

## The polypill: from concept and evidence to implementation

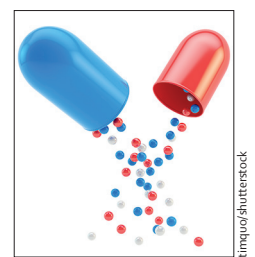


About 18 million deaths occur due to cardiovascular diseases each year, of which 80% are in low-income and middle-income countries,<sup>1</sup> and three times as many individuals have non-fatal cardiovascular diseases. These diseases are widespread and demand global, population-wide action, but the approach to their control has been based on individualised treatment plans, leaving the majority of people at risk neglected.

Although people with previous cardiovascular diseases have about a four-fold higher risk of death or non-fatal events than people without previous cardiovascular diseases, 80% of all events occur in the latter group. Therefore, a strategy focused solely on secondary prevention would not address 80% of the cardiovascular disease burden. Although so-called controlling of elevated risk factors (eg, hypertension or elevated low-density lipoprotein cholesterol [LDL-C]) is advocated, it has had only a modest effect overall, with control of blood pressure being achieved in under 15% of people with hypertension,<sup>2</sup> statins being used in under 5% of people without cardiovascular diseases, and low use of proven therapies (statins, aspirin, ACE inhibitors, and betablockers) for secondary prevention.<sup>3,4</sup> Furthermore, the traditional approach to risk factor control requires screening and risk stratification, which are complex and expensive. Clearly, the current strategy in primary and secondary prevention has been only modestly successful in most countries, including high-income countries.

Over the past 2–3 decades, it has become clear that the risk of cardiovascular diseases associated with elevated blood pressure and LDL-C is continuous,<sup>5,6</sup> and that lowering LDL-C and blood pressure is effective even in people with average LDL-C and blood pressure values. Indeed, in the early 2000s it was proposed that a combination of blood-pressure-lowering agents, a statin, and low-dose aspirin could reduce cardiovascular diseases by 75–80% in both primary and secondary prevention.<sup>7,8</sup> However, few products that combined multiple blood-pressure-lowering drugs and statins (with or without aspirin) are available, and in the few countries where they are available use is low.

This systemic failure is a global tragedy as many premature deaths from cardiovascular diseases could be avoided. Therefore, there is a clear need to implement new strategies for both primary and secondary prevention of cardiovascular diseases. There are now data from three independent, large, and long-term trials in primary prevention showing that a combination of blood-pressure-lowering agents and statins at low doses (with or without aspirin) reduces the risk of cardiovascular diseases by about 38% and the effects are a nearly 50% relative risk reduction when aspirin is included in the polypill.<sup>9–12</sup> Benefits are seen in people with a wide range of LDL-C or blood pressure values, with or without diabetes, and with or without other risk factors. However, the benefits



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were smallest in people younger than 55 years. The most common adverse side-effect with the polypill was dizziness, which was readily reversible by reducing the dose or stopping medications.<sup>12</sup> A fourth trial reported that a polypill consisting of statins, an ACE-inhibitor, and aspirin reduced cardiovascular disease events by about 25% compared with usual care after myocardial infarction.<sup>13</sup> These data indicate that using a polypill in a broad range of individuals aged 55 years or older can safely and substantially reduce the risk of future cardiovascular diseases, without special approaches to screening. Combined with an avoidance of smoking, it is probable that the polypill could reduce the cardiovascular disease burden by more than half. The polypill should not be considered a new drug, but instead a low-cost implementation strategy to efficiently reduce cardiovascular diseases in countries all around the world.

Even with only 50% adoption, our estimates suggest the use of the polypill could avoid approximately 2 million cardiovascular disease deaths and 4 million cardiovascular events each year. These substantial benefits are crucial in achieving WHO's Sustainable Development Goal of reducing deaths from non-communicable diseases by 30% globally by 2030 (at 50% adoption) and by 50% by 2040 (at 80% adoption). Several analyses indicate that the polypill can be cost-effective (a dominant effect—ie, avoiding deaths and saving money).<sup>14</sup>

So, how can the use of polypills be increased? First, although some small companies have manufactured and marketed the polypill in a few countries, sales have been relatively modest. Most large pharmaceutical companies have not been willing to invest in developing and testing polypills. However, given the proven benefit and their widespread applicability, we hope that this reluctance will change. Second, polypills are not included in current guidelines for cardiovascular disease prevention or in the WHO's Essential Medicines List. Given the robust data on the benefits, safety, and cost-effectiveness of the polypill, we hope that the polypill will be included in the Essential Medicines List and in guidelines for both primary and secondary cardiovascular disease prevention. This would encourage governments and insurance companies, especially in low-income and middle-income countries, to include it in their formularies and encourage clinicians to

recommend its use. Bulk purchases will substantially reduce the costs of the polypill and further increase the financial accessibility. Third, companies should develop newer polypills with larger blood-pressure-lowering effects (eg, by combining low doses of three or four classes of blood-pressure-lowering drugs along with statins and low doses of aspirin), which could result in greater clinical benefits. By using generic components and marketing them at locally sensitive prices, it could both be affordable to most people around the world and still profitable to the companies. Fourth, the polypill combined with advice to improve lifestyles (provided by trained non-physician health workers in the community) can facilitate wide implementation.<sup>15</sup> The polypill delivered by non-physician health workers is not a replacement for physicians, who can focus on managing individuals with more complex conditions. Such a combined strategy could facilitate care for many more individuals than the current approach, which is solely focused on individualised management by physicians, and could serve as the foundation to reduce cardiovascular diseases by a large degree globally and also save costs.

The evidence for the benefits of the polypill is now substantial. It is time to use the polypill widely to save millions of lives each year.

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- 1 World Health Organization. Global status report on noncommunicable diseases 2010. 2011. <https://apps.who.int/iris/handle/10665/44579> (accessed May 1, 2022).
- 2 Chow CK, Teo KK, Rangarajan S, et al. Prevalence, awareness, treatment, and control of hypertension in rural and urban communities in high-, middle-, and low-income countries. *JAMA* 2013; **310**: 959–68.
- 3 Yusuf S, Islam S, Chow CK, et al. Use of secondary prevention drugs for cardiovascular disease in the community in high-income, middle-income, and low-income countries (the PURE Study): a prospective epidemiological survey. *Lancet* 2011; **378**: 1231–43.
- 4 Marcus ME, Manne-Goehler J, Theilmann M, et al. Use of statins for the prevention of cardiovascular disease in 41 low-income and middle-income countries: a cross-sectional study of nationally representative, individual-level data. *Lancet Glob Health* 2022; **10**: e369–79.

- 5 McQueen MJ, Hawken S, Wang X, et al. Lipids, lipoproteins, and apolipoproteins as risk markers of myocardial infarction in 52 countries (the INTERHEART study): a case-control study. *Lancet* 2008; **372**: 224–33.
- 6 Lewington S, Clarke R, Qizilbash N, Peto R, Collins R. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. *Lancet* 2002; **360**: 1903–13.
- 7 Wald NJ, Law MR. A strategy to reduce cardiovascular disease by more than 80%. *BMJ* 2003; **326**: 1419.
- 8 Yusuf S. Two decades of progress in preventing vascular disease. *Lancet* 2002; **360**: 2–3.
- 9 Yusuf S, Joseph P, Dans A, et al. Polypill with or without aspirin in persons without cardiovascular disease. *N Engl J Med* 2021; **384**: 216–28.
- 10 Yusuf S, Lonn E, Pais P, et al. Blood-pressure and cholesterol lowering in persons without cardiovascular disease. *N Engl J Med* 2016; **374**: 2032–43.
- 11 Roshandel G, Khoshnia M, Poustchi H, et al. Effectiveness of polypill for primary and secondary prevention of cardiovascular diseases (PolyIran): a pragmatic, cluster-randomised trial. *Lancet* 2019; **394**: 672–83.
- 12 Joseph P, Roshandel G, Gao P, et al. Fixed-dose combination therapies with and without aspirin for primary prevention of cardiovascular disease: an individual participant data meta-analysis. *Lancet* 2021; **398**: 1133–46.
- 13 Castellano JM, Pocock SJ, Bhatt DL, et al. Polypill strategy in secondary cardiovascular prevention. *N Engl J Med* 2022; **387**: 967–77.
- 14 Lamy A, Tong W, Joseph P, et al. The Cost Implications of a Polypill for Primary Prevention in the TIPS-3 Trial. *Eur Heart J Qual Care Clin Outcomes* 2021; published online Dec 28. <https://doi.org/10.1093/ehjqcco/qcab101>.
- 15 Schwalm J-D, McCready T, Lopez-Jaramillo P, et al. A community-based comprehensive intervention to reduce cardiovascular risk in hypertension (HOPE 4): a cluster-randomised controlled trial. *Lancet* 2019; **394**: 1231–42.