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**American Journal of Cardiovascular Drugs**

ISSN 1175-3277

Am J Cardiovasc Drugs  
DOI 10.1007/s40256-015-0114-7



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# Integrated Preclinical Cardiovascular Prevention: A New Paradigm to Face Growing Challenges of Cardiovascular Disease

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**Abstract** Cardiovascular disease (CVD) still represents the leading cause of mortality and morbidity worldwide. Despite considerable improvements in the prognosis of CVD and the significant reduction of CVD mortality obtained during the past half century, patients developing CVD, even though satisfactorily treated, still carry coronary artery disease and remain at risk for advanced CVD. Thus, the healthcare and socioeconomic burden linked to CVD remains high. As a result, more effective CVD prevention strategies remain crucial. ‘Population strategies’ and ‘high-risk’ approaches both have limitations and have often been viewed as alternative solutions. This persistent dualism could be overcome with the promotion of integrated prevention strategies based on a systematic evaluation of the total risk of disease, at both a population and an individual level. New approaches are also needed to reach people earlier in the course of the vascular disease and, possibly, to prevent risk factors and reduce CVD clinical manifestation.

## Key Points

Since cardiovascular disease (CVD) remains the leading cause of death worldwide despite the recent advantages in cardiovascular diagnosis and therapy, a more efficient approach to CVD prevention is necessary.

A possible improvement could be derived from a strategy that integrates the two traditional preventive approaches, the ‘high-risk approach’ and the ‘population approach’.

In this regard, it could be reconsidered a so-called ‘polypill’ approach, which could be widely applicable, especially in low and middle-income countries.

## 1 The Toll of Cardiovascular Disease at the Dawn of the Third Millennium

Cardiovascular disease (CVD) remains the main cause of death in Europe this century and a great cause of morbidity, with coronary artery disease (CAD) and stroke representing the most common clinical manifestations [1]. Recently, there is also worrying evidence that the former decline in CVD mortality is generally levelling off, particularly among young adults [2–4], and hospital discharge rates for CVD have increased in the majority of European countries [5].

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Moreover, according to the World Health Organization (WHO), 80 % of the mortality attributable to non-communicable diseases (NCDs) occurs in low- and middle-income countries (LMICs), and CVD accounts for most of this burden. For example, the mortality attributable to CVD in Africa, South-East Asia, and the Eastern Mediterranean regions is projected to increase from 20 to 35 % by the year 2020 [6]. It is estimated that more than 30 million adults in Africa have hypertension, and 75 % of all deaths in Africa will be attributable to hypertension by the year 2020 [7].

In coming decades, estimated disability-adjusted life-years (DALYs) is expected to rise from a loss of 85 million DALYs in 1990 to a loss of >150 million DALYs globally in 2020, with CVD remaining the leading cause of productivity loss [8].

Although early CVD mortality may have declined by 75 % during the past half century [9], survivors still have CAD and remain at risk for subsequent episodes of ischemic myocardial damage, left ventricular dysfunction, atrial fibrillation, and heart failure (HF). Thus, one might conclude that, with the continued increase in life expectancy and progressive aging of the population, chronic CVD, such as HF, will remain a major health and socioeconomic problem [7]. As a consequence, the socio-economic burden remains heavy: in 2006, total CVD costs in the EU exceeded €190 billion [4].

The escalating epidemics of hypertension, diabetes, and obesity, and the increasing number of people who are adopting sedentary lifestyles and unhealthy diets, threaten to stall or even reverse the favorable gains related to better trends in individual risk factor (RF) management [10–15]. Data from the WHO predict that patients at high CVD risk will increase from the current 300 million to 600 million in 2020 [16]. The adverse trend in some of these established RFs could be identified as the main reason for the stalling of the decline in CVD death rate and the growing level of CVD morbidity [2–4, 13].

## 2 Cardiovascular Prevention Strategies: An Historical Dualism Between Population and High-Risk Approaches

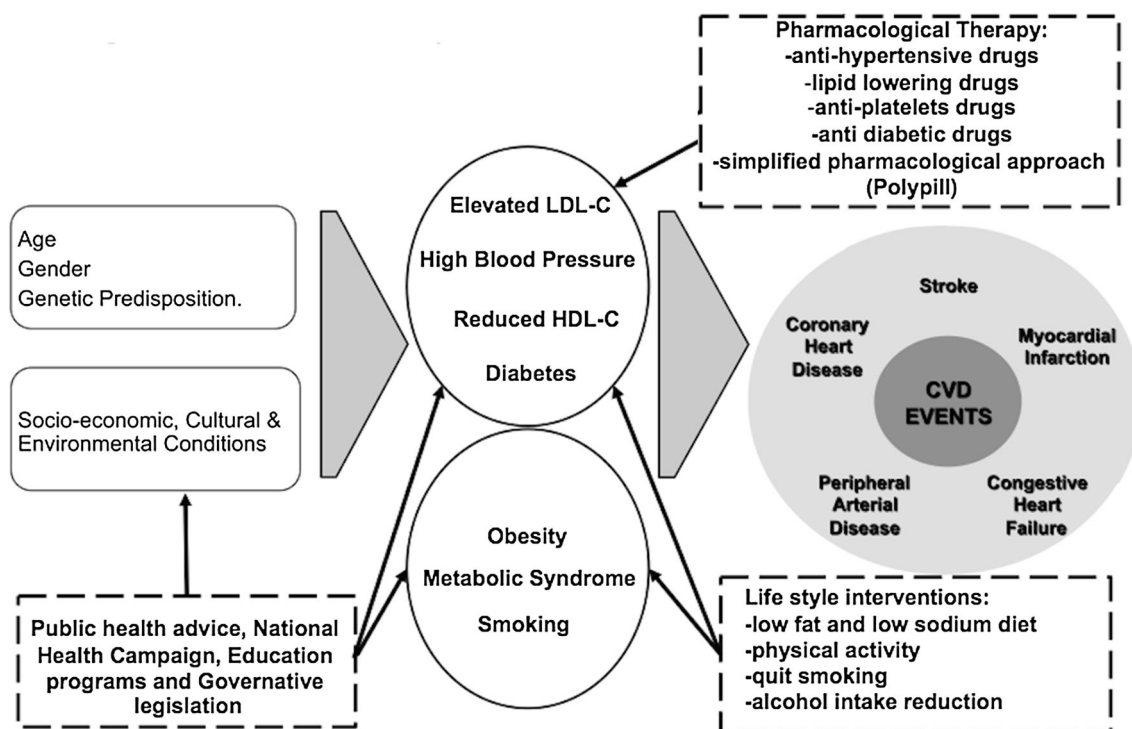
With such a background and an undeniably increasing number of patients with chronic NCDs, we, as treating physicians, cannot be satisfied with the outcomes achieved by CVD prevention strategies so far. Evidently, it is vitally important to contemplate the possibility of medical interventions at a preclinical level to avoid even early development of the disease and the subsequent development of cardiovascular (CV) events. Identification of RFs, abnormal biomarkers and markers of target organ damage should prompt earlier interventions [17, 18].

Over 20 years ago, Geoffrey Rose, one of the ‘fathers’ of preventive medicine, identified a key message that, despite that CV high-risk individuals gain most from preventive measures, the greatest number of deaths due to CVD occurs in low- or medium-risk individuals, simply because they represent a much larger group [15, 19]. Therefore, primary prevention of CVD may benefit from two complementary approaches, ‘the mass or population approach’ and the ‘high-risk individual approach’. The first aims to control the determinants of CVD in the entire population. Shifting the RF distribution in a more favorable way through community-based interventions is most appropriate for reducing the incidence of disease. It has traditionally focused on lifestyle modifications through health education, societal, and economic measures to reduce exposures and encourage ‘healthy’ behaviors [20]. The ‘mass approach’ leads to the ‘prevention paradox’: ‘a measure that brings large benefits to the community offers little to each participating individual’. This implies that we should not expect too much in terms of individual health benefits [15, 21].

The second approach, in turn, aims to identify individuals at high risk and reduce their susceptibility to CVD [18, 22]. For a long time the population strategy has been considered to be more cost effective than the high-risk approach, and the two approaches have been viewed as substantially alternative. Since the introduction of highly effective lipid-lowering drugs, improvements in smoking-cessation programs, and the lower costs and ease of access to antihypertensive drugs, the effectiveness of the high-risk approach has become less ‘complex’ and more widely adopted [23].

## 3 Overcoming the Dualism

Nowadays, consensus is growing that a larger preventive effect can be achieved when the ‘population’ and the ‘high-risk’ strategies are combined (Fig. 1). The current approaches to primary prevention include public health advice and treatment of an individual’s RFs by health-care providers. However, even this kind of global strategy can have considerable limitations. In fact, global prevention should include multiple strategies: health policy, environmental changes, and individual behavioral changes. Lifestyle interventions are attractive because of their inherent ‘natural’ appeal, perceived low cost, simplicity, and safety. However, behavioral interventions to modify individual lifestyles are costly, generally have only a modest and unsustainable impact, and have often resulted in marginal measurable benefits in reducing CVD events when tested in large, long-term trials [24, 25].



**Fig. 1** Integrated interventions to optimize cardiovascular disease prevention. *CVD* cardiovascular disease, *HDL-C* high-density lipoprotein cholesterol *LDL-C* low-density lipoprotein cholesterol

Furthermore, public health advice to exercise, eat healthier, and quit smoking has largely been shown to be ineffective, with the possible exception of smoking cessation (smoking rates among adults have declined by almost 50 % over the past 40 years), probably thanks to population-wide fiscal and legislative interventions [26]. A recent review showed that health education or intervention programs in primary care settings among patients at low risk still appear to be of little benefit [27].

On the other hand, ‘high-risk’ strategies need to be widely used to have appreciable general impact [28], which means appropriate screening and full adherence to therapy of ‘high-risk’ individuals [29]. However, in clinical practice, we are far from achieving this level of intervention. For example, in the USA, approximately 60 % of patients with diabetes (high-risk patients) still do not receive a lipid-lowering agent [30], and less than one-third of patients with chronic kidney disease receive lipid-lowering drugs and only 40 % are at low-density lipoprotein cholesterol (LDL-C) goal [31]. Personalized care does not reach everyone, especially in the poorly organized primary care environment of some developed countries. In the PURE (Prospective Urban Rural Epidemiology) study, involving 154,000 individuals from 628 communities and 17 countries, 41 % of participants had hypertension. Of those with hypertension, only 46 % were aware of having elevated blood pressure (BP) and only 41 % were receiving

pharmacological treatment. As a consequence, merely 13 % of all hypertensive patients had their BP controlled to recommended values [32].

The issue raised by Rose about the relative benefits of a population-wide approach to intervention compared with a targeted approach has been quantitatively considered. The two approaches have been explored using cost-effectiveness simulations for each approach. As a specific example, the two approaches have been compared with regards to BP to reduce CVD [33]. The risk curve for CVD based on the Framingham equation was applied to a real population distribution of high BP. A targeted intervention and population-wide intervention for high BP was then applied. The effects of each intervention in relation to the change in BP distributions based on realistic values of BP reductions from medication (for the targeted approach) and from the results of a population-wide intervention (for the population-wide approach) were modelled. The population-wide treatments costing \$US100 or less are more beneficial and cost effective than any of the targeted treatments. However, the targeted treatments with lower cut-offs for treatment provided more advantage for the benefit fraction and the disease prevented (systolic BP [SBP] >140 mmHg). For the higher costs of the population-wide treatment, the cut-off chosen for BP determines the relative benefit/cost effectiveness of the two approaches. In all the targeted and population-wide intervention scenarios, the benefit exceeds

the cost for a population-wide treatment with a cost of only \$US60 per person or less.

Since high-income western countries started to systematically fight CVD many decades ago, much experience has been developed to better understand this challenge, and health systems have been progressively adjusted. In LMICs, the rapidity of changes, the scale of these changes, and the large populations involved have rapidly outstripped healthcare systems, and available infrastructures are still unable to cope with the growing burden of CVD. Thus, the LMIC cannot simply reproduce the approaches taken by high-income countries. They must instead develop more cost-effective and equitable ways of countering NCDs [34]. The evidence for the cost effectiveness of interventions in LMICs is growing but remains insufficient and is often restricted to pharmacological interventions [35]. Identification of individuals at high risk for CV events will also be needed, and, in some resource-limited settings, non-laboratory-based methods are preferred [36, 37]. For instance, in a recent modelling study, Wald et al. [38] showed that screening for future events by age alone yielded detection and false-positive rates comparable with the accuracy of current more expensive methods [38].

#### 4 Treatment of Risk Factors at a Preclinical Level and Lifetime Risk

With regard to CV risk, the fact that considerable vascular damage can occur even before RFs are identified and treated is crucial. New approaches are needed to reach more people earlier in the course of CVD. The vascular damage that leads to CV accidents begins years before RFs such as high BP and cholesterol reach diagnostic thresholds for hypercholesterolemia and hypertension, and years before the first clinical event. Therefore, to prevent diseases, RFs need to be addressed before the age at which the CVD incidence peaks and such efforts should be continued indefinitely [39]. With this regard a clinical trial has shown that treatment with an angiotensin-receptor blocker may delay clinically defined hypertension from emerging in individuals with prehypertension [40].

Similarly, in a recent meta-analysis of more than 300,000 subjects, a Mendelian randomization approach was used to estimate the clinical benefit of lowering LDL early in life. As a proxy, the authors used a treatment that would decrease LDL-C beginning at birth, which is the inherited allocation for the protective genotype (for nine single-nucleotide polymorphisms [SNPs] associated with lower LDL-C). Results showed that a low LDL-C concentration, following this random natural allocation, decreased the risk of CAD by 54.5 % for each mmol/l LDL-C reduction. Comparatively, for the same level of LDL

decrease, statin therapy started later in life would only reduce CAD by 24 %. The authors concluded that exposure to LDL-C-lowering drugs earlier in life is associated with a greater reduction of CAD compared with the current practice of starting lipid-lowering pharmacological strategies later in life [41]. The deleterious effects of early and long-term exposure to dyslipidemia were studied in the CARDIA (Coronary Artery Risk Development In young Adults) study, wherein authors compared the risk of coronary calcium (an intermediate surrogate for CAD) in subjects with optimal LDL concentration <70 mg/dl. They found that, in healthy subjects exposed to slightly suboptimal LDL-C (70–99 mg/dl), the presence of coronary calcium was 1.5-fold higher, and subjects with concentrations marginally higher (100–129 mg/dl) had a significantly higher risk of coronary calcium of 2.4-fold [42]. Moreover, results from the large MEGA (Management of Elevated Cholesterol in the Primary Prevention Group of Adult Japanese) trial also showed similar trends. Irrespective of their level of risk, all patients seen in clinical practice showed a clear benefit from statin therapy, even at low doses, such as pravastatin 10 mg [43]. Therefore, this pharmacological approach could paradoxically be cost effective when not only reserved to the high-risk population [44].

The significance of lifetime CV risk estimate plays a major role in this frame. Indeed, short-term risk estimates have important limitations, classifying most adults aged <50 years and most women as being low risk, regardless of RF burden [45, 46]. In contrast, estimates of lifetime risk provide a significantly different classification of individual risk and probably represent a real snapshot of the individual susceptibility to CV events during the following decades. Therefore, national guidelines in both the USA and Europe have recently encouraged the use of long-term or lifetime risk as an adjunct to short-term risk communication in primary prevention.

Several studies have examined the association between short-term perceived and predicted risk for CVD [47–50]. Most of these studies observed that incorrect perception of short-term CVD risk was not uncommon due to an 'optimism bias', in which people (and even physicians) generally underestimate their personal risk for CVD [51]. A recent paper [52] reported the perceived lifetime risk for CVD in the general population, demonstrating that the perception of lifetime risk for CVD is often also inaccurate and generally mainly influenced by personal factors (i.e., subjective perception of stress and personal health) compared with traditional CV RFs. Despite most study participants (64 %) having a high predicted lifetime risk for CVD, most did not perceive themselves as being at high risk. This evidence is alarming. In fact, it has been shown that patients' awareness of CV risk level is a motivating

factor for them to make lifestyle changes and eventually to adhere to pharmacological treatment with BP and cholesterol-lowering medications, resulting in a reduction in CV RF burden [52]. Self-perception of low CVD risk, in contrast, decreases motivation to engage in lifestyle modification and has deleterious influence on the acceptance of and adherence to pharmacological treatment. Thus, it is important to introduce population-level education programs, and to develop easy and cheap tools to assess CV risk, for example, a calculator of lifetime risk, such as that recently developed by the British Joint Societies to help patients become aware of their actual lifetime CV risk [53].

## 5 The Polypill Approach

Following the assumption that preventing RF from emerging is probably more effective than treating them once they are established, a decade ago a novel preventive approach was proposed: pharmacotherapy with multiple drugs combined in a single preparation, called a 'polypill' [54, 55]. This is clearly not an example of an integrated preventive approach, but it does represent a widely manageable tool for 'high-risk' targeted preventive strategies. As originally described by Wald and Law [54], the polypill contained three antihypertensive drugs (e.g., thiazide diuretics, beta-blockers, angiotensin-converting enzyme [ACE] inhibitors, angiotensin receptor blockers [ARBs], and calcium channel blockers) at half a standard dose, low-to moderate-dose statin (e.g., atorvastatin 10 mg or simvastatin 20–40 mg), folic acid, and low-dose aspirin. Based on the results of previous meta-analyses [56, 57], they estimated that this six-component polypill, with full adherence to preventive treatment, would reduce an individual's risk of coronary heart disease and stroke by about 80 % [54].

A large level of evidence supports the use of pharmacological treatment for the secondary prevention of CVD in patients with prior CV events. Antiplatelet agents, beta-blockers, lipid-lowering agents, and ACE inhibitors have all individually demonstrated improvements in mortality and morbidity and are recommended for secondary prevention of CVD by a diverse group of professional organizations. However, in spite of well-documented international guidelines, there are still substantial gaps in terms of the adequate use of secondary interventions for prevention of CVD [32]. More than half of patients with prior ischemic heart disease or stroke receive no secondary medications, and <10 % receive three of the four proven medications. This situation is much worse in LMICs, where more than three out of four patients with CVD take no medication. Reasons for this include limited access to health practitioners, inadequate prescription of medicines,

incomplete awareness of the importance of lifelong therapy by both physicians and patients, poor adherence, lack of availability of key medications and unaffordable costs of even generic drugs compared with local incomes. Fixed-dose combination (FDC) therapy that combines CVD secondary preventive medicines appears to overcome many of these barriers, as shown in large trials such as TIPS (The Indian Polycap Study) conducted in LMICs [58]. In particular, FDC therapy has been shown to improve adherence by 33 % compared with usual care in CVD secondary prevention [59]. Thus, CVD secondary prevention with polypill therapy has been deemed a "best buy" by the WHO [60], given its efficacy, adherence, scalability, and cost effectiveness.

With regard to primary prevention, in view of the fact that age is the strongest predictor of adverse CV events [61], Wald and Law [54] proposed that anyone aged >55 years, regardless of their starting RF levels, should use preventive treatment. In other words, treatment should not be limited to people with 'hypertension' or 'hypercholesterolemia', but everyone above a specified age (e.g., 55 years) should receive the polypill, regardless of their individual RF profile.

The polypill has been shown to significantly reduce both serum cholesterol and BP, while issues in terms of adherence and tolerability of the polypill remain [62–65]. The HOPE (Heart Outcomes Prevention Evaluation)-3 trial is evaluating the concept of combined BP and cholesterol-lowering for 6 years in 12,705 individuals from five continents without known CVD but at moderate CVD risk. All participants receive structured lifestyle advice; primary outcomes are CVD events and secondary outcomes are cognitive and renal function, with results expected in 2016 [66]. The TIPS-3 trial will include 5500 individuals from India, the Philippines, Canada, China, Brazil, Argentina, Chile, Colombia, and additional countries. The aim of the study is to estimate the impact on major CVD events of a four-drug combination pill versus placebo in a primary prevention population over 5 years. The participants are men aged >55 years and women aged >60 years without CVD and with an elevated INTERHEART risk score of  $\geq 10$  (which corresponds to a projected annual CV event rate in the control group of 0.1 %) [67]. The HOPE-4 community cluster randomized trial will evaluate an evidence-based program for CVD risk assessment, treatment, and control involving simplified screening and treatment algorithms implemented by non-physician health workers (often public health nurses or nursing assistants) coupled with lifestyle counselling and combination-pill therapy. The initial risk factor phase of the study will assess BP and cholesterol changes in Colombia and Malaysia (50 communities), with plans to expand to 190 communities in eight countries to evaluate CVD events over 6 years [68].

The PolyIran open-label cluster randomized controlled trial aims to determine the effects of a combination pill versus minimal care in primary and secondary prevention of CVD in 7000 adults aged 50–79 years from Iran. The primary outcome at 5 years is the time to first major CV event, and the results are expected in 2018 or 2019 [69].

Many issues remain to be addressed regarding the use of the polypill. The first is to determine the ideal pharmaceutical formulation of the polypill. The value of aspirin in primary prevention continues to be debated, as the modest reduction in CV events is counterbalanced by an increased incidence of major bleeds [70]. Thus, a polypill used for primary prevention of CVD should not include aspirin [71], although recent data showing that aspirin reduces the incidence of cancer could substantially modify this risk–benefit ratio [72, 73]. Polypill adherence issues and the acceptance of the polypill by both patients and physicians will need to be addressed. Indeed, as a treatment for primary prevention in ‘healthy’ subjects who may not be motivated to use medications long term, it is important to consider that even minor side effects to one component of the polypill may cause its discontinuation and hence loss of benefit from all component drugs. Emphasis on education about CV prevention, low cost, and tolerability is of key importance for the acceptance of the polypill by both patients and physicians.

Finally, a concern related to the use of combination therapy is that it would replace efforts to promote healthy lifestyles and that the entire population may be unnecessarily ‘medicalized’ upon age criteria alone. Indeed, if treating when benefit outweighs harm is accepted, treating risk rather than RF thresholds may not be easily agreed upon.

However, many people with clinically defined hypertension or dyslipidemia are not aware of these conditions, thus treating everyone reduces the possibility of CVD due to unrecognized risk [74]. Moreover, by avoiding complex algorithms to identify individuals at high CV risk who require therapy, and by increasing the ease of prescribing, costs of screening may be considerably diminished, so that more at-risk individuals can be treated. This strategy also permits the prevention of the numerous CV events that occur in people with a mild burden of known RFs who are not included in the high-risk group. These considerations are of particular importance for people living in developing countries who currently receive little or no preventive care. In addition, a polypill might represent a useful strategy to improve adherence to pharmacological therapy, thereby reducing costs [75, 76].

We can conclude that, although the polypill has been suggested as a simple and largely useful means of prevention, its target population has not yet been recognized, and its cost effectiveness, not only in terms of efficacy on CV hard endpoints in the long term but also in terms of side

effects, adherence rates, ethical concerns, and economic burden, is still debated.

## 6 Conclusion

While advances in medical research over the last century have resulted in a significant decrease of CVD-related mortality, it remains the leading cause of death and morbidity, particularly in western countries. The prevention strategies conducted so far have achieved positive results; however, these results are far from satisfactory. These days, the perceived dualism between population-based strategies and a ‘high-risk’ approach is obsolete and should be overcome with the promotion of an integrated prevention strategy. Based on data collected so far, it seems that policy choices in clinical prevention can be improved based on the total risk of disease at both a population and an individual level. Easy estimation of CVD lifetime risk could help progression into a more modern age of CVD prevention, thus increasing the spread of useful therapeutic measures.

The polypill could be a way forward, but still lacks evidence, mostly with regards to its effect on mortality and morbidity in the long term. Future studies should be conducted to assess the net benefits of this strategy on major CV events.

**Acknowledgments** The authors wish to acknowledge the Board of Scientific Societies for Reduction of Cardiovascular Risk (Consulta delle Società Scientifiche per la Riduzione del Rischio Cardiovascolare) for the revision of this manuscript.

**Conflicts of interest** No external funding was used in the preparation of this manuscript. None of the authors have any potential conflicts of interest that might be relevant to the contents of this review.

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