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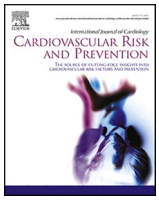

Reducing premature mortality from cardiovascular diseases in low and middle income countries: The role of Polypill in public health policy

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ABSTRACT

Premature deaths account for about half of all fatalities in developing countries. In low- and middle-income countries, cardiovascular diseases have consistently been the primary cause of premature mortality for men and women during the past three decades.

Current evidence indicates that fixed-dose combination therapy, the so-called Polypill, effectively reduces the burden of cardiovascular diseases, with greater benefits observed in combinations that include aspirin. Polypill demonstrates high adherence and an acceptable safety profile, with adverse drug events being comparable between the groups receiving treatment and those in the control group.

Therefore, this paper advocates for the broader implementation of Polypill in low and middle-income countries, emphasizing its efficacy in the primary and secondary prevention of cardiovascular diseases. The strategy could also benefit high-risk groups with special conditions, such as non-alcoholic fatty liver disease and chronic kidney disease. The cost-effectiveness of Polypill and its potential to address health inequities in low and middle-income countries underscore its value as a public health strategy. Policymakers are encouraged to consider Polypill as a viable option to enhance cardiovascular health outcomes and reduce premature deaths in low-resource settings.

1. Introduction

Premature deaths, defined as fatalities occurring before the age of 70 years, account for about half of all fatalities in developing countries [1]. In alignment with sustainable development goal 3.4 (SDG 3.4), which aims for a one-third reduction in premature mortality caused by non-communicable diseases (NCDs) by the year 2030, it is critical for all countries to monitor the burden of cardiovascular diseases (CVD) as the main causes in the category of NCDs [2]. In 2021, cardiovascular conditions were responsible for almost 20 million deaths, accounting for approximately 28.6 % of all deaths worldwide. Notably, ischemic heart disease has emerged as the primary cause of premature death among men in 146 countries and among women in 98 countries [1,2]. Low- and middle-income countries (LMICs) carry a disproportionate burden, contributing to 80 % of the global cardiovascular mortality and the burden is forecasted to show a substantial rise in low-resource countries [3].

Despite extensive efforts, current strategies for primary and secondary prevention of CVD have achieved only modest success. This gap represents a global public health issue, as many premature deaths from CVD are preventable [4]. This situation underscores the urgent need for innovative treatment paradigms and a more inclusive healthcare strategy to address the growing global burden of CVD [4].

One innovative approach to preventing cardiovascular disease is fixed-dose combination (FDC) therapy, commonly known as Polypill. Combining multiple drugs into a single daily pill, the Polypill, addresses key risk factors such as high blood pressure and high cholesterol levels. Typically, Polypill consist of one or more antihypertensive medications

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along with a statin, with some formulations also incorporating an antiplatelet medication. Since its inception around 20 years ago, various Polypill formulations have been evaluated in numerous studies worldwide [5,6]. However, despite its potential, Polypill is still not widely available or commonly used [7]. In 2023, the World Health Organization included the cardiovascular Polypill in its list of essential medicines, marking a pivotal step towards broader implementation [8].

This article will discuss the importance and challenges of using the Polypill in Iran as an LMIC.

2. The burden of cardiovascular disease in Iran

In Iran, a LMIC in the Middle East with a population exceeding 88 million, CVD has consistently been the foremost cause of mortality for both men and women during the past three decades, resulting in a high rate of premature fatalities. Between 1990 and 2021, the age-standardized mortality rate due to CVD declined from 446.3 per 100,000 (95 % uncertainty interval (UI): 411.5–471.3) to 254.5 per 100,000 (95 % UI: 230.2–271.4). Despite the decreasing rate, the number of deaths caused by CVD in Iran increased from over 86 thousand deaths in 1990 to almost 170 thousand deaths in 2021, mainly due to population growth and ageing. In 1990, a total of 47 thousand deaths due to CVD (55 % of total deaths) were premature, while the corresponding number reached over 56 thousand (33 % of total deaths) in 2021 [1,2]. Research indicates that CVDs tend to manifest at an earlier age in Iran compared to high-income countries [9,10]. In addition to mortality, CVD also causes significant disability among the general population in Iran. The results of the Global Burden of Disease study demonstrate that CVD caused over 2.4 million disability-adjusted life years in 1990 in Iran, which increased to over 3.7 million years lost due to both mortality and disability in 2021 in both sexes combined [11]. These estimates emphasize the critical need for targeted interventions and comprehensive strategies within Iran's healthcare system to effectively curb the increasing burden of CVDs, including both mortality and disability in this country.

3. Challenges in current CVD management

Despite the significant advancements in cardiovascular medicine over the past five decades, many communities remain unable to access the essential tools and knowledge necessary to enhance cardiovascular health. These resources, crucial for diagnosing, preventing, and treating CVDs, are often out of reach for those most in need. Notably, around 80 % of CVD-related deaths occur in LMICs, such as Iran, while advancements in cardiovascular health are predominantly concentrated in high-income countries. This stark disparity underscores an inequity in health that demands proper action. The primary challenge in these regions stems from inadequate infrastructure and insufficient financial resources. However, investing in preventive strategies offers a critical opportunity for long-term cost savings.

In Iran, the situation is further complicated by international sanctions, which, according to recent studies, have been directly linked to an increase in mortality from NCDs among the Iranian population [12]. Additionally, Iran struggles with a lack of comprehensive knowledge on burden and cost of cardiovascular diseases in the general population, a significant challenge given the high prevalence of CVDs in the country that needs to be addressed [13].

4. The Polypill: an innovative approach

Preventing CVDs can be effective by targeting key modifiable risk factors such as hypertension, diabetes, dyslipidemia, low physical activity, and smoking. Although individuals with a history of cardiovascular diseases have a four-fold higher risk of death or non-fatal events, 80 % of all cardiovascular events occur in those without prior CVD. This underscores the need to prioritize both primary and secondary prevention strategies, ensuring a comprehensive approach to tackling cardiovascular disease [4].

While personalized medicine and individualized risk factor control are theoretically ideal, these approaches require extensive screening and risk stratification, which are both complex and costly. In many LMICs such methods are impractical. This reality highlights the urgent need for more inclusive and scalable prevention strategies [4].

About twenty years ago, Professors N. J. Wald and M. R. Law introduced the concept of the Polypill. Their research suggested that a Polypill formulation—including a statin, three blood pressure lowering medications, folic acid, and aspirin—could potentially prevent over 80 percent of heart attacks and strokes if taken by all individuals aged 55 and older, as well as by individuals with existing cardiovascular disease. They postulated that the Polypill can have an acceptable safety profile and concluded that its widespread use could significantly enhance disease prevention in the Western world, more than any other individual measure [6].

Since then, three main randomized controlled clinical trials (RCTs) have been conducted worldwide on the effectiveness of Polypill. These include the Heart Outcomes Prevention Evaluation (HOPE)-3 trial [14–16], International Polycap Study (TIPS)-3 [17,18], and PolyIran [19]. The characteristics of these studies is demonstrated in Table 1. All three trials included over 1000 participants followed for a median of at least 2 years and all of them demonstrated a statistically significant reduction in the risk of major cardiovascular events, defined as a composite of cardiovascular death, myocardial infarction, stroke, or arterial revascularization.

Later, a notable individual participant data (IPD) meta-analysis in 2021 combined data from these three significant trials and focused on primary prevention of CVD. This analysis included 18,162 participants free from previous CVD, with a mean age of 63 years and an estimated 10-year CVD risk of 17.7 %. Over a median follow-up of five years, major cardiovascular events occurred less frequently in the Polypill group than in the control group, resulting in a hazard ratio (HR) of 0.62 (95 % CI 0.53–0.73, $p < 0.001$). Greater benefits were observed in groups that included aspirin. Although the incidence of gastrointestinal bleeding was slightly elevated in the aspirin group, the difference was not statistically significant. Other adverse events, including hemorrhagic stroke, fatal bleeding, and peptic ulcer disease, were infrequent and showed no significant differences between groups. However, dizziness was more frequently reported in the Polypill group [20]. Another IPD meta-analysis from these trials, stratified by age, demonstrated larger benefits in major cardiovascular events for older age demographics (HR: 0.58, 95 % CI 0.42 to 0.78 for ages 60–65 years, and 0.57, 95 % CI 0.47 to 0.70 for ages 65 and older). The effect was significantly greater with combinations that include aspirin. Dizziness was the most commonly reported adverse effect, particularly in those younger than 65 years. There was no significant increase in bleeding with aspirin use [21].

In 2023, a systematic review and meta-analysis of RCTs evaluated the effects of Polypill on treatment adherence and cardiovascular outcomes in comparison to standard care for the secondary prevention of CVDs. This review encompassed eight RCTs involving a total of 6541 participants, with half of them receiving the Polypill. The follow-up periods varied between 6 and 60 months. The results demonstrated that for patients with existing CVD, Polypill was linked to reduced cardiovascular mortality and enhanced adherence to therapy, indicating that the pill could be a favorable option for this group of patients [22].

Ultimately, in 2016 an RCT called PolyPars, was launched in south of Iran. This trial replicated the exact protocol of PolyIran. However, the population in PolyPars was quite different from PolyIran in terms of ethnicity, diet, and culture. This study enrolled 4415 participants aged 50–75 years, with 2200 in the intervention group and 2215 in the control group. The protective effect of Polypill was replicated for incidence of major cardiovascular events. The HR for the primary outcome was 0.50 (95 % CI 0.38 to 0.65) when comparing the Polypill group to the control group. However, results were not significant for CVD

Table 1
Study characteristics: HOPE-3, TIPS-3, PolyIran, PolyPars.

	Number of participants	Study design	Median follow-up (years)	Components of Polypill	Control	Locations
TIPS-3	5713	Double-blind, placebo-controlled 2 × 2 × 2 factorial design	4·4 (3·2–5·9)	simvastatin 40 mg, ramipril 10 mg\ atenolol 100 mg hydrochlorothiazide 25 mg aspirin 75 mg	Matching placebos	Bangladesh, Canada, Colombia, India, Indonesia, Malaysia, Philippines, Tanzania, Tunisia
HOPE-3	12,705	Double-blind, placebo-controlled 2 × 2 factorial design	5·5 (5·1–6·2)	rosuvastatin 10 mg candesartan 16 mg hydrochlorothiazide 12·5 mg	Matching placebos	Argentina, Australia, Brazil, Canada, China, Colombia, Czech Republic, Ecuador, Hungary, India, Israel, South Korea, Malaysia, Netherlands, Philippines, Russia, Slovakia, South Africa, Sweden, UK, Ukraine
PolyIran	6838	Pragmatic, cluster-randomised	5·0 (4·9–5·0)	atorvastatin 20 mg hydrochlorothiazide 12·5 mg enalapril 5 mg (or valsartan 40 mg) aspirin 81 mg	Minimal care	Iran
PolyPars	4415	Pragmatic, cluster-randomised	5·0 (4·9–5·0)	atorvastatin 20 mg hydrochlorothiazide 12·5 mg enalapril 5 mg (or valsartan 40 mg) aspirin 81 mg	Minimal care	Iran

mortality. No notable differences in adverse drug effects were observed between the groups [23,24].

5. Polypill implementation in Iran

Improving cardiovascular health globally requires tailored approaches, as each population faces unique risk factors influenced by their location and lifestyle. At the global scale, in 2021 almost 20.0 % of all CVD deaths were attributable to joint metabolic risk factors. Specifically, 15.3 % were attributable to high blood pressure, 6.6 % were attributable to particulate matter pollution, 5.4 % were attributable to high LDL, 3.3 % were attributable to smoking, 3.3 % were attributable to high fasting plasma glucose, 3.1 % were attributable to kidney dysfunction, and 2.8 % were attributable to high body mass index (BMI) [25]. However in Iran, a total of 22.3 % of all CVD deaths were attributable to joint metabolic risk factors, ranked in descending order by high blood pressure (15.8 %), high LDL (7.4 %), particulate matter pollution (6.8 %), high BMI (5.4 %), and high fasting plasma glucose (4.1 %). Smoking ranked 9th as a risk factor for CVD mortality [25]. The contribution of specific risk factors to CVD mortality further varies between men and women, between age groups, and across provinces in Iran. Policies should therefore, be tailored to specific needs of subpopulations vulnerable to each of these risk factors. Yet, considering the high contribution of high blood pressure and high LDL to CVD mortality, the utilization of the Polypill that exactly addresses these two risk factors further justifies its use at large scale.

6. Assessing the efficacy of the Polypill in high-risk groups

Recently, the understanding of cardio-metabolic diseases has evolved, highlighting their complexity and interrelated nature. Cardiometabolic diseases encompass a range of interconnected conditions that significantly impact cardiovascular and metabolic health, including non-alcoholic fatty liver disease (NAFLD), chronic kidney disease (CKD), and their overlap with diabetes and metabolic syndrome.

Many of the risk factors for NAFLD, such as central obesity, high blood pressure, high fasting plasma glucose, and dyslipidemia overlap with those for CVD. While individual risk factors play a role, the presence of NAFLD independently elevates the risk of CVD compared to individuals who share the same risk factors but do not have the disease. NAFLD is linked to a heightened long-term risk of both fatal and non-fatal CVD events. This risk becomes even greater as liver disease progresses, particularly in cases with higher stages of fibrosis [26,27]. Preventing CVD, a leading cause of death among individuals with NAFLD, is a critical management goal, despite the lack of effective medical treatments for the liver condition itself. A pragmatic RCT in Iran, the PolyLiver study, demonstrated significant benefits of the Polypill in patients with NAFLD. PolyLiver had the same protocol as the original PolyIran study. However, the presence of non-alcoholic steatohepatitis was determined by ultrasonography and elevated liver enzymes at the beginning of the study. Results of the study demonstrated that Polypill is safe and effective for preventing CVD even among participants with elevated liver enzymes and fatty liver. These findings suggest that Polypill is safe and effective in preventing CVD, highlighting its potential for broader use in managing cardiovascular health in high-risk populations [28,29]. Additionally, results of a clinical trial including 1596 participants showed that Polypill was particularly effective in reducing cardiovascular events among metabolic dysfunction associated fatty liver disease patients compared to the general population [30].

Similarly, patients with CKD face a heightened risk of cardiovascular outcomes. This is particularly concerning as CKD presents an increasingly significant health concern. Even in the early stages of CKD, the incidence and prevalence of cardiovascular events are significantly higher compared to the general population. This risk escalates substantially in the advanced stages of CKD (stages 4–5). In fact, in this high-risk population, CVD is the leading cause of death, exceeding the mortality rate from end-stage kidney disease [31]. An IPD meta-analysis that assessed the effect of Polypill among CKD patients showed that in participants with low glomerular filtration rate (eGFR), Polypill was significantly more effective (HR = 0.49; 95 % CI: 0.36 to 0.66) compared to participants with normal GFR (HR = 0.68; 95 % CI: 0.57 to 0.81). The combination strategies that included aspirin showed a greater relative risk reduction compared to those without it. Except for occasional dizziness, the side effects between the treatment and control groups showed no significant difference, irrespective of kidney function stage. Results showed that Polypill is both effective and safe for preventing cardiovascular disease across various levels of kidney function, with adults having low eGFR experiencing greater relative and absolute risk reductions [32].

7. Cost-effectiveness of the fixed-dose combination pill

A 2022 systematic review demonstrated that Polypill meets or falls

below widely accepted cost-effectiveness thresholds. It enhances adherence and improves quality of life at a cost comparable to or lower than that of multiple monotherapies in primary and secondary prevention of CVD. Key factors influencing the cost-effectiveness of the Polypill include its price, patient adherence, age, baseline CVD risk, and the specific drug combination used. However, the study noted that further long-term economic evaluations are necessary to validate these findings across larger and more diverse populations over extended periods [33]. A 2024 IPD meta-analysis of three large RCTs (HOPE-3, PolyIran, and TIPS-3) assessed the cost-effectiveness of Polypill-based strategy for primary CVD prevention. The analysis revealed that in high-income countries, the Polypill is cost-neutral when produced at cost-effective prices. Governments in LMICs and upper-middle-income countries should evaluate these findings against their own cost-effectiveness thresholds and healthcare priorities. Focusing on this approach for patients with a high 10-year risk of CVD may be an effective starting point [34].

8. Future-Proofing health systems for the Elderly

The current study focuses on the need to curb the increasing trend in premature deaths due to CVD in Iran, but it is also essential to consider the wider issue of an aging population. When international health authorities and ministries of health were first established, life expectancy at birth ranged from approximately 50 to 70 years. Since then, healthcare systems have struggled to adapt to the needs of people who now often live beyond 70 years, lacking proper incentives for this adaptation.

To effectively support older populations, healthcare systems should be redesigned. This includes addressing the impact and costs associated with chronic conditions, emphasizing value-based healthcare, and prioritizing the prevention of chronic diseases rather than solely treating them. Currently, there are robust screening and health visit programs for infants and younger individuals, but similar initiatives for older populations are lacking. Regular check-ups and physical examinations, such as blood pressure monitoring and abdominal circumference measurements, are essential for this age group. Strengthening public health initiatives, investing in long-term care improvements, and utilizing big data and advanced analytics to enhance preventive care will be crucial. These steps will help ensure that the additional years people are living are healthier and more fulfilling through reducing disability.

9. Conclusion

This article highlights the potential of Polypill to substantially lower premature CVD mortality and disability in Iran. Evidence from multiple trials, including the PolyIran study, demonstrates that fixed-dose combination therapies, especially those with aspirin, effectively reduce the CVD burden with a very good safety profile.

Broad implementation of Polypill in Iran can provide substantial benefits, particularly for high-risk groups such as those with NAFLD and CKD. Its cost-effectiveness and ability to address health inequities make it a valuable public health strategy. Policymakers are encouraged to adopt Polypill in order to improve cardiovascular health outcomes and reduce premature CVD deaths in Iran.

Author agreement form

This statement is to certify that all authors have seen and approved the manuscript being submitted, have contributed significantly to the work, attest to the validity and legitimacy of the data and its interpretation, and agree to its submission to the *International Journal of Cardiology*.

We attest that the article is the Authors' original work, has not received prior publication and is not under consideration for publication elsewhere. We adhere to the statement of ethical publishing as appears in the International of Cardiology (citable as: Shewan LG, Rosano GMC, Henein MY, Coats AJS. A statement on ethical standards in publishing scientific articles in the International Journal of Cardiology family of journals. Int. J. Cardiol. 170 (2014) 253–254 DOI:10.1016/j.ijcard.2013.11).

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All authors are requested to disclose any actual or potential conflict of interest including any financial, personal or other relationships with other people or organizations within three years of beginning the submitted work that could inappropriately influence, or be perceived to influence, their work. If there are no conflicts of interest, the COI should read: "The authors report no relationships that could be construed as a conflict of interest".

CRediT authorship contribution statement

Sadaf G. Sepanlou: Conceptualization, Investigation, Methodology, Writing – original draft, Writing – review & editing. **SeyedehFatemeh Mousavi:** Conceptualization, Investigation, Writing – original draft, Writing – review & editing. **Hossein Poustchi:** Conceptualization, Investigation, Methodology, Writing – review & editing. **Fatemeh Malekzadeh:** Conceptualization, Investigation, Methodology, Writing – review & editing. **Gholamreza Roshandel:** Conceptualization, Investigation, Methodology, Writing – review & editing. **Reza Malekzadeh:** Conceptualization, Methodology, Project administration, Supervision, Writing – review & editing.

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Declaration of competing interest

Authors declare no conflict of interests.

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