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PERSPECTIVE

The Polypill Revisited

Why We Still Need Population-Based Approaches in the Precision Medicine Era

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Nearly 2 decades ago, Wald and Law proposed "a strategy to reduce cardiovascular disease by more than 80%" by administering a polypill to everyone 55 years of age and older.[1] Their bold proposal had its roots in the debate surrounding risk-based versus population-based approaches to prevention, as described by Rose.[2] In risk-based approaches, preventive measures are targeted specifically at higher risk individuals, with medication therapy tailored to each patient's risk factor profile. The identification of higher risk patients typically relies on clinical and laboratory-based prediction algorithms, the traditional approach endorsed in most practice guidelines. In contrast, population-based approaches aim to shift the entire risk distribution, even modestly, with measures implemented at the population level. The latter necessitates interventions that are low in cost and have a low incidence of side effects. These are among the proposed advantages of the polypill, a fixed-dose combination of cardiovascular medications, usually including a statin and several antihypertensive drugs.

One of the objections to the Wald and Law proposal was that large numbers of low-risk individuals would end up receiving unneeded and/or unindicated drug therapy. Thus, despite randomized trials supporting the tolerability of various polypill formulations and regulatory approval in multiple countries outside the United States, momentum in the field shifted toward viewing the polypill primarily as a strategy for high-risk individuals with established cardiovascular disease. The problem is that a one-size-fits-all approach to pharmacotherapy may not be optimal for patients with established disease, for whom aggressive cholesterol and blood pressure targets often require titration of multiple medications. Furthermore, secondary prevention patients often have comorbidities such as diabetes that influence the choice of therapy.

Thus, several decades since Wald and Law's original proposal, there remains little clarity regarding the role of the polypill in cardiovascular care. This has coincided with the rising interest in precision medicine, a contemporary embodiment of the risk-based approach in the Rose framework. A natural question, then, is whether there is any place for a population-based strategy using the polypill in the present era with so much focus on precision medicine.

We believe the answer is yes. One key reason is that there are public health needs that risk-based approaches may never solve. In the past 60 years, cardiovascular mortality has decreased by nearly 75% in the United States and in other developed countries, but these gains have been unequally distributed.[3] In the United States, individuals of low socioeconomic status have been particularly vulnerable, experiencing persistently high rates of cardiovascular death. Multiple factors underlie the observed disparities, including inadequate access to healthcare, economic barriers, and very low penetration of evidence-based therapies.

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Risk-based strategies do not address these barriers and may exacerbate them. They typically require frequent clinic visits for testing and medication adjustment, thus working best when there is good access to care. Also, while focusing efforts to improve utilization of evidence-based therapies in those at highest individual risk is an attractive concept, the majority of cardiovascular events occur in individuals classified as low or intermediate risk by traditional prediction algorithms. Furthermore, the available evidence suggests that traditional risk calculators may underestimate risk in low socioeconomic status populations, compounding this problem.

Tackling cardiovascular health disparities necessitates a renewed focus on high-risk populations, not just high-risk people. Although we do not fully understand the causes of health disparities, we should commit to alleviating them using safe, effective, and evidence-based interventions. Several features of the polypill make it an attractive option in this regard. The simplicity of a once-daily pill improves adherence and reduces the need for monitoring and dose titration. Furthermore, multiple medications at low doses are often better tolerated than 1 or 2 medications at higher doses, because side effects of most cardiovascular medications are dose-dependent. The use of generic components ensures that the pill can be provided to large numbers of people at low cost.

Two recent randomized trials in high-risk, primary prevention populations lend further support to this concept. The large PolyIran trial (Prevention of Cardiovascular Disease in Middle-aged and Elderly Iranians Using a Single PolyPill) tested use of a polypill in a network of villages in Iran, focusing on a low socioeconomic status, largely primary prevention population.[4] The polypill was associated with a 35% reduction in the risk of major cardiovascular events over a mean follow-up of 5 years.

Because there are few data on the use and feasibility of the polypill in US communities, we recently conducted the Southern Community Cohort Study Polypill Trial in a federally qualified health center in Mobile, Alabama.[5] A total of 303 individuals (96% black) without cardiovascular disease were randomized to a daily polypill or usual care; of these participants, 75% had an annual income below $15 000. At 12 months, the polypill was associated with significant reductions in systolic blood pressure (mean, −7 mmHg [95% CI, −12 to −2]; P=0.003) and low-density lipoprotein cholesterol (−11 mg/dL; 95% CI [−18 to −5]; P<0.001), compared with usual care. Median adherence to the polypill was 86%, as measured by pill counts. As in prior polypill trials, the pill was well-tolerated, with rates of myalgias, hypotension, and liver function abnormalities each 1% or less.

It is worth emphasizing that population-based and risk-based strategies are not mutually exclusive. The current cholesterol guidelines already reflect a hybrid approach. Further incorporation of a polypill in high-risk populations, to shift the overall risk distribution, could be a logical extension. One could envision a combined approach whereby the polypill serves as a foundational therapy, with the option of add-on medications or supplemental dosing for those with residual risk factor elevations and good adherence. The polypill does not preclude or minimize the importance of other interventions either, including counseling and lifestyle modification.

We are sensitive to concerns that this approach amounts to overmedicating a large group of people. It is true that many people in the target population may never experience a cardiovascular event. This is the case with other population-based interventions as well. For example, the majority of people who undergo vaccination or cancer screening would likely never develop the associated diseases. Ultimately, it comes down to the tradeoff between the low (but present) risks of a daily pill versus a set of benefits that are coming into better focus. One wonders whether the idea of a polypill would be easier to accept if, instead of being portrayed as a bundle of 4 medications, it was described as a daily supplement that lowers blood pressure and cholesterol, has a great safety record, costs less than $1 per day, and reduces cardiovascular risk by 20 to 40%.

Last, we recognize that the idea of distributing a polypill in socioeconomically vulnerable communities might strike some as paternalistic. That concern should be weighed against the hazards of continuing along the present course, with widening health disparities between low- and high-socioeconomic status communities. A polypill-based strategy might well benefit all communities, but it seems logical to start with communities in which the needs—and the barriers to access—may be greatest. Our own experience working with healthcare providers and patients in underserved communities suggests that many individuals are receptive to practical approaches to improving their cardiovascular health, including the use of a polypill. At the very least, the success of recent trials should motivate large-scale implementation studies comparing a polypill-based strategy with the best available alternatives.

ARTICLE INFORMATION

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