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EVIDENCE-BASED MEDICINE, CLINICAL TRIALS AND THEIR INTERPRETATIONS (K. NASIR, SECTION EDITOR)

Polypills in Cardiovascular Disease Prevention: Mass-Strategy Approach, Precision Medicine, or an Essential Intertwine Between Them?

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Abstract

Purpose of Review This review considers the framework of high-risk vs. population approaches as proposed in the Rose's axiom within the context of cardiovascular diseases, including its benefits and limitations. We also contextualize the use of precision medicine in primary prevention therapy and contrast that with population approach.

Recent Findings Although the high-risk strategy aims at individualized care, the complexity of pharmacologic regimens and other limitations reduces its real-life impact. On the other hand, broad population strategies include treatment of a substantial number of low-risk individuals who are unlikely to benefit from treatment. The use of additional strategies to identify those low-risk individuals, instead of targeting at identifying the high-risk population, is and alternative strategy to be considered. Evidence of the potential use of coronary artery calcium score and polypills for this strategy is discussed.

Summary A more targeted population approach to primary prevention in cardiovascular diseases with the use of polypills and coronary artery calcium score might be considered in a structured mass-strategy approach to risk reduction.

Keywords Polypill · Calcium score · Personalized medicine · Cardiovascular disease

Introduction: ASCVD and Economy Affects

Despite the reduction in the incidence of deaths from atherosclerotic cardiovascular disease (ASCVD) in the last 50 years, the current economic impact is still alarming. Annually in the USA, heart disease causes spending close to US$ 218 billion; stroke costs an additional US$ 45 billion and the other peripheral vascular diseases, US$ 30 billion. Projections show that direct costs with all ASCVD may exceed $ 750 billion (more than half in hospital expenses) by 2035, besides US$ 350 billions in disease-related productivity losses [1].

Globally, developed countries show different scenarios from developing countries. In low- and middle-income countries, declines in ASCVD mortality rates are much less prominent and account for 75% of the 15.2 million people who died of heart disease and stroke worldwide in 2016. In addition, these countries comprise 86% of all premature deaths from ASCVD, resulting in cumulative losses of $ 7 trillion from 2013 to 2028 [2].

Among the public health problems that still contribute to the worrying cardiovascular disease incidence in the world (such as unhealthy diet, physical inactivity, smoking, access to quality health care), adherence to drug treatment is a topic discussed more three decades that is remain unresolved [3, 4]. Several well-known circumstances hamper the success of the therapy, both by the health system, including issues such as difficult access to the system and its continuity in treatment, incomplete communication between the health team and the patient, high medication costs, and patient-related challenges, such as impaired social support, physical or cognitive

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limitations, socioeconomic limitations. However, the most explicit problem associated with pharmacological therapy is the treatment complexity, with several daily doses of different drugs and multiple timeframes and frequent changing in medication regimen. In addition, the patient often has no symptoms of his disorders [5]. Based on this scenario, the thought of a structure systematization of this treatment might act directly on this problem and indirectly on the other aforementioned ones.

Cardiovascular Disease and Rose's Axiom

Although most of the population is not classified as high risk for cardiovascular events, those non-high-risk individuals account for most of the absolute number of events. This is known as Rose's axiom, "A large number of people exposed to low-risk is likely to produce more cases than a small number of people exposed to a high-risk." [6] In the American population, for example, about 90% of the people have up to two risk factors and are likely to be risk stratified as low or intermediate risk for cardiovascular events by most of the current calculators available for use [7].

The first cardiovascular risk calculators were based on population scoring algorithms based on traditional risk factors and were the cornerstone of preventive cardiology [8]. From this segmentation of risk levels, those detected at the top of the risk are referred for specific preventive treatment. This classic approach based on the risk factors that select "high-risk" individual is singly successful, but it has a limited impact on the overall burden of the disease [9].

In this scenario, the American Heart Association published the Life's Simple 7 (LSS), seven criteria to define "cardiovascular health" based on traditional risk factors: smoking, body mass index, physical activity level, healthy diet, total cholesterol, blood pressure, and fasting glucose. Studies using the LSS show how a sizeable proportion of the community is exposed through at least one of these non-ideal factors: in a registry with >200,000 veterans, only 1% was in an ideal condition in 5 or more LSS metrics [10]. The LSS strategy suggests that non-pharmacological and pharmacologic interventions should be targeted at those 7 characteristics even for individuals who are not at high risk of events.

Mass-Strategy Approach vs Precision Medicine

The *mass-strategy approach* is focused on efforts to reduce the risk by shifting the entire distribution of a risk factor through measures in which the entire population, or at least a substantial part, is involved. Examples include dietary interventions, moderation of salt intake, anti-smoking programs, whose potential benefits can be compared with what is currently achieved by the specific disease detection and treatment strategies [11]. Although the broad approach is necessary and definitive to answer high prevalence conditions, it offers little to each participating individual. This means several individuals will derive only small or no benefit at all. Yet, the population level benefit would be substantial. In this "prevention paradox," the interventions that bring enormous benefits to the community may not generate individual motivation due to the low measurable individual impact [9].

One attempt to sort this conundrum is and improvement in risk stratification with the inclusion of additional patient characteristics such as additional tests to better identify higher risk individuals. This strategy tries to improve individual patient selection to better tailor the high-risk approach to a refined risk stratification strategy. The concept of adding several additional biomarkers such as genetic information from polygenic risk scores has been referred to as *precision medicine*. This is emerging as a promising strategy, aiming at prevention and treatment based on specific differences in genetics, environmental exposures, and lifestyle that determine an individual's disease phenotype. Precision medicine seeks to identify beyond those stratified at "high risk" [12]. The ideal approach would be unique and not based on the average population; it would include an individualized profile with additional data such as from metabolomics, proteomics, transcriptomics, and epigenomics analyses. In other areas of medicine, especially oncology, this is an already established approach to the patient diagnosis, treatment, and prognosis based on its molecular profile [13]. However, its real-life implementation is more complex and harder, more complex than it may sound. There are several issues related to external validation of such biomarkers in different populations with variable genetic background, racial, ethnic, socioeconomic, environmental, and behavioral characteristics. Thus, unless additional risk information provided by those markers is robust to those characteristics, the routine use of strategies based on such findings can be flawed. Still, when adequately validated, precision medicine and additional risk stratification can provide unique important clinical prognostic information to aid in decision-making.

Although population-based strategies and precision medicine may be seen as opposing treatment choices, a more critical understanding of their use may allow to understand them as complementary. In the present document, we provide a rationale as to why the critical understanding for the combination of both therapies is likely to fill the gap between the two strategies with a more selective use of population-based strategies.

Polypills in the Mass-Strategy Approach: Is It Really for All Mass?

Due to the complexity of a multifaceted pharmacologic strategy to reduce cardiovascular risk, several authors have

proposed the use of a fixed dose, single pill prescription to reduce cardiovascular risk at a population level. This strategy as a conceptualized pharmacologic approach to reduce cardiovascular risk base on Rose's axiom and the shift in the distribution of all risk factors with an intervention targeted at the entire middle age and older population, regardless of the risk burden.

Those polypills are a combination of fixed-dose medications with a long half-life, making them easy to administer leading to reduced time to take the medications and improved adherence. Second, the systematic use of the polypill would probably reach most people who need drug intervention for vascular risk factor diseases. Although each of the proposed polypills presented in the literature has a slightly different composition, they all include a statin, and most include other anti-hypertensive medications, aspirin, and other primary prevention pills. Details of various proposed polypill are presented in Table 1.

All those polypills include a low dose of each medication. This would allow its use in those with mildly abnormal risk factors and would reduce the risk of dose-dependent side effects. Although this could lead to suboptimal risk factor control if an individual risk factor is highly abnormal, it would still allow a substantial risk reduction as all other risk factors would also be partially controlled. This strategy would also allow its use with more restricted follow-up appointment and tests to adjust medication dosage. Collectively, those numerous advantages and the low cost and ease of distribution of a single pill would increase the likelihood of widespread prescription and patient adherence.

It is interesting to point out that although the polypill strategy has always been proposed as a population strategy in contrast to the usual risk factor and risk stratification strategies, none of the proposed recommendations framed is use for the entire population. The published studies related to polypills usually include a combination of age and risk factor burden to define the inclusion of patients. In the context of the current discussion, this can be understood as a rather primitive individualization of a population-based strategy. As an example, in primary prevention the TIPS study listed in India adults from 40 years old with at least 1 cardiovascular risk factor [14]; and the PILL Collaborative Group recruited those aged ≥18 years and a Framingham 5-year CVD risk ≥ 7.5% [15]. Even the pragmatic PolyIran study presents an extensive list of exclusion criteria. Also, several studies enrolled only very high CVD risk or secondary prevention [16•].

Polypills in Precision Medicine: Selection of Non-responders?

There is an inaccurate view that there are not several formulations to serve specific populations. Therefore, polypills might fill gaps in the precision medicine landscape. First, the "one size fits all" cliché may not be the best way to define the rationale of the polypill treatment strategy: given variety of pills, it is practical to choose different compositions and doses according to regional or national demands. Second, treatment with polypills must be faced not only as an exclusive therapy but also as a tool in reducing pills per day [17•] or targeting the non-high-risk individuals. If necessary, introducing additional drugs must be considered and selected high-risk individuals may be managed with more granular drug dosage adjustments. While some Kanyini-GAP trial analyzes note that 44% of the studied population needed additional medication [15], it is of utmost importance to emphasize that the most people benefited from single medication with its beneficial profile of lower cost and easiness of use.

Thus, knowing that precision medicine is still under development in cardiology, polypill use might be considered as a basic therapy and other specific adjustments could be made, either with conventional drugs or other polypill formulations and doses. As precision medicine in cardiology is costly and its genetic profile still needs to be better understood to be included in translational medicine, selecting patients who are really non-responders may be an interesting step to optimize the individual benefit of this strategy with more advanced tools.

Polypills in Clinical Profile-Based: One Foot in Mass Strategy, the Other One in Precision Medicine

Over time, new data has been incorporated into aforementioned cardiovascular disease risk calculators [8]. Non-traditional individual factors (such as metabolic syndrome, autoimmune diseases, human immunodeficiency virus infection), biomarkers, and the use of non-invasive techniques increased the discriminative power to identify more people at risk, to allow a better direction in taking decision-making for treatment. However, to date, most strategies have focused on the identification of high or higher risk individuals. This leads to a substantial reduction in the number of individuals treated and can be understood as a modified high-risk strategy. Since the selection of high-risk individuals has significant limitations, those strategies are likely to be limited by the same constraints known from the high-risk approach as delineated in the Rose's axiom.

One alternative solution to combine personalized data to population-based strategies is to flip the population selection strategy. Instead of focusing the selection process in the identification of low-risk individuals, one could use tools to identify those low-risk individuals who are unlikely to benefit from pharmacologic risk reduction strategies and target the use of polypills in

Table 1 Detailed information on the main polypill studies published to date: olypill studies characteristics

Study	TIPS	PolyIran Pilot	Sri Lanka Polypill Study	PILL Collaborative Group	Wald	TIPS-2	UMPIRE	Kanyini-GAP	FOCUS	HOPE-3	PolyIran	HOPE-4	SCCS	Mariani
Year	2009	2010	2011	2011	2012	2012	2013	2014	2014	2016	2019	2019	2019	2020
Country	India	Iran	Sri Lanka	Several	UK	India	Multinational	Australia	Multinational	Multinational	Iran	Colombia and Malaysia	USA	Argentina
Primary prevention	√	√	√	√	√					√	√	√	√	
Secondary prevention						√	√	√			√			√
n	2053	468	216	378	86	518	2004	623	2118	12,705	50,045	1371	303	100
Age (years-old)	45–80	50–79	Men ≥40 Women ≥50		≥50	≥40	≥18	≥18	≥40	Men ≥55 Women ≥65	40–75	≥50	45–75	≥
Inclusion	≥ 1 CVD risk factor	No CVD	10-y CV risk score ≥ 20%	5-y CV risk score > 7.5%	No C-V-D	CVD or diabetes mellitus	CVD or 5-y CV risk score >15%	CVD or 5-y CV risk score >15%	AMI within the last 2 years	≥ 1 CVD risk factor	With or without priorCVD	Hypertension	No CV-D	AMI within the last 7 days
Diuretic	√	√	√	√	√	√	√§	√§		√	√	√	√	
Beta-blocker	√					√	√*	√*						√
ACEI/ARB	√	√	√	√	√	√	√	√	√	√	√	√	√	√
Statin	√	√	√	√		√	√	√	√	√	√		√	√
Aspirin	√	√	√	√	√	√	√	√	√		√			√
Calcium Channel blocker					√							√	√	

CVD, cardiovascular disease; *AMI*, acute myocardial infarction; *ACEI*, angiotensin-converting enzyme inhibitor; *ARB*, Angiotensin II receptor blocker

§ *Included* only in combination 1. *Included only in combination 2

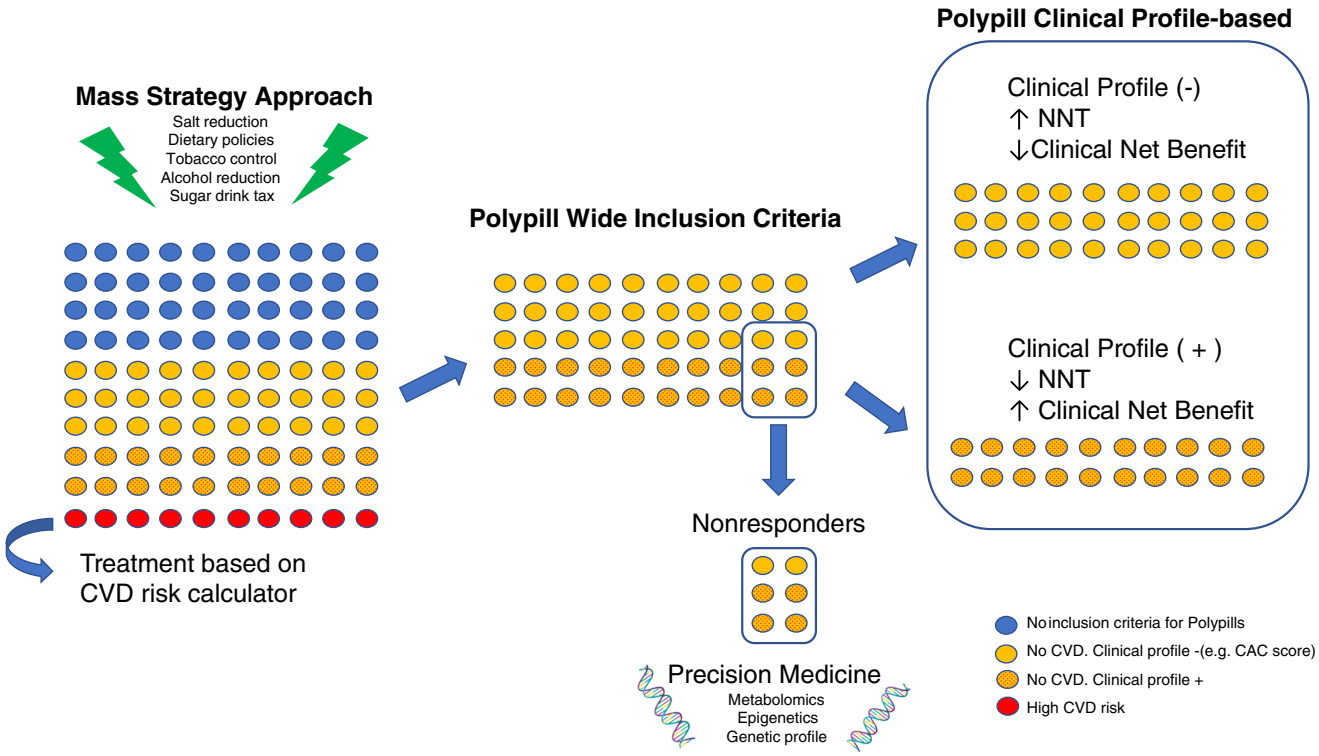

Fig. 1 Population example of the various strategies. From the entire population, on the left, a high-risk approach based on a CVD risk calculator would only recommend interventions to a smaller group of individuals (*in red*) for each of the risk factors. With a population wide strategy, such as with the use of a polypill, all additional individuals in yellow would be treated, though their risk is highly heterogeneous. Precision medicine can be used to better select higher risk individuals. However, the identification of very low-risk individuals, aiming to target treatment at the non-low-risk can still maintain the mass-strategy benefits despite focusing on a more targeted approach

the rest of the population. By design this would lead to a reduction in the population targeted at other polypill strategies, but it would still focus in a much broader population that high-risk approaches. Although very low-risk individuals who are unlikely to benefit from treatment are excluded, low- to intermediate-risk individuals are likely to be included. The key issue for such strategy is the identification of a risk stratification tool with a high specificity, which would allow the identification of lower risk individuals with a high degree of confidence, while still identifying most of the higher risk individuals with an accessible, cost efficient and reproducible test (Fig. 1).

Among these tools, the CT-acquired coronary artery calcium score is a well-known powerful data in prediction for

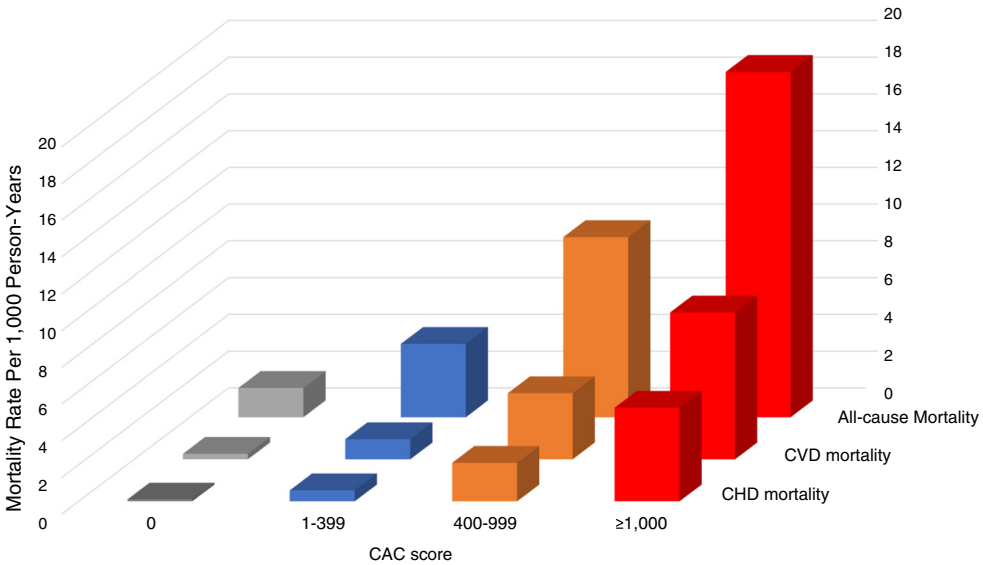

Fig. 2 Mortality rate for CVD, CHD, and all-cause mortality by CAC Score Group. CHD, coronary heart disease; CVD, cardiovascular disease; CAC, coronary artery calcium. (Figure designed based on data from [20].)

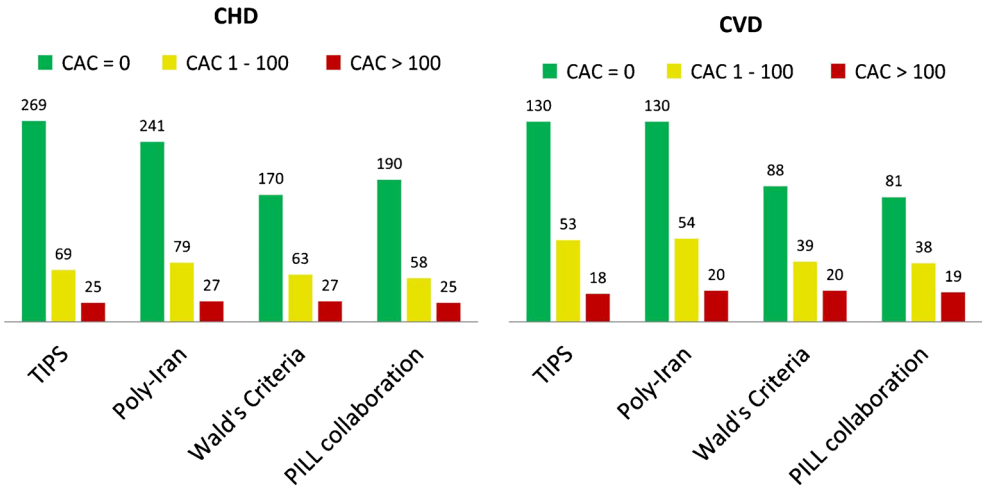

Fig. 3 Number needed to treat (NNT) according to CAC scores. CHD, coronary heart disease; CVD, cardiovascular disease. (Reproduced from: Bittencourt et al. *J Am Coll Cardiol*. 2014;63(5):434–43, with permission from Elsevier) [21]

cardiovascular events in the asymptomatic population [18]. While there is a consistent very low incidence of outcomes in patients without detectable CAC, cardiovascular risk increases progressively the higher the CAC score: a study found that, when compared to people with no CAC, incidence rates of death from coronary heart disease are six times higher in those with CAC <400, 20 times higher in CAC 400–999, and 50 times in those with CAC ≥ 1000 (Fig. 2) [19, 20].

A study in the MESA cohort [21] estimated the potential impact of a polypill on CVD risk reduction according to CAC score. When adding the CAC score to the inclusion criteria of 4 large polypill studies, the authors observed 2 interesting effects: first, considering the treatment focused on those with CAC> 100, the polypill treatment would cause a NNT below 20 for a 5-year cardiovascular risk, while NNT is about 81–130 in whose with no CAC (Fig. 3). Second, after this stratification, less than a third of the people would be included in treatment protocol. It is interesting to note that despite a substantial reduction in the population to be treated, most events are still likely to be reduced with the use of such strategy.

Some limitations of such strategy should be noted. First, there is a small, yet known, risk from radiation exposure though current doses of a CAC test are less than 1 mSV. Second, access to testing may be an issue in some countries, though most CT scanners are now able to perform CAC acquisitions. Yet, the main topic discussed is about cost effectiveness. In the USA, the CAC score average cost is about US$ 133, which is considered a cost-effective value in a study that used CAC to guide the initiation of statin treatment. Although we must consider that those with a CAC of zero are likely to repeat the test in the future, current evidence suggests the "warranty period" might be as long as 15 years for most individuals.

Conclusions

Since the first proposal for a fixed-dose drug combination strategy in a single pill by Wald [22], the concept of the use of polypills in cardiovascular prevention has accumulated robust evidence of efficacy [14, 15, 16•, 17•, 23, 24] and cost effectiveness [25–27] in several clinical settings. However, its implementation in the real world is still rudimentary due to some regulatory, political, economic, and clinical barriers. This also includes the potential criticism of medicalization of extremely low-risk individuals. Thus, more precise strategies to tailor the use of polypill such as the proposed strategy using CAC should be considered.

Declarations

Conflict of Interest Dr. Generoso has nothing to disclose.

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Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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