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REVIEW

The polypill as an alternative for preventing and treating cardiovascular disease

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Addressing multiple risk factors with one pill is an attractive approach to reducing cardiovascular disease (CVD). This article explores the polypill as an alternative to CVD prevention and reviews evidence from clinical trials regarding its efficacy and potential side effects.

Keywords: cardiovascular disease, polypill, adherence

Introduction

Globally, cardiovascular disease (CVD) remains the most important cause of death and a common cause of disability.[1] While the burden of CVD has slightly decreased in high-income countries, it remains disproportionately higher in low- to middle-income countries. Ischemic heart disease and stroke are the leading contributors of CVD. Several risk factors contribute to increased risks of CVD, including hypertension, elevated LDL cholesterol, high blood sugar, and behavioural factors such as physical inactivity, smoking, poor diet and obesity.[1]

Randomised controlled trials (RCTs) have demonstrated the effectiveness of proven therapies for the prevention and treatment of CVD. However, globally, poor adherence to prescribed medication and early discontinuation result in insufficient drug exposure, high variability in clinical response, and inadequate control of CVD risk factors.[2] Adherence to medication can be defined as the process whereby patients take their medication as prescribed.[3] It is estimated that in primary CVD prevention, 50% of patients fail to adhere to prescribed treatment and for secondary prevention 64% of patients fail to adhere to prescribed treatment at 2 years after prescription.[4] Poor medication adherence is estimated to cause about 9% of cardiovascular events as shown in a meta-analysis.[5] Nonadherence may actually be regarded as a hidden CVD risk factor.

The idea of a polypill

A polypill is a single pill containing several different medications aimed at reducing the overall risk of CVD and thus targeting several conditions or risk factors at once. It was first promoted by Wald and Law in 2003.[6] The recommended polypill consisted of low-dose aspirin, a statin, three blood pressure-lowering drugs, and folic acid to address four cardiovascular risk factors. It was estimated that this combination could reduce ischemic heart disease events by 88% and stroke by 80%, with an acceptable safety profile. The idea was to administer the polypill to everyone over 55 years of age, regardless of their cardiovascular risk level or individual risk factors.

Contemporary polypills contain multiple medications, each proven in RCTs to lower cardiovascular risk. The polypill typically includes one or more blood pressure-lowering drug (1–4 drugs), a moderate-strength statin, and may or may not include aspirin. There is no single polypill formulation, as various combinations exist. Different agents are presented in a single pill and are designed to simplify treatment, improve adherence and address overall CVD risk.[7] The polypill differs from fixed dose combinations (FDC) of two drugs at a fixed dose, or single pill combinations (SPC) of three drugs in various dosage forms, that address only one risk factor, usually hypertension.

The effects of a polypill

Initially, small RCTs tested the effects of a polypill in limited populations over short periods, demonstrating reductions in blood pressure and cholesterol levels, along with improved adherence to prescribed treatments.[8]

In 2019, the POLYIRAN cluster-randomised trial reported the first long-term outcomes in a largely primary-prevention population. This polypill containing 81 mg aspirin, 20 mg atorvastatin, 12.5 mg hydrochlorothiazide, and either 5 mg enalapril or 40 mg valsartan, was compared to usual care. The polypill group showed a 34% lower risk of major cardiovascular events.[9]

Joseph et al. conducted an individual participant data meta-analysis of three large RCTs, involving 18 162 participants with a 5-year follow-up. The polypill was compared to a control strategy (either placebo or usual care), specifically to determine the effect of the polypill with and without aspirin. The primary outcome was a composite of cardiovascular death, myocardial infarction, stroke, or arterial revascularisation.[10] The polypill, whether or not it included aspirin, reduced the primary outcome rate to 3.0% compared to 4.9% in the control group, representing a 38% reduction in hazard risk (95% CI: 27%–47%, $p < 0.0001$), with a number needed to treat (NNT) of 52 over 5 years. Reductions were observed for each individual component of the primary outcome.

An important aim of this meta-analysis was to assess the contribution of aspirin in lowering risk. Without aspirin, the NNT to prevent a primary endpoint over 5 years was 66. In contrast, for the strategy that included aspirin in the polypill, the NNT was significantly reduced to 37 over 5 years. The publication of this study represented the largest body of evidence from randomised trials quantifying the effects of a fixed-dose polypill treatment strategy. Regarding safety outcomes, the risk of dizziness was increased in the polypill group, with a relative risk increase (RRI) of 27% (95% CI: 17%–39%).

In 2022, Mohammed et al. conducted a meta-analysis to evaluate the effect of the polypill on controlling blood pressure, dyslipidaemia, and reducing future cardiovascular events.[11] Involving 18 RCTs with 26 483 participants, the analysis demonstrated that the polypill significantly reduced both systolic and diastolic blood pressure, as well as LDL-cholesterol levels, compared to standard treatment. Additionally, it significantly decreased cardiovascular mortality and major adverse cardiac events (MACE). The use of the polypill was associated with an increase in adherence to 88.0%. Overall, the polypill was found to significantly reduce cardiovascular risk factors and events, including mortality, compared to standard therapy.

Sedhom et al.'s meta-analysis evaluated the efficacy of a polypill in both primary and secondary prevention of CVD.[12] They analysed 11 RCTs involving 25 389 participants with follow-up ranging from 1 to 5.6 years. The polypill strategy, compared to standard care, was associated with a significant reduction in major adverse cardiovascular and cerebrovascular events (MACCE), with rates of 5.8% versus 7.7%, corresponding to a relative risk reduction (RRR) of 22% (95% CI: 9%–33%). This reduction was consistent across both primary and secondary prevention. The polypill approach also showed a higher degree of adherence. There were no significant differences in serious side effects between the polypill and standard care arms.

This year (2024), Agarwal et al. conducted a meta-analysis of studies published between 2016 and 2022 to evaluate the efficacy of the polypill in reducing CVD risk factors and events.[13] This analysis included 26 trials with 27 317 participants, with a mean age of 52 years. The studies, primarily focused on primary prevention, demonstrated a 29% RRR in fatal and non-fatal atherosclerotic cardiac events. Additionally, an adequately powered secondary prevention trial found that the polypill reduced major adverse cardiovascular events (MACE) by 24%. The polypill was also associated with significant reductions in risk factors such as blood pressure and cholesterol, along with increased adherence.

Concluding remarks

A polypill has been shown to significantly reduce the risk of CVD by addressing multiple risk factors with a single pill. This approach complements non-pharmacological strategies and simplifies treatment by avoiding the need to make separate decisions about using blood pressure-lowering or lipid-lowering drugs based on the absolute levels of these risk factors. At least six RCTs (TIPS-3, SECURE, UMPIRE, IMPACT, Kayani GAP, and POLYIRAN) have shown that the polypill is associated with a RRR of 21% to 34% in major adverse cardiovascular events (MACE) across both primary and secondary prevention populations.[7] While some studies indicate an increased risk of dizziness, others have not found a significant increase in serious side effects compared to standard treatments.

Polypills also improve adherence and persistence to drug therapy, which leads to better outcomes in cardiovascular events. While a polypill approach might seem to contrast with the emerging concept of precision medicine—based on pharmacogenomics and pharmacogenetics—there is substantial evidence supporting the effectiveness of the polypill in reducing the risk of CVD and in decreasing cardiovascular events.

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