An original scientific paper:

Effectiveness of polypill for primary and secondary prevention of cardiovascular diseases (PolyIran): a pragmatic, cluster-randomised trial

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I- General remarks:

- The PolyIran study was carried out in Iran, funded by Tehran University of Medical Sciences, Barakat Research Foundation and Alborz Darou Pharmaceutical Company.

- Participants were enrolled beginning from Febreuary 2013, with a 5-year follow-up. The results were published on August 24, 2019, in Volume 394 on the weekly peer-reviewed medical journal The Lancet, founded in 1823, with an impact factor of 53 (2nd in the world). This paper also appeared in several other prestigious publications, most notably in The European Journal of Preventive Cardiology.

II- Research in context:

- Cardiovascular diseases are major causes of health loss worldwide, with an estimated 422.7 million prevalent cases and 17.92 million deaths in 2015,1 and a 16% increase in disability-adjusted life-years (DALYs) during the past decade.

- However, data from the global burden of disease project suggest that, with current trends, the UN Sustainable Development Goal (SDG) to reduce premature mortality due to cardiovascular disease by a third in 2030 will not be possible for most low-income and middle-income countries (LMICs). Many factors have been implicated in this failure of cardiovascular disease prevention, despite, the existence of effective pharmacological and nonpharmacological interventions..

II- Research in context:

- In LMIC, the high cost of drugs make them prohibitively expensive as preventive measures. On the other hand, dose complexity and the number of pills used per day are inversely related to adherence and contribute to the shortfall in prevention coverage.

- As one of the solutions to this problem, these drugs could be provided as a low cost polypill to improve the availability and affordability of the preventive drugs and the subjects' adherence.

II- Research in context:

- A fixed-dose combination therapy—the so-called polypill—was proposed more than 15 years ago as an acceptable and cost-saving approach to reduce cardiovascular disease risk. Since then, different formulations of polypill have been used in several studies worldwide.

- However, long-term effects of the polypill on fatal and non-fatal hard endpoints (such as mortality or cardiovascular events) have not yet been firmly established, particularly in primary prevention settings. As a result, the different formulations of the polypill are not yet widely available to clinicians and patients.

II- Research in context:

- **Evidence before this study:**

- Two systematic reviews showed that the published polypill trials had small to moderate sample sizes and relatively short follow-up durations, limiting their power to study the long-term effects of polypills on secondary and primary prevention of cardiovascular disease. The two largest previous studies, TIPS (2053 patients) and UMPIRE (2004 patients), had follow-up durations of 12 weeks and 15 months, respectively.

- There has been also a pilot study of a polypill from Iran, consisting of aspirin, enalapril, atorvastatin, and hydrochlorothiazide. This fixed-dose combination was well tolerated with satisfactory participant adherence and resulted in some reductions in blood pressure and lipid concentrations.

II- Research in context:

- **The value of this study:**

- Based on these preliminary findings, the PolyIran study was designed to assess the effectiveness of a four-component fixed-dose polypill including aspirin, atorvastatin, hydrochlorothiazide and either enalapril or valsartan, for primary and secondary prevention of cardiovascular disease, comparing the risk of major cardiovascular events between polypill and minimal care groups during 5 years of follow-up, with the aim of recruiting a large group of participants and follow-up these individuals for a longer period than previous trials being to allow studying major cardiovascular event endpoints with adequate statistical power.

- According to the research team, the PolyIran study is the first large-scale, long-term, pragmatic randomised trial to investigate the effects of a fixed-dose combination therapy on primary or secondary prevention of cardiovascular disease,

III– Methods:

1 Participant identification

Participants of the GCS who lived in rural areas (villages of three districts of Golestan province) and were aged 50 years and older constituted the sampling frame for the PolyIran study; from the PolyIran sampling frame, 13 875 individuals were selected using a simple stratified random selection procedure by statisticians at the University of Birmingham (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 Randomisation

Villages (ie, clusters) were randomly allocated to study group; all subjects within a cluster were randomly assigned to receive the same intervention; randomisation was stratified by the three districts with the village as the unit of randomisation; we used a balanced randomisation algorithm; balancing was implemented using block sizes of 20 and balancing over cluster size or natural log of the cluster size; randomisation was done 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 masked auxiliary health workers locally called behvarz to attend their local health house (study site)

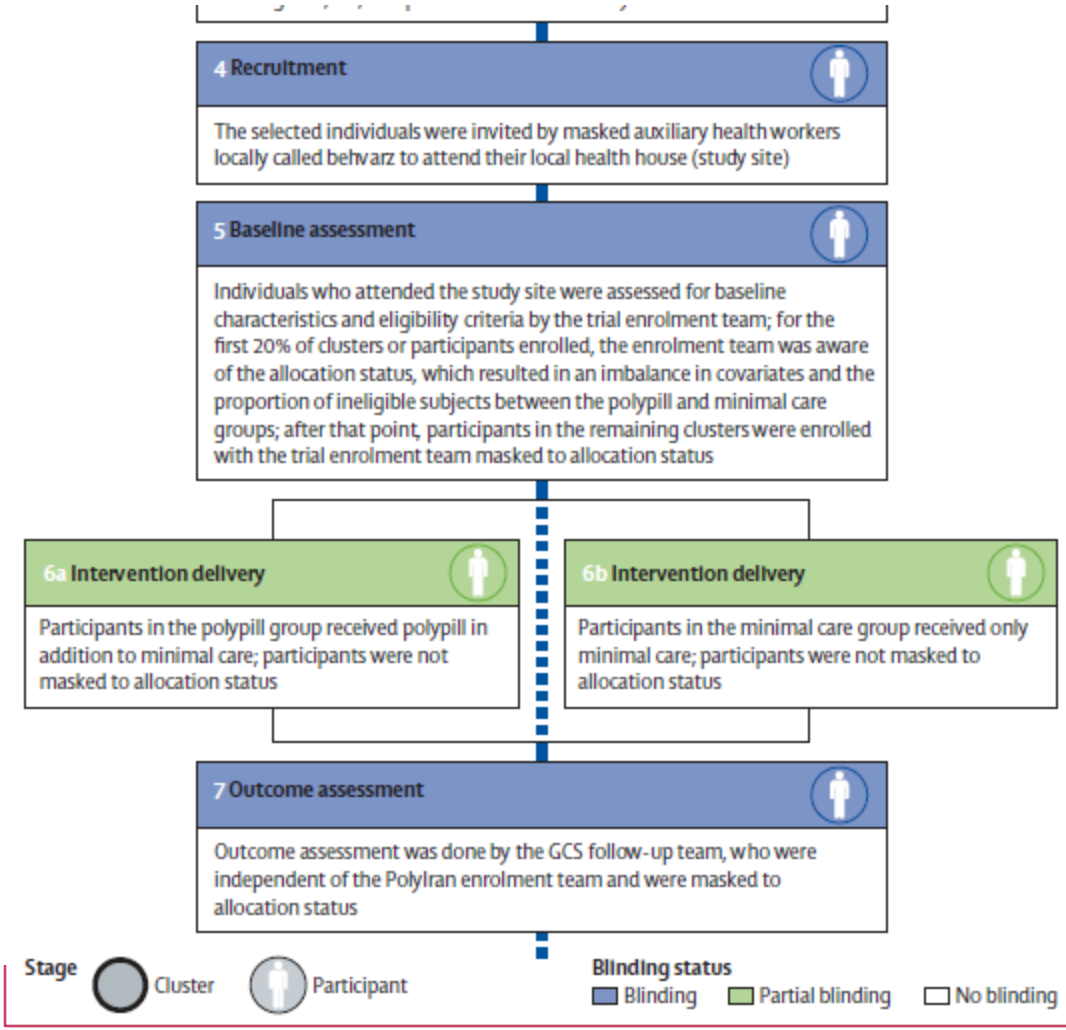

Figure 2: **Timeline cluster diagram of PolyIran study**
GCS=Golestan Cohort Study.

III- Methods:

- This study is a two-group, pragmatic, cluster-randomised trial, which was nested within the **Golestan Cohort Study (GCS)**: a cohort study with 50 045 participants aged 40–75 years from the Golestan in northeast Iran, where ischaemic heart disease accounts for 34% of premature deaths, followed by stroke (14%).

- The fact that this study was conducted within an established cohort study and its infrastructure allowed for considerable economies of resources and, in consequence, a significantly larger scope the previous studies.

III- Methods:

- Written informed consent was obtained from all study participants. The protocol of the PolyIran study was reviewed and approved by the Institutional Review Board of the Digestive Diseases Research Institute and Tehran University of Medical Sciences.

- According to the research team, funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

III- Methods:

- Very briefly, from the PolyIran sampling frame, **n=13,875** individuals were selected using a simple stratified random selection procedure weighted according to the number of eligible inhabitants in each village. Those randomly selected within each village constituted a cluster (262 clusters).

- Cluster randomization was used to avoid contamination that would likely arise from medication sharing within clusters. Randomisation was done at a fixed point in time (Jan 28, 2011) by statisticians at the University of Birmingham (Birmingham, UK), independent of the local study team

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 <90mmHg 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

III- Methods:

- These clusters were then randomly allocated to either a package of non pharmacological preventive interventions alone (minimal care arm; 6,883 individuals, 132 clusters) or together with a once daily polypill tablet (polypill arm; 6,992 individuals, 130 clusters).

- The two study arms were balanced with respect to gender, history of pre-existing cardiovascular disease, hypertension, diabetes mellitus, smoking, age group, and other potential confounders

III- Methods:

- All subjects in the minimal care arm received a package of **non-pharmacological preventive interventions** included: educational training about healthy lifestyle—eg, healthy diet with low salt, sugar, and fat content, exercise, weight control, and abstinence from smoking and opium).
- They were delivered by the PolyIran field visit team at months 3 and 6, and then every 6 months thereafter. This was supplemented by a short text messages (SMS) twice monthly and a well-designed pictorial pamphlet.
- Alongside this, participants had biannual blood pressure measurement to identify hypertensive subjects; these participants receive education about the impact of hypertension on CVD and are referred to their local family physicians for blood pressure control.

III- Methods:

- In addition to minimal care, participants assigned to the polypill group received a **polypill tablet** .

- Two formulations of the polypill tablet were used in this study, both offered by Alborz Darou Pharmaceutical Company. Participants were first prescribed Polypill One (hydrochlorothiazide 12·5 mg, aspirin 81 mg, atorvastatin 20 mg, and enalapril 5 mg). Participants who developed cough during follow-up were switched by a trained study physician to Polypill Two, which included valsartan 40 mg instead of enalapril 5 mg.

III- Methods:

- Participants were followed up for **60 months**. Field Follow-up visits were scheduled to occur at months 1, 2, 3, 6 and then every 6 months in the polypill arm and at months 3, 6 and then every 6 months in the minimal care arm.

- At follow-up visits, all participants were offered minimal care, and in the polypill arm, tablets were dispensed and pill counts were 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.

III- Methods:

- The primary and secondary outcomes were centrally assessed by the GCS follow-up team, who were masked to allocation status, as well as several prespecified subgroup analyses (gender, age group, preexisting CVD, pre-existing hypertension, preexisting diabetes mellitus, ethnicity, history of smoking, baseline cholesterol level, and adherence to polypill).

- An intention-to-treat analyses by including all participants who met eligibility criteria in the two study groups was done.

III- Methods:

- The **primary outcome**: occurrence of **major cardiovascular events (MCVE) ,** including: hospitalisation for acute coronary syndrome, fatal myocardial infarction, sudden death, heart failure, coronary artery revascularisation procedures, and non-fatal and fatal stroke).

- The **Secondary outcomes**: 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 trial.

IV- Results and discussion:

	Major cardiovascular events	HR* (95% CI)	Adjusted HR† (95% CI)	p value
Study groups				
Minimal care group	301/3417 (8·8%)	1 (ref)	1 (ref)	..
Polypill group	202/3421 (5·9%)	0·66 (0·55–0·79)	0·66 (0·55–0·80)	..
Sex	..	..	..	0·29
Female				
Minimal care group	122/1679 (7·3%)	1 (ref)	1 (ref)	..
Polypill group	95/1761 (5·4%)	0·74 (0·55–0·99)	0·74 (0·55–0·99)	..
Male				
Minimal care group	179/1738 (10·3%)	1 (ref)	1 (ref)	..
Polypill group	107/1660 (6·4%)	0·61 (0·48–0·78)	0·60 (0·47–0·77)	..
Age group (years)				
≤65	..	..	..	0·90
Minimal care group	211/2779 (7·6%)	1 (ref)	1 (ref)	..
Polypill group	145/2813 (5·2%)	0·67 (0·53–0·84)	0·66 (0·53–0·83)	..
>65				
Minimal care group	90/638 (14·1)	1 (ref)	1 (ref)	..
Polypill group	57/608 (9·4%)	0·65 (0·46–0·92)	0·63 (0·44–0·90)	..
Pre-existing cardiovascular disease	..	..	..	0·19
Yes				
Minimal care group	72/349 (20·6%)	1 (ref)	1 (ref)	..
Polypill group	66/388 (17·0%)	0·81 (0·58–1·13)	0·80 (0·57–1·12)	..
No				
Minimal care group	229/3068 (7·5%)	1 (ref)	1 (ref)	..
Polypill group	136/3033 (4·5%)	0·59 (0·47–0·73)	0·61 (0·49–0·75)	..
Allocation concealment	..	..	..	0·23
Pre-existing hypertension	..	..	..	0·85
Yes				
Minimal care group	202/1696 (11·9%)	1 (ref)	1 (ref)	..
Polypill group	134/1676 (8·0%)	0·65 (0·52–0·82)	0·64 (0·50–0·81)	..
No				
Minimal care group	99/1721 (5·8%)	1 (ref)	1 (ref)	..
Polypill group	68/1745 (3·9%)	0·67 (0·49–0·93)	0·67 (0·48–0·93)	..
Pre-existing diabetes	..	..	..	0·36
Yes				
Minimal care group	76/532 (14·3)	1 (ref)	1 (ref)	..
Polypill group	59/497 (11·9%)	0·82 (0·58–1·15)	0·76 (0·53–1·08)	..
No				
Minimal care group	225/2883 (7·8%)	1 (ref)	1 (ref)	..
Polypill group	143/2923 (4·9%)	0·61 (0·50–0·76)	0·62 (0·50–0·77)	..

	Major cardiovascular events	HR* (95% CI)	Adjusted HR† (95% CI)	p value
(Continued from previous page)				
Baseline cholesterol (mg/dL)	..	..	..	0·69
≤198				
Minimal care group	142/1693 (8·4%)	1 (ref)	1 (ref)	..
Polypill group	95/1711 (5·6%)	0·65 (0·50–0·85)	0·62 (0·47–0·82)	..
>198				
Minimal care group	159/1724 (9·2%)	1 (ref)	1 (ref)	..
Polypill group	107/1709 (6·3%)	0·67 (0·52–0·85)	0·69 (0·53–0·88)	..
Ever smoked	..	..	..	0·95
Yes				
Minimal care group	20/186 (10·8%)	1 (ref)	1 (ref)	..
Polypill group	10/135 (7·4%)	0·68 (0·32–1·45)	0·68 (0·31–1·47)	..
No				
Minimal care group	281/3231 (8·7%)	1 (ref)	1 (ref)	..
Polypill group	192/3286 (5·8%)	0·66 (0·54–0·80)	0·66 (0·55–0·80)	..
Adherence				
Minimal care group	301/3417 (8·8%)	1 (ref)	1 (ref)	..
Polypill group (high)	86/2144 (4·0%)	0·44 (0·34–0·56)	0·43 (0·33–0·55)	..
Polypill group (medium or low)	116/1277 (9·1%)	1·04 (0·83–1·30)	1·08 (0·86–1·35)	..

Data are n/N (%) unless otherwise indicated. HR=hazard ratio. *We obtained HRs and 95% CIs by Cox regression models with shared frailty. †Adjusted models were adjusted for age, sex, pre-existing major cardiovascular events, diabetes, and hypertension. For subgroup analyses, we did not enter the subgroup variable into the model.

Table 2: **Major cardiovascular events in polypill and minimal care groups**

IV- Results and discussion:

- **The risk of major cardiovascular events in participants with high adherence to polypill tablet was significantly lower when compared with the minimal care group** (adjusted HR 0 · 43, 95% CI0 · 33–0 · 55), corresponding to a number needed to treat of NNT= 20.7 to prevent one major cardiovascular event: During follow-up, 301 (8.8%) of 3417 participants in the minimal care group had major cardiovascular events compared with 202 (5.9%) of 3421 participants in the polypill group (adjusted HR 0.66%)

IV- Results and discussion:

- The risk of fatal and non-fatal ischaemic heart disease and fatal and non-fatal stroke was significantly lower in the polypill group than the minimal care group.

	Polypill group (n=3421)	Minimal care group (n=3417)	HR* (95% CI)	Adjusted HR† (95% CI)	p value
Fatal ischaemic heart diseases	21 (0·6%)	41 (1·2%)	0·50 (0·29–0·85)	0·51 (0·30–0·87)	0·014
Non-fatal ischaemic heart diseases	127 (3·7%)	169 (4·9%)	0·75 (0·59–0·96)	0·74 (0·58–0·96)	0·021
Fatal stroke	8 (0·2%)	21 (0·6%)	0·37 (0·17–0·81)	0·38 (0·18–0·82)	0·013
Non-fatal stroke	17 (0·5%)	39 (1·1%)	0·43 (0·23–0·81)	0·44 (0·23–0·82)	0·010
Sudden death	19 (0·6%)	28 (0·8%)	0·68 (0·36–1·28)	0·69 (0·36–1·32)	0·26
Heart failure	15 (0·4%)	18 (0·5%)	0·83 (0·42–1·65)	0·80 (0·40–1·59)	0·53
Non-cardiovascular causes of death	149 (4·4%)	123 (3·6%)	1·23 (0·95–1·58)	1·26 (0·98–1·62)	0·071
Overall mortality	202 (5·9%)	222 (6·5%)	0·90 (0·74–1·09)	0·93 (0·77–1·11)	0·43

Data are n (%) unless otherwise indicated. HR=hazard ratio. *We obtained HRs and 95% CIs by Cox regression models with shared frailty. †Adjusted models were adjusted for age, sex, pre-existing major cardiovascular events, diabetes, and hypertension.

Table 3: Risk of secondary outcomes in polypill and minimal care groups

IV- Results and discussion:

- A significantly greater reduction in systolic (but not diastolic**) blood pressure** in the polypill group at month 24 (mean difference –3.05 mm Hg). At month 60, the reductions in both the systolic and diastolic blood pressures were slightly greater in the polypill group compared with the minimal care group, but these differences were not significant.

- Reductions in baseline **LDL cholesterol** levels were significantly greater in the polypill group, both at month 24 (mean difference –24.65 mg/dL) and at the end of the study (–19.54 mg/dL).

IV- Results and discussion:

- Adverse events were comparable between the polypill arm and the minimal care arm, respectively, suggesting that polypill tablet could reduce cardiovascular outcomes without additional adverse events:

* Intracranial hemorrhage: 10 participants (0.29%) to 11 participants (0.32%), respectively.
* Peptic ulcer disease: 34 participants (1.13%) to 35 participants (1.18%), respectively.
* Upper gastro-intestinal bleeding:13 participants (0.43%) to 9 participants (0.30%), respectively.

IV- Results and discussion:

- The results were consistent among men and women, younger and older individuals, and those with or without preexisting hypertension or a high blood cholesterol level.

- As a post-hoc analysis, it was found that a longer duration of polypill use was associated with a stronger protective effect.

- A greater reduction (57%) in the risk of MCVE in participants with high adherence to the polypill.

IV- Results and discussion:

- This study showed relatively high adherence to polypill (median adherence=80.5%) which remained stable through the study period. The proportion of participants with high adherence to polypill was significantly greater in men and those with preexisting hypertension, and significantly lower in participants with pre-existing cardiovascular disease and smokers.

- 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. However, it is important to note that PolyIran was conducted within the framework of GCS. The participants in GCS have been followed up for over 12 years and the well-established GCS infrastructure and participants' involvement may have influenced the adherence rate to some extent.

IV- Results and discussion:

- Between the **Polypill group and the Minimal care group, respectivelt,** we found **no significant differences** in the risk of:
- overall mortality (5.9% to 6 · 5%),
- non-cardiovascular event mortality (4.4% to 3.6%),
- sudden death (0.6% to 0.8%)
- and heart failure (0.4% to 0.5%).

V- Limitations:

- A fixed-dose combination pill for all participants, including primary and secondary prevention individuals. Flexible options (i.e. different dosage levels for each drug and different combinations to tailor for specific clinical settings) may improve drug adherence and efficacy.

- Healthy lifestyle education (e.g., face-to-face training 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 have underestimated the size of the benefits of the polypill.

- In this study polypill was not associated with a significant reduction in the overall mortality rate. This may be due to the relatively short follow-up (5 years). Further studies with longer periods of polypill use and more extended follow-up can allow to evaluate the potential effects on overall mortality.

VI- Conclusion:

- Prior to The PolyIran study, the duration of trials on the polypill concept were short and mostly focused on LDL-cholesterol and blood pressure as the primary outcome. The present fully powered large scale trial over 5 years in a rural population in Iran allowed the direct assessement the value of the polypill compared to lifestyle modification on CVD-related mortality and morbidity.

- One of the strengths of this study is that it comprises subjects with or without a history of CVD and addresses the effectiveness of the polypill in both primary and secondary prevention.

VI- Conclusion:

- The PolyIran Study, using a fixed-dose combination of aspirin, atorvastatin, and two blood pressure lowering drugs was associated with a significantly lower risk of major cardiovascular events in 50-75 year-old individuals in a real-life setting.

- This pragmatic trial provides evidence that a low-cost polypill could be considered as part of the preventive strategies to reduce CVD burden among eligible adults, especially in the LMICs.

Thank you for your attention