants in polypill and minimal care arms in total and by the status of allocation concealment

Characteristics	Clusters enrolled without allocation concealment		Clusters enrolled with allocation concealment		Total	
	Polypill Arm (n = 1070)	Minimal care Arm (n = 766)	Polypill Arm (n = 2351)	Minimal care Arm (n = 2651)	Polypill Arm (n = 3421)	Minimal care Arm (n = 3417)
Gender, No. (%)						
Male	502 (46.9)	376 (49.1)	1158 (49.3)	1362 (51.4)	1660 (48.5)	1738 (50.9)
Female	568 (53.1)	390 (50.9)	1193 (50.7)	1289 (48.6)	1761 (51.5)	1679 (49.1)
Pre-existing CVD, No. (%)	115 (10.7)	82 (10.7)	273 (11.6)	267 (10.1)	338 (11.3)	349 (10.2)
Pre-existing HTN, No. (%)	501 (46.8)	314 (41.0)	1175 (50.0)	1382 (52.0)	1676 (49)	1696 (49.6)
Pre-existing DM, No. (%)	181 (16.9)	114 (14.9)	316 (13.4)	418 (15.8)	497 (14.5)	532 (15.6)
Age group, No (%)						
≤65	918 (85.8)	650 (84.9)	1895 (80.6)	2129 (80.3)	2813 (82.2)	2779 (81.3)
>65	152 (14.2)	116 (15.1)	456 (19.4)	522 (19.7)	608 (17.8)	638 (18.7)
Cholesterol level, No. (%)						
≤198 mg/dL	563 (52.6)	355 (46.3)	1148 (48.8)	1338 (50.5)	1711 (50.0)	1693 (49.5)
>198 mg/dL	507 (47.4)	411 (53.7)	1202 (51.1)	1313 (49.5)	1709 (50.0)	1724 (50.5)
Smoking ever, No. (%)						
Yes	45 (4.2)	62 (8.1)	90 (3.8)	124 (4.7)	135 (3.9)	186 (5.4)
No	1025 (95.8)	704 (91.9)	2261 (96.2)	2527 (95.3)	3286 (96.1)	3231 (94.6)
Ethnicity, No. (%)						
Turkmen	885 (82.7)	628 (82.1)	1998 (85.0)	2111 (79.6)	2883 (84.3)	2739 (80.2)
Non-Turkmen	185 (17.3)	137 (17.9)	353 (15.0)	540 (20.4)	538 (15.7)	677 (19.8)
Low-density lipoprotein cholesterol, mean (95%CI), mg/dL	115.0 (112.0-118.0)	119.2 (113.8-124.7)	118.2 (115.8-120.6)	116.3 (113.1-119.5)	117.21 (115.24-119.18)	116.96 (114.18-119.74)
Body mass index, mean (95%CI), kg/m ²	27.0 (26.4-27.6)	26.5 (25.6-27.5)	26.4 (26.0-26.9)	26.4 (26.0-26.8)	26.62 (26.29-26.96)	26.45 (26.08-26.81)

Table 3. Hazard ratios and 95% confidence intervals for comparing major cardiovascular events (MCVE) between polypill and minimal care arms

	Polypill arm; No./Total (%)	Minimal care arm; No./Total (%)	HR (95% CI)	Adjusted HR (95% CI)	P-value for interaction
Study arms	202/3421 (5.9)	301/3417 (8.8)	0.66 (0.55-0.79)	0.66 (0.55-0.80)	-
Gender					
Male	107/1660 (6.45)	179/1738 (10.30)	0.61 (0.48-0.78)	0.60 (0.47-0.77)	0.29
Female	95/1761 (5.39)	122/1679 (7.27)	0.74 (0.55-0.99)	0.74 (0.55-0.99)	
Age group					
≤65 years	145/2813 (5.15)	211/2779 (7.59)	0.67 (0.53-0.84)	0.66 (0.53-0.83)	0.90
>65 years	57/608 (9.38)	90/638 (14.11)	0.65 (0.46-0.92)	0.63 (0.44-0.90)	
Pre-existing MCVE					
Yes	66/388 (17.01)	72/349 (20.63)	0.81 (0.58-1.13)	0.80 (0.57-1.12)	0.19
No	136/3033 (4.48)	229/3068 (7.46)	0.59 (0.47-0.73)	0.61 (0.49-0.75)	
Allocation concealment					
Without concealment	49/1070 (4.58)	61/766 (7.96)	0.59 (0.37-0.95)	0.53 (0.33-0.85)	0.23
Concealed allocation	153/2351 (6.51)	240/2651 (9.05)	0.71 (0.58-0.87)	0.73 (0.61-0.86)	
Pre-existing HTN					
Yes	134/1676 (8.00)	202/1696 (11.91)	0.65 (0.52-0.82)	0.64 (0.50-0.81)	0.85
No	68/1745 (3.90)	99/1721 (5.75)	0.67 (0.49-0.93)	0.67 (0.48-0.93)	
Pre-existing DM					
Yes	59/497 (11.87)	76/532 (14.29)	0.82 (0.58-1.15)	0.76 (0.53-1.08)	0.36
No	143/2923 (4.89)	225/2883 (7.80)	0.61 (0.50-0.76)	0.62 (0.50-0.77)	

Baseline Cholesterol level					
≤198 mg/dL	95/1711 (5.55)	142/1693 (8.39)	0.65 (0.50-0.85)	0.62 (0.47-0.82)	0.69
>198 mg/dL	107/1709 (6.26)	159/1724 (9.22)	0.67 (0.52-0.85)	0.69 (0.53-0.88)	
Smoking ever					
Yes	10/135 (7.41)	20/186 (10.75)	0.68 (0.32-1.45)	0.68 (0.31-1.47)	0.95
No	192/3286 (5.84)	281/3231 (8.70)	0.66 (0.54-0.80)	0.66 (0.55-0.80)	
Adherence					
Polypill arm (High)	86/2144 (4.0)		0.44 (0.34-0.56)	0.43 (0.33-0.55)	-
Polypill arm (Medium/low)	116/1277 (9.08)		1.04 (0.83-1.30)	1.08 (0.86-1.35)	
Minimal care arm	301/3417 (8.8)		Ref.	Ref.	
<ul style="list-style-type: none"> - MCVE included either hospitalization for acute coronary syndrome (non-fatal myocardial infarction and unstable angina), fatal myocardial infarction, sudden death, heart failure, coronary artery revascularization procedures, non-fatal and fatal stroke. - Hazard ratios (HR) and 95% confidence intervals were obtained using Cox regression models with shared frailty. - Adjusted models are adjusted for age, gender, preexisting major cardiovascular events, diabetes mellitus, and hypertension. For subgroup analyses, the subgroup variable was not entered into the model. 					

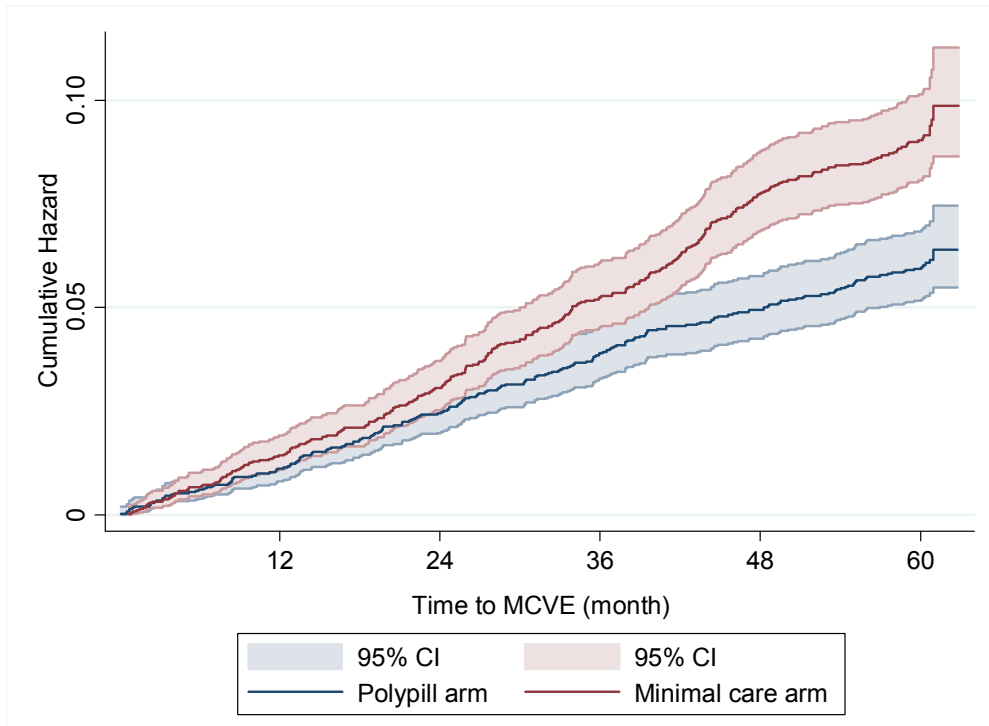


Figure 3. Cumulative Hazard function for major cardiovascular events (MCVE) in the two arms (The clustering effects were adjusted using frailty model)

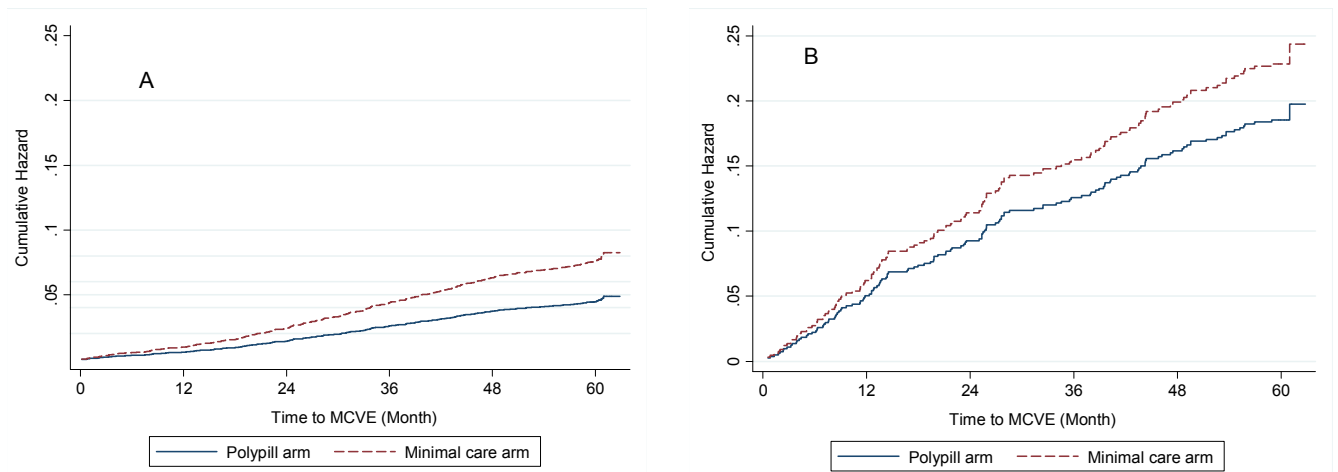


Figure 4. Cumulative Hazard function for major cardiovascular events (MCVE) as primary outcomes in the study arms in participants without pre-existing CVD (A) (primary prevention group) and with pre-existing CVD (B) (secondary prevention group). (The clustering effects were adjusted using frailty model)

Table 4. Hazard ratios and 95% confidence intervals for comparing major cardiovascular events (MCVE) between polypill and minimal care arms by duration of follow up interval

	Follow up time (Persons-month)	MCVE, No./Total (%)	HR (95% CI)	Adjusted HR (95% CI)
Follow up intervals				
Month 0- Month 60				
Polypill arm	200237.5	202/3421 (5.9)	0.66 (0.55-0.79)	0.65 (0.54-0.88)
Minimal care arm	197105.5	301/3417 (8.8)	Ref.	Ref.
Month 13- Month 60				
Polypill arm	199977.2	160/3379 (4.7)	0.63 (0.52-0.77)	0.64 (0.52-0.78)
Minimal care arm	196730.8	246/3362 (7.3)	Ref.	Ref.
Month 25- Month 60				
Polypill arm	199115.5	114/3333 (3.4)	0.58 (0.46-0.74)	0.59 (0.46-0.75)
Minimal care arm	195599.9	189/3305 (5.7)	Ref.	Ref.
Month 37- Month 60				
Polypill arm	197655.3	67/3286 (2.0)	0.52 (0.39-0.70)	0.52 (0.39-0.70)
Minimal care arm	193581.3	123/3239 (3.8)	Ref.	Ref.
<ul style="list-style-type: none"> - MCVE included either hospitalization for acute coronary syndrome (non-fatal myocardial infarction and unstable angina), fatal myocardial infarction, sudden death, heart failure, coronary artery revascularization procedures, non-fatal and fatal stroke. - Hazard ratios (HR) and 95% confidence intervals were obtained using Cox regression models with shared frailty. - All models are adjusted for age, gender, preexisting major cardiovascular events, diabetes mellitus, and hypertension 				

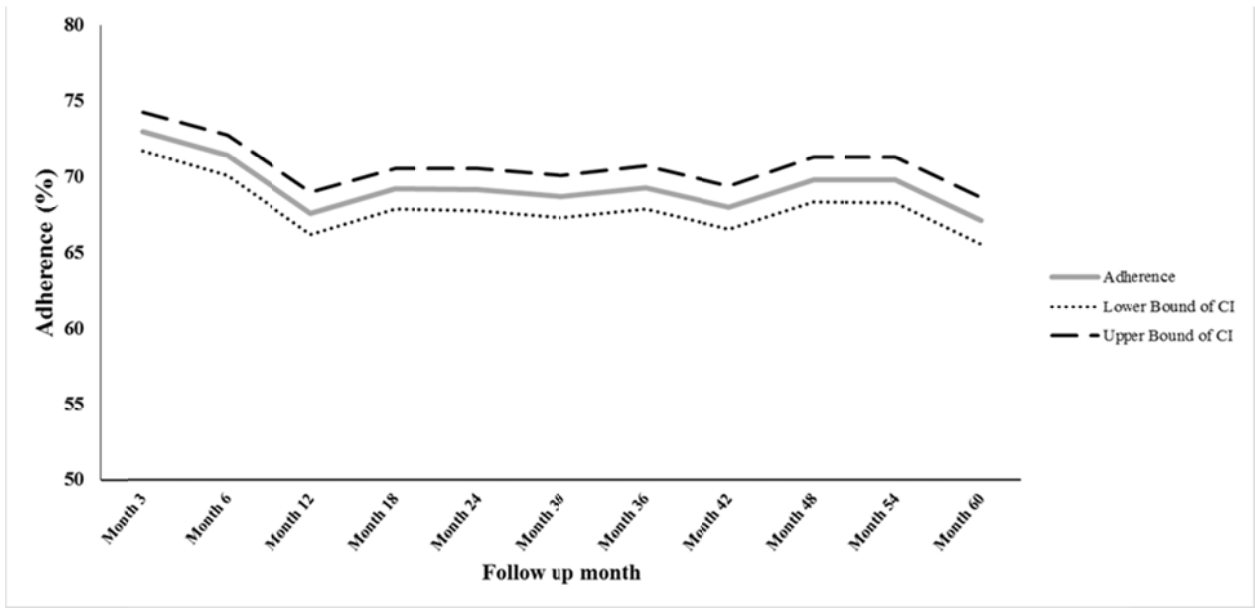


Figure 5. Adherence to polypill tablet in participants of the PolyIran study by follow up month

Table 5. Predictors of high adherence (>=70%) to polypill tablet in the PolyIran study

Covariates	high adherence, No./Total (%)	Odds Ratio (95% CI)*	Adjusted Odds** Ratio (95% CI)
Gender			
Male	1093/1660 (65.8)	1.28 (1.10-1.48)	1.39 (1.19-1.62)
Female	1051/1761 (59.7)	Ref.	Ref.
Pre-existing CVD			
Yes	225/388 (58.0)	0.78 (0.63-0.98)	0.72 (0.57-0.90)
No	1919/3033 (63.3)	Ref.	Ref.
Pre-existing HTN			
Yes	1114/1676 (66.5)	1.48 (1.27-1.72)	1.57 (1.34-1.83)
No	1030/1745 (59.0)	Ref.	Ref.
Smoking, No. (%)			
Yes	73/135 (54.1)	0.78 (0.54-1.13)	0.68 (0.46-0.99)
No	2071/3286 (63.0)	Ref.	Ref.
Pre-existing DM			
Yes	313/497 (63.0)	1.06 (0.86-1.31)	-
No	1830/2923 (62.6)	Ref.	
Age group, No (%)			
≤65	1764/2813 (62.7)	1.00 (0.82-1.21)	-
>65	380/608 (62.5)	Ref.	
Cholesterol level, No. (%)			
≤198 mg/dL	1058/1711 (61.8)	0.93 (0.80-1.08)	-
>198 mg/dL	1085/1709 (63.5)	Ref.	
Ethnicity, No. (%)			
Turkmen	1794/2883 (62.2)	0.99 (0.74-1.32)	-
Non-Turkmen	650/538 (65.1)	Ref.	

* All odds ratios were obtained using mixed-effects logistic regression models

** Adjusted for gender, smoking, pre-existing major cardiovascular events and hypertension

Table 6. Hazard ratios and 95% confidence intervals for comparing the risks of secondary outcomes between polypill and minimal care arms

	Polypill arm; No./Total (%)	Minimal care arm; No./Total (%)	HR* (95% CI)	Adjusted HR** (95% CI)	P-value
Fatal ischemic heart diseases	21/3421 (0.61)	41/3417 (1.20)	0.50 (0.29-0.85)	0.51 (0.30-0.87)	0.01
Non-fatal ischemic heart diseases	127/3421 (3.71)	169/3417 (4.95)	0.75 (0.59-0.96)	0.74 (0.58-0.96)	0.02
Fatal stroke	8/3421 (0.23)	21/3417 (0.61)	0.37 (0.17-0.81)	0.38 (0.18-0.82)	0.01
Non-fatal stroke	17/3421 (0.50)	39/3417 (1.14)	0.43 (0.23-0.81)	0.44 (0.23-0.82)	0.01
Sudden death	19/3421 (0.56)	28/3417 (0.82)	0.68 (0.36-1.28)	0.69 (0.36-1.32)	0.26
Heart failure	15/3421 (0.44)	18/3417 (0.53)	0.83 (0.42-1.65)	0.80 (0.40-1.59)	0.53
Non-cardiovascular causes of death	149/3421 (4.35)	123/3417 (3.60)	1.23 (0.95-1.58)	1.26 (0.98-1.62)	0.07
Overall mortality	202/3421 (5.90)	222/3417 (6.50)	0.90 (0.74-1.09)	0.93 (0.77-1.11)	0.43

* Hazard ratios (HR) and 95% confidence intervals were obtained using Cox regression models with shared frailty

** All models are adjusted for age, gender, preexisting major cardiovascular events, diabetes mellitus, and hypertension

Table 7. Effects of polypill tablet on blood pressure and LDL-cholesterol levels as secondary outcomes of the PolyIran study

	Polypill arm; Mean (95%CI)	Minimal care arm; Mean (95%CI)	Mean difference (95% CI)	P-value*
Change in systolic blood pressure (mmHg) from baseline to				
Month 24	-2.46 (-3.26 to -1.66)	0.59 (-0.22 to 1.40)	-3.05 (-4.19 to -1.91)	0.01
Month 60	-5.58 (-6.41 to -4.75)	-4.18 (-4.99 to -3.37)	-1.40 (-2.56 to -0.24)	0.08
Change in diastolic blood pressure (mmHg) from baseline to				
Month 24	-0.67 (-1.15 to -0.18)	0.07 (-0.40 to 0.55)	-0.74 (-1.43 to -0.06)	0.30
Month 60	-4.31 (-4.80 to -3.83)	-2.91 (-3.41 to -2.41)	-1.40 (-2.10 to -0.70)	0.09
Changes in LDL-C** (mg/dl) from baseline to				
Month 24	-26.73 (-28.04 to -25.41)	-2.08 (-3.31 to -0.84)	-24.65 (-26.45 to -22.85)	<0.01
Month 60	-35.39 (-36.65 to -34.12)	-15.85 (-17.13 to -14.57)	-19.54 (-21.33 to -17.74)	<0.01

* P-values were obtained using mixed effects linear regression models (with log transformation for variables with non-normal distribution). All models are adjusted for age, gender, preexisting major cardiovascular events, diabetes mellitus, and hypertension

** Low density lipoprotein cholesterol

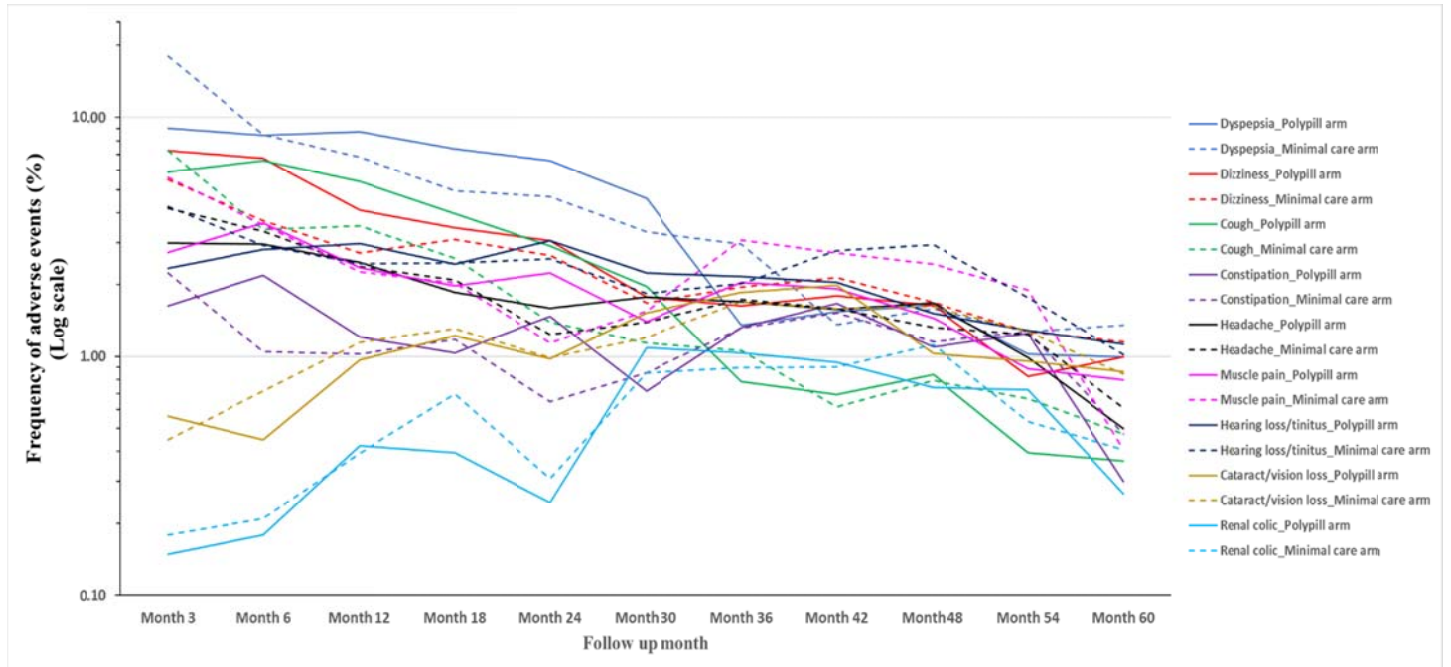


Figure 6. Frequency of adverse events in Polypill and minimal care arms by follow up visits

Table 8. Hazard ratios and 95% confidence intervals for comparing major cardiovascular events (MCVE) between polypill arm, minimal care arm and usual care group (additional comparison)

	No. (%) of subcategory in the study arm	MCVE, No./Total (%)	HR (95% CI)	Adjusted HR (95% CI)
Study arms				
Polypill arm	-	308/4233 (7.3)	0.73 (0.63-0.84)	0.79 (0.68-0.92)
Minimal care arm		404/4177 (9.7)	0.98 (0.85-1.12)	1.05 (0.91-1.21)
Usual care group		414/4305 (9.6)	Ref.	Ref.
Gender				
Male				
Polypill arm	2056 (48.6)	159/2056 (7.73)	0.71 (0.57-0.89)	0.78 (0.63-0.98)
Minimal care arm	2077 (49.7)	228/2077 (10.98)	1.04 (0.83-1.28)	1.12 (0.90-1.38)
Usual care group	1583 (36.8)	164/1583 (10.36)	Ref.	Ref.
Female				
Polypill arm	2177 (51.4)	149/2177 (6.84)	0.71 (0.58-0.88)	0.80 (0.65-0.99)
Minimal care arm	2100 (50.3)	176/2100 (8.38)	0.89 (0.73-1.07)	0.99 (0.81-1.20)
Usual care group	2722 (63.2)	250/2722 (9.18)	Ref.	Ref.
Age group, No (%)				
≤65				
Polypill arm	3357 (79.3)	198/3357 (5.90)	0.77 (0.63-0.93)	0.76 (0.62-0.92)
Minimal care arm	3276 (78.4)	257/3276 (7.84)	1.02 (0.85-1.23)	1.01 (0.84-1.21)
Usual care group	2927 (68.0)	218/2927 (7.45)	Ref.	Ref.
>65				
Polypill arm	876 (20.7)	110/876 (12.56)	0.84 (0.66-1.07)	0.84 (0.66-1.06)
Minimal care arm	901 (21.6)	147/901 (16.32)	1.12 (0.91-1.38)	1.11 (0.89-1.38)
Usual care group	1378 (32.0)	196/1378 (14.22)	Ref.	Ref.

- MCVE included either hospitalization for acute coronary syndrome (non-fatal myocardial infarction and unstable angina), fatal myocardial infarction, sudden death, heart failure, coronary artery revascularization procedures, non-fatal and fatal stroke
- Hazard ratios (HR) and 95% confidence intervals were obtained using Cox regression models with shared frailty
- All models are adjusted for age and gender, except the variable for which stratification is done.

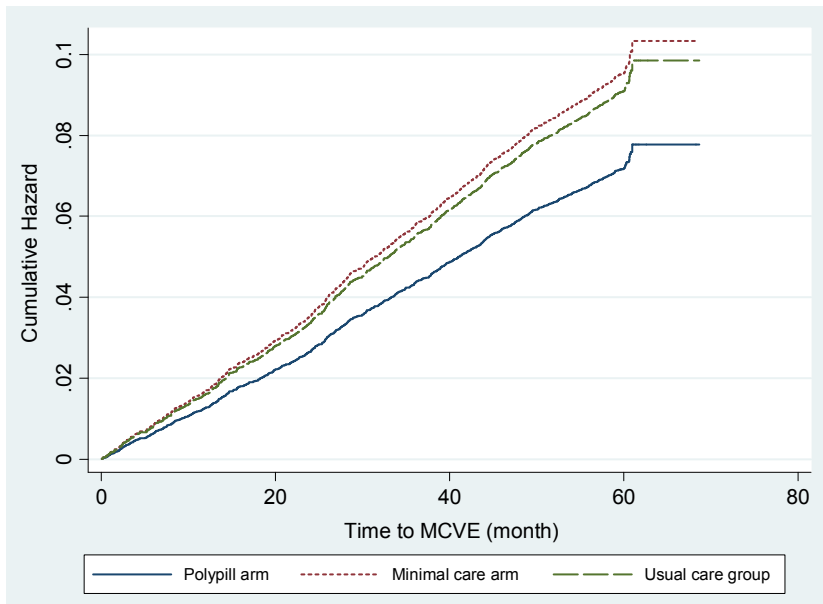


Figure 7. Cumulative Hazard function for major cardiovascular events (MCVE) in polypill arm, minimal care arm and usual care group of the PolyIran study (additional comparison). (The clustering effects were adjusted using frailty model)

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