Polypills for the prevention of cardiovascular disease: a framework for wider use

Combinations of cardiovascular medications taken in a single pill — known as polypills — are effective but not widely used, requiring a global shift from physicians, regulators and drug developers.

Anushka Patel, Dike Ojji, H. Asita de Silva, Stephen MacMahon and Anthony Rodgers

Cardiovascular diseases (CVDs) are the leading cause of premature death and disability globally, with disease burden continuing to rise in low- and middle-income countries (LMICs)[1]. Safe and effective preventive treatments for CVDs, such as blood-pressure-lowering drugs, statins and aspirin, have been available for decades. However, most people in LMICs that are at sufficiently increased CVD risk to warrant use of these medications do not receive them[2,3]. Even among those at greatest risk, namely those who have survived a prior CVD event, only a small minority receive most recommended medicines and most receive no treatment whatsoever[2]. Similarly, for people with hypertension — which affects more than a billion people globally — most individuals do not receive any treatment, let alone the multiple drugs usually required for adequate blood pressure control[4].

The term polypill has been used to describe a single pill containing fixed-dose combinations of cardiovascular medications. The rationale for polypill-based strategies is to simplify treatment, provide all necessary generic components in a single once-a-day low-cost pill, bypass therapeutic inertia and support patient adherence. However, more than 20 years after the concept was first proposed, polypills are not widely available or used.

What will it take for CVD polypills (including those used for hypertension) to emerge from the shadows? Successful scale-up will require simultaneous progress on three fronts: a global shift in treatment paradigms; addressing market failures; and tackling implementation challenges.

Treatment paradigms

For those who have survived or are at high risk of experiencing a CVD event (secondary and high-risk primary prevention), a typical guideline-recommended approach to preventive medication use anticipates that treatment will commence with the provision of all necessary drugs at the time of diagnosis, with rigorous follow-up to ensure prescription of all medications at an appropriate dose. In global practice, patients are often started on separate medicines sequentially, with doctors expected to titrate the doses by monitoring individual risk factors such as blood pressure and cholesterol. This is a recipe for therapeutic inertia and, as a consequence, most people remain on inadequate doses of an insufficient number of medications.

The multi-visit individualized-titration approach is also not feasible for the vast majority of people in LMICs, given the lack of physicians and other healthcare workers, competing demands on strained health budgets, and out-of-pocket cost burden to patients. Such as approach is undesirable even in high-income settings where treatment gaps remain substantial, despite cost and access playing lesser roles.

Follow the data

The sheer scale of the number of undertreated people helps inform the need for new approaches, but some have questioned whether the existing evidence is sufficient to warrant a shift to using polypills. However, between 2013 and 2019, clinical trials conducted in countries across the economic spectrum demonstrated that for secondary and high-risk primary CVD prevention, including the treatment of hypertension, polypill-based strategies resulted in important improvements in

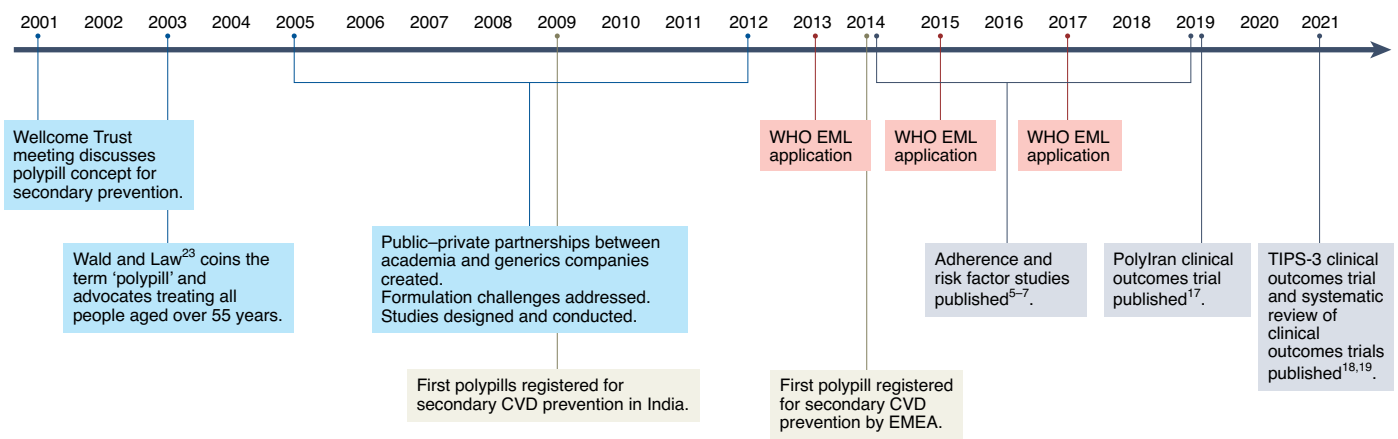

Fig. 1 | Timeline in the development of cardiovascular polypills. The timeline shows the development of polypills containing blood-pressure-lowering drugs, a statin and aspirin for the prevention of CVD, as well as key subsequent events in the development of polypills. EML, List of Essential Medicines. Ref. [25] is cited in the figure.

Table 1 | Key trials evaluating cardiovascular polypills

	Trial	Description	Summary of results
Cardiovascular prevention[a]	SPACE Collaboration[5]	Prospective individual participant data meta-analysis of three trials (Australia; New Zealand; UK, Ireland, the Netherlands and India) of polypill-based strategy versus usual care among people with established CVD or at high risk of CVD ($n = 3,140$). Main outcomes: adherence to combination therapy, blood pressure and cholesterol at 12 months.	The polypill-based strategy, compared to usual care, was associated with significantly greater adherence to combination therapy (80% versus 50%), lower systolic blood pressure (−2.5 mm Hg) and lower LDL cholesterol (−0.1 mmol l^{-1}).
	FOCUS[6]	Randomized trial in Europe and Latin America of a polypill versus component drugs provided separately among people with a history of myocardial infarction within the prior 2 years ($n = 695$). Main outcomes: adherence, blood pressure, cholesterol, safety and tolerability at 9 months.	Polypills, compared to separate medications, were associated with significantly greater adherence (51% versus 41%), with no statistical differences seen for all other outcomes.
	Muñoz et al[7].	Randomized trial in a socioeconomically vulnerable minority population in the United States of a polypill-based strategy versus usual care among people at high CVD risk ($n = 303$). Main outcomes: blood pressure, cholesterol at 12 months.	The polypill-based strategy, compared to usual care, was associated with significantly lower systolic blood pressure (−7 mm Hg) and LDL cholesterol (−0.3 mmol l^{-1}).
	PolyIran[17]	Cluster randomized trial in Iran of a polypill strategy versus augmented usual care among people aged 40–75 years, with or without CVD ($n = 6,838$). Main outcomes: major cardiovascular events, adverse events.	The polypill-based strategy, compared to augmented usual care, was associated with a 34% relative reduction of major cardiovascular events over 5 years, with a similar incidence of adverse events between groups.
	TIPS-3 (ref. [18])	Multi-country factorial randomized trial of a polypill with and without aspirin, compared to matching placebos, among individuals at intermediate CVD risk ($n = 2,850$ for the polypill plus aspirin versus double placebo). Main outcomes: major cardiovascular events, adverse events.	The polypill with aspirin, compared to double placebo, was associated with a 31% relative reduction in major cardiovascular events over a mean of 4.5 years, with similar rates of discontinuation due to adverse events between groups.
Hypertension treatment[b]	TRIUMPH[8]	Randomized trial in Sri Lanka of a low-dose triple-combination blood-pressure-lowering pill versus usual care ($n = 700$). Main outcomes: achievement of blood pressure target, blood pressure, and adverse events at 6 months.	The triple-combination pill, compared to usual care, was associated with a significant improvement in achieving blood pressure target (70% versus 55%) and reduction in systolic blood pressure (−9.8 mm Hg), with similar rates of drug discontinuation rates due to adverse events between groups.
	QUARTET[9]	Randomized trial in Australia of an ultra-low-dose quadruple low-dose combination blood pressure lowering pill versus initial monotherapy ($n = 591$). Main outcomes: blood pressure, achievement of blood pressure target, and adverse events at 3 months.	The quadruple-combination pill, compared to initial monotherapy, was associated with a significantly lower systolic blood pressure (−6.9 mm Hg) and greater achievement of blood pressure target (76% versus 58%), with similar rates of treatment withdrawals due to adverse events between groups.

[a]Randomized trials evaluating polypills (containing blood-pressure-lowering drugs, a statin and aspirin) versus usual care, separate drugs or placebo. [b]Randomized trials evaluating polypills containing at least three blood-pressure-lowering drugs versus single drugs or usual care. An additional 5 trials have randomized participants to a combination of blood-pressure-lowering drugs and statins (or placebo), and these trials also demonstrates reductions in cardiovascular events, to a degree dependent on the extent of risk factor reduction[16]. LDL, low-density lipoproteins.

adherence and reductions in relevant CVD risk factor levels, compared to usual care[5–9]. The beneficial effects of polypills were greatest among those who were undertreated at baseline, a scenario that reflects the current situation in the vast majority of LMIC populations[5]. Even among people already taking all indicated classes of drugs individually, the switch to a polypill — sometimes referred to as a substitution approach — resulted in benefits, albeit more modest benefits, probably due to improved patient adherence. Discontinuation rates due to adverse events were either not increased with polypill use or not more than expected from the amount of increased medicine use[5–9].

Modeled economic analyses indicate that polypill-based strategies were highly cost-effective across a range of settings and — depending on polypill pricing — could be cost-saving in some[10–12]. Qualitative research conducted within some of these studies found high levels of patient acceptability of polypills, with most wishing to continue treatment long-term[13–16]. Prescribers involved in the trials, mainly general practitioners, expressed largely favourable views about using polypills. Concerns are more commonly raised by specialists, although these were mainly in surveys of physicians who did not have experience using polypills. But it is clear that despite the now extensive evidence base (Table 1), some doctors remain sceptical about the benefits of a polypill-based approach compared to individualized drug selection and dosing[13,14].

The evidence base for polypills has recently been boosted significantly by the

publication of findings from large-scale randomized clinical trials showing benefits on major cardiovascular outcomes[17,18]. These trials, largely conducted in middle-income countries among individuals at intermediate CVD risk, have shown a 30–40% reduction in major CVD events among individuals assigned polypill treatment (containing at least two blood-pressure-lowering drugs and a statin, with or without aspirin) compared to control (placebo or augmented usual care). In a meta-analysis of these trials, the incidence of serious adverse events associated with polypills was low and was not statistically different to the rate among participants randomized to the control group[19].

Clinical guidelines

A different approach is needed to achieve a paradigm shift. We have reached a point in time where clinical guidelines need to emphatically recognize that traditional paradigms contribute to treatment gaps and that sufficient evidence now exists to preferentially recommend polypill-based approaches. This needs to be promoted by authoritative voices, such as multilateral agencies and professional societies, but also by healthcare workers in communities where the need for more effective treatment is greatest, such as in LMICs.

So far, there have been three applications to include aspirin–statin–blood-pressure-lowering polypills for people with established CVDs on the World Health Organization (WHO) Model List of Essential Medicines, all of which have been unsuccessful[20]. The reasons for rejection have varied. For earlier applications, health benefits were perceived to be insufficiently clear, with a lack of market availability at the time being an additional issue. For the most recent application, there were concerns about the lack of authoritative guidance on use and strategies for scale-up. Across all applications, there was concern about the number of polypills that might be listed — either too few versions impeding flexibility, or too many versions causing complexity. Most urgently, simple treatment protocols including polypills need to be developed and promulgated. Ultimately, prescriber familiarity will be critical for a successful paradigm shift, which will only occur once polypills are widely available, recommended for use in health systems, reimbursed where possible and supported by continuous medical education provided by relevant professional societies.

Market failures

Wider use of polypills will require the broad availability of affordable formulations, particularly in LMIC markets. Polypills are currently available in several countries for secondary or high-risk primary prevention of CVD and the treatment of hypertension. The robust generics industry in India has produced a substantial number of such products since 2010, but these have generally been premium priced at or above the sum of the individual components, and utilization remains low. Similarly, there have been triple-combination hypertension pills available in several European, Latin American and sub-Saharan African countries since 2009, and polypills for secondary CVD prevention since 2014. These suffer similar pricing and utilization issues but, critically, regulatory approvals are restricted to a substitution indication among already well-treated individuals, where both the need for and benefits of a polypill strategy are modest.

The barriers to wider market availability, specifically for indications beyond simple substitution, can be broadly categorized into industry and regulatory constraints. From an industry perspective, polypill development has fallen in the gap between innovator companies that focus on new patented blockbuster products and generics companies that focus on older off-patent products. Innovator companies generally depend on high margins, resulting in limited market size given unaffordability for broad use, whereas generic companies depend on patent expiry, low margins and large market size. Given the high cost of the regulatory research programs required to bring a polypill to the market for a non-substitution indication, generic drug companies have been unwilling to make the necessary investment. Innovator companies have been unwilling to invest without patent protection from generic competition. From a regulatory perspective, new drug approvals are generally based on evidence of the efficacy and safety of new chemical entities. They are not based on evidence of improved access and effectiveness, and progress in extending approval pathways to include polypills has been very slow. There are also problems with inconsistencies in the requirements of different national regulatory agencies.

Although many technical challenges to polypill formulation and production have been overcome, more needs to be done so that affordable polypills can get to market. More innovation would be facilitated by greater certainty about the requirements for commercial development through regulatory harmonisation and the establishment of clear standards for quality and safety through participation in the WHO prequalification program. A greater focus on development of innovative polypills eligible for patent protection may generate more private sector investment. Closer engagement between polypill manufacturers, payers and providers is likely to be critical to achieving scale, but this may require additional access tools — such as advanced market commitments, pooled procurement and volume guarantees — to secure impact investment.

Implementation challenges

Even with a shift in recommended treatment paradigms and greater market availability of affordable products, impact from polypill-based approaches will only be realized with effective procurement, supply and delivery. Even in settings where there is market availability of inexpensive generic drugs, such as in India, a large proportion of middle- and low-wealth households are unable to afford such treatment[21]. A particular issue for CVD prevention is that those who require treatment are largely asymptomatic and, consequently, do not seek care. Additionally, because of inadequate data systems, demand forecasting can be particularly challenging and delivery systems cannot rely on individuals presenting for care to traditional healthcare facilities. There is also growing concern about the quality of CVD preventive medicines in the push towards universal healthcare, although these medications have received much less attention than others with respect to the risks of substandard or falsified products[22]. But these issues are not unique to polypills, and there is a compelling case to be made that even without overcoming prevailing implementation challenges, changing the current paradigm of single-drug-focused strategies to polypill-based strategies will likely deliver important population level health benefits. This would be facilitated by large context-specific demonstration projects showing the value of polypill-based strategies.

Comparisons between largely unsuccessful attempts to scale-up CVD polypills and previous success with the scale-up of fixed-dose combination antiretroviral therapy for HIV/AIDS and tuberculosis may provide useful lessons. Comparisons should be tempered by the large differences in the size of populations at risk (in 2019, there were around 500 million people with CVD, compared with about 40 million with HIV/AIDS and about 10 million with tuberculosis) and the timeframe over which these epidemics evolved. For both CVD and HIV/AIDS, combination treatment is more effective, although for HIV/AIDS individual drug resistance was a critical driver for the acceptance of multidrug treatment.

Initial provider resistance to combination treatments was probably less of a barrier for what was then the relatively new problem of HIV infection, compared to CVD for which decades-old treatment paradigms are deeply ingrained. Use of combination therapy for HIV/AIDs was also driven by recognition of the therapeutic emergency posed by HIV, which facilitated paradigm shifts, regulatory approvals and essential medicines listings, all of which led to the rapid scale up of affordable fixed-dose combination treatment for individuals with HIV infection. These drivers of uptake do not exist for CVD.

Since the concept was first discussed just over 20 years ago, there has been substantial activity relating to CVD polypill development, research and advocacy (Fig. 1). But scale up remains elusive. Encouragingly, some progress has been made with polypills for hypertension, with the WHO Model List of Essential Medicines listing dual-combination blood-pressure-lowering drugs for initial treatment in 2019, followed more recently by a matching recommendation in updated WHO hypertension guidelines[23,24]. Although this may herald a trend toward promoting polypill-based approaches, realizing their potential will only happen with a global shift in treatment paradigms, new business models and solutions to implementation challenges. This in turn requires urgent consensus building among consumers, providers, payers, manufacturers and a range of other major private and public stakeholders. The risks of delay might be another 20 years before any meaningful progress occurs, at the cost of countless avoidable premature deaths globally. ❐

Anushka Patel[1]✉, Dike Ojji[2], H. Asita de Silva[3], Stephen MacMahon[1,4] and Anthony Rodgers[1,4]

[1]The George Institute for Global Health, University of NSW, Sydney, NSW, Australia. [2]Department of Medicine, University of Abuja, Abuja, Nigeria. [3]Clinical Trials Unit, Department of Pharmacology, Faculty of Medicine, University of Kelaniya, Kelaniya, Sri Lanka. [4]School of Public Health, Imperial College London, London, UK.

✉*e-mail: apatel@georgeinstitute.org*

Published online: 31 January 2022

https://doi.org/10.1038/s41591-021-01635-9

References

1. Roth, G. A. et al. *J. Am. Coll. Cardiol.* **76**, 2982–3021 (2020).
2. Yusuf, S. et al. *Lancet* **378**, 1231–1243 (2011).
3. Peiris, D. et al. *PLoS Med.* **18**, e1003485 (2021).
4. NCD Risk Factor Collaboration. *Lancet* **398**, 957–980 (2021).
5. Webster, R. et al. *Int. J. Cardiol.* **15**, 147–156 (2016).
6. Castellano, J. M. et al. *J. Am. Coll. Cardiol.* **64**, 2071–2082 (2014).
7. Muñoz, D. et al. *N. Engl. J. Med.* **381**, 1114–1123 (2019).
8. Webster, R. et al. *JAMA* **320**, 566–579 (2018).
9. Chow, C. K. et al. *Lancet* **398**, 1043–1052 (2021).
10. Lin, J. K. et al. *Lancet Glob. Health* **7**, e1346–e1358 (2019).
11. Lung, T. L. et al. *Lancet Glob. Health* **7**, e1359–e1366 (2019).
12. Gaziano, T. A. et al. *Am. Heart J.* **214**, 77–87 (2019).
13. Liu, H. et al. *Circ. Cardiovasc. Qual. Outcomes* **8**, 301–308 (2015).
14. Wood, F. et al. *BMJ Open* **5**, e008018 (2015).
15. Cosin-Sales, J. et al. *J. Comp. Eff. Res.* **10**, 975–985 (2021).
16. Wang, N. et al. *Int. J. Cardiol.* **341**, 96–99 (2021).
17. Roshandel, G. et al. *Lancet* **394**, 672–683 (2019).
18. Yusuf, S. et al. *N. Engl. J. Med.* **384**, 216–228 (2021).
19. Joseph, P. et al. *Lancet* **398**, 1133–1146 (2021).
20. Kishore, S. P. et al. *J. Am. Coll. Cardiol.* **71**, 564–574 (2018).
21. Khatib, R. et al. *Lancet* **387**, 61–69 (2016).
22. Do, N. T. et al. *BMJ Glob. Health* **6**, e006523 (2021).
23. Salam, A. et al. *J. Clin. Hypertens.* **22**, 1769–1779 (2020).
24. WHO. *Guideline for the Pharmacological Treatment of Hypertension in Adults* (2021).
25. Wald, N. J. & Law, M. R. *BMJ* **326**, 1419 (2003).

Author contributions

A.P. wrote the first draft. All other authors made critical revisions.

Competing interests

A.P., S.M. and A.R. are employed by The George Institute for Global Health (TGI), which holds patents for ultra-low-dose-fixed combination products for the treatment of hypertension and diabetes. S.M. and A.R. are listed as inventors on these patents. S.M. is a Director on the boards of George Health Enterprises Pty Ltd (GHE) and the social enterprise arm of TGI, as well as its subsidiary George Medicines Pty Ltd (GM); these companies have received funding from public and private investors to conduct trials of fixed combination products for regulatory approval. A.R. is seconded part-time to GM. A.P., S.M. and A.R. do not have direct financial interests in any of the patent applications or investments. D.O. and H.A.d.S. declare no competing interests.