Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: **Effectiveness of Polypill for Primary and Secondary Prevention of Cardiovascular Disease (PolyPars): A Pragmatic Cluster-Randomized Controlled Trial**

Supplementary Table 1. Reasons for not referring

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

Supplementary Table 2. Baseline demographic characteristics of invitees referring versus non-referring invitees to participate in the study.

	Referring	Non-referring	All	P-value
All	5,004	426	5,430	
Sex				
Female N (%)	2,762 (55.2%)	221 (51.9%)	2,983 (54.9%)	0.186
Male N (%)	2,242 (44.8%)	205 (48.1%)	2,447 (45.1%)	
Age years mean (SD)	57.1 (6.9)	57.5 (7.5)	57.1 (6.9)	0.266
Ethnicity				
Fars	2,840 (56.7%)	219 (51.4%)	3,059 (56.3%)	0.089
Turk	1,920 (38.4%)	186 (43.7%)	2,106 (38.8%)	
Other	244 (4.9%)	21 (4.9%)	265 (4.9%)	
Marital Status				
Married	4,393 (87.8%)	361 (64.7%)	4,754 (87.6%)	0.067
Non-married	611 (12.2%)	65 (15.3%)	676 (12.4%)	
Education				
Literate	1,889 (37.7%)	138 (32.4%)	2,027 (37.7%)	0.028
Illiterate	3,115 (62.3%)	288 (67.6%)	3,403 (62.7%)	
Wealth score				
Quintile 1	1,231 (24.6%)	145 (34.0%)	1,376 (25.3%)	< 0.001
Quintile 2	867 (17.3%)	74 (17.4%)	941 (17.3%)	
Quintile 3	1,126 (22.5%)	81 (19.0%)	1,207 (22.2%)	
Quintile 4	851 (17.0%)	59 (13.9%)	910 (16.8%)	
Quintile 5	929 (18.6%)	67 (15.7%)	996 (18.4%)	

Supplementary Table 3. The 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 last 3 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 haemophilia	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%)
Severe 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%)
Haemoglobin<10 mg/dl in females and <11 mg/dl in males	50 (1.81%)	32 (1.43%)	82 (1.64%)
Systolic blood pressure <90 mmHg and diastolic blood pressure <60 mmHg	60 (2.17%)	48 (2.14%)	108 (2.16%)
Medical/psychiatric comorbidities	46 (1.67%)	29 (1.29%)	75 (1.50)

Supplementary Table 4. Baseline anthropometric measurements, blood pressure level, and main lab markers in Polypill and Control arms.

	Polypill	Control	All	P-value
All	2,200	2,215	5,430	
BMI mean (SD)	25.9 (4.7)	25.7 (4.6)	25.8 (4.6)	0.194
SBP mean (SD)	123.5 (19.3)	126.3 (20.0)	124.9 (19.7)	<0.001
DBP mean (SD)	77.8 (11.8)	79.6 (12.0)	78.7 (12.0)	<0.001
Total Cholesterol mean (SD)	201.3 (42.6)	201.1 (42.2)	201.2 (42.4)	0.874
HDL	47.2 (11.5)	49.1 (11.4)	48.2 (11.5)	<0.001
LDL	122.0 (34.5)	119.2 (34.7)	120.6 (34.6)	0.0078
Triglyceride	160.9 (97.0)	164.5 (88.7)	162.7 (92.9)	0.193
FBS	107.7 (38.6)	108.8 (37.4)	108.2 (38.0)	0.324
Creatinine	0.99 (0.22)	1.00 (0.31)	1.00 (0.27)	0.400
AST	19.0 (9.4)	18.7 (9.9)	18.9 (9.7)	0.335
ALT	17.9 (10.5)	18.1 (13.7)	18.0 (12.2)	0.653
ALP	247.3 (72.8)	246.4 (73.8)	246.8 (73.3)	0.684
GGT	23.3 (16.5)	23.5 (18.1)	23.4 (17.3)	0.674
Hemoglobin	13.4 (1.5)	13.4 (1.5)	13.4 (1.5)	0.452
Platelet	248.9 (65.8)	247.0 (76.9)	247.9 (71.6)	0.381

Supplementary Table 5. Side effects and adverse events

	Control	Polypill	P-value
Participants included in analysis	2,215	2,200	
Muscle pain	158 (7.1%)	217 (9.9%)	<0.001
Dizziness	668 (30.2%)	1,033 (47.0%)	<0.001
Dyspepsia	1,077 (48.6%)	1,245 (56.6%)	<0.001
Regurgitation of food or liquid	585 (26.4%)	690 (31.4%)	<0.001
Heart burn	546 (24.7%)	777 (35.3%)	<0.001

Data are n (%). P-values are based on chi square test.

Effectiveness of Polypill for Primary and Secondary Prevention of Cardiovascular Disease (PolyPars)

Statistical Analysis Plan

Introduction: There is accumulating evidence regarding the impact of fixed-dose combination treatment strategies (Polypill) on primary prevention of cardiovascular disease, myocardial infarction, stroke, and cardiovascular death. Recently, large-scale randomized controlled trials (RCTs) were conducted on primary prevention of cardiovascular diseases by FDC therapies. More recently, a systematic review was performed and three main RCTs (TIPS-3, HOPE-3, and PolyIran)[1-3] were included in an individual participant data meta-analysis.[4] The primary outcome was time to first occurrence of a composite of cardiovascular death, myocardial infarction, stroke, or heart failure. Additional outcomes included individual cardiovascular outcomes and death from any cause. The results were published in the Lancet, indicating significant reductions in the primary outcome and its components in the analyses of Polypill with and without aspirin, with greater reductions for strategies including aspirin. Treatment effects were similar at different lipid and blood pressure levels, and in the presence or absence of diabetes, smoking, or obesity.[4]

The current study is an extension to the previous studies for primary and secondary prevention of CVD using fixed-dose combination strategy in a distant rural area in south of Iran

Objective: To quantify effects related to Polypill therapy in primary and secondary CVD prevention among participants aged 50 years and over.

to estimate the effect of Polypill versus control (minimal care) for the following clinical endpoints:

a. composite of acute coronary syndrome (non-fatal myocardial infarction and unstable angina), fatal myocardial infarction, non-fatal and fatal stroke, sudden death, and heart failure (primary outcome),
b. Each component CV outcome, and
c. Non-CVD mortality
d. Total mortality

Baseline variables:

- Sex
- Age
- Baseline 10-year CVD risk based on WHO 2019 risk charts
- History of hypertension, diabetes, dyslipidemia
- Smoking history
- Alcohol use history

- Measures of obesity
- Systolic and diastolic blood pressure
- Cholesterol measures (LDL, HDL, total cholesterol, non-HDL cholesterol)
- Dysglycemia measures (HgbA1C, Fasting blood glucose)

Follow-up variables (including primary clinical end-points of interest):

- Death (cause specific)
- Myocardial infarction
- Stroke
- Heart failure
- Cardiac arrest
- Angina (new or worsening)

Statistical analysis: De-identified cleaned data will be used for statistical analysis. Standard descriptive summary measures (means for continuous variables, percentages for categorical variables) will be examined to understand their distribution across the included studies.

For the time to event data, Cox proportional hazard regression models will be used. The plausibility of the proportional hazards assumption will be assessed using standard log (-log survival) versus log time plots. To account for the cluster randomization, shared frailty models will be used, with cluster effects as random effects. Study treatment will be used as a covariate in the model. Effect sizes on the primary outcome will be estimated for pre-specified subgroups of sex, age, pre-existing hypertension, pre-existing diabetes, baseline cholesterol, smoking, and pre-existing CVD. Effect sizes will be estimated for secondary outcomes. Effect sizes will be reported as hazard ratios with 95% confidence intervals, and where p-values are reported a value of 0.05 or less will be considered statistically significant. Both unadjusted and adjusted models will be reported. Adjustment will be made for sex, age, diabetes mellitus, hypertension, and history of major cardiovascular events. Adverse events and side effects will also be compared between Polypill and control groups. Absolute risk reductions and corresponding numbers needed to treat to prevent a CV event will be calculated. Trends in blood pressure will be monitored throughout the study.

References

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