Cardiovascular disease (CVD) has been the leading cause of morbidity and mortality worldwide, now affecting half of all individuals in their lifetime \([1]\) with even higher prevalence in lower-middle income countries \([2]\). Extensive research has revealed many modifiable risk factors for lifetime CVD risk, including hypertension and dyslipidemia, and most guidelines now recommend polytherapy with aspirin, high-dose statins, beta blockers, and angiotensin-II receptor blockers (ARBs) or ACE inhibitors for CVD patients, or for those with a 10-year CVD event risk of >10% \([3-5]\) (although Aspirin is falling out of favor for primary prevention following recent trials\([6-8]\)). Controlling hypertension alone has been shown to improve by combining BP-lowering drugs, due to the presumed additive effect of multiple agents \([9,10]\) and the ability to use lower therapeutic doses which are better tolerated. These guidelines and strategies have resulted in many patients on 2-5+ pills all geared towards the treatment and/or prophylaxis of CVD, despite polytherapy’s association with poor adherence and inadequate prescription \([11,12]\). This encouraged the theory that if provided in a single pill, a multidrug strategy could retain its synergistic effects whilst improving adherence through decreased dosing frequency and pill burden, along with alleviating costs. So the polypill for CVD was enthusiastically proposed nearly two decades ago, and quickly faced both successes and challenges.

The PolyIran study was an influential investigation into the effects of the polypill on primary or secondary prevention of cardiovascular disease, and the first large-scale and long-term randomized trial which showed a significant reduction in cardiovascular event risk in the polypill group over 5 years \([13]\). However, concerns prevailed regarding its generalizability to the United States given its origin in a low-resource nation \([14]\). Another modest-sized randomized trial conducted in Tennessee showed greater reductions in SBP and LDL-C in a polypill group compared to those receiving standard care \([15]\), but this trial was criticized as being too underpowered to detect differences in CVD incidence or mortality \([14]\). Many of the subsequent studies along with ongoing trials were summarized in a review article by Bramlage et al \([16]\). In terms of adherence, studies comparing the polypill strategy to usual-care methods showed improved adherence in all cases \([17-20]\), albeit to varying degrees attributed to differences in study design. Adjustments for socioeconomic determinants such as social support, insurance coverage and treatment complexity still resulted in significantly higher adherence in polypill patients, suggesting benefits irrespective of patient circumstances \([17]\). Studies directed towards patient quality of life showed patient satisfaction with the simplicity of the polypill regimen \([20]\), and no significant change in patient weight, BMI or lifestyle choices \([19]\) which was a proposed concern with a “fix-all” pill. Overall, with respect to clinical outcome the polypill has exhibited comparable-to-superior control of systolic blood pressure (SBP) and low-density lipoprotein cholesterol (LDL-C) compared to usual care, particularly in larger-scale trials \([19]\) and especially in previously non-adherent patients. Additionally, the polypill has shown promise as a cost-effective primary care measure in a variety of healthcare systems \([21,22]\), which may improve adherence and availability especially in low-income and high-risk populations.

Several concerns have been raised regarding the polypill despite its advantages regarding adherence and comparable safety profile. Standard practice commonly involves titrating medications to therapeutic doses on an individual patient basis, and this fine-tuning ability is lacking in a fixed-dose polypill. One study found that the side effects associated with the polypill were generally those associated with its components, and led to 23% of patients discontinuing
polypill therapy over 12 weeks. This raised the concern that the unpleasant effect of any one component could result in the discontinuation of all the drugs. In addition, despite the initial excitement and rapid availability of the polypill in certain countries, an increase in usage among physicians was not appreciated. This may be due to the concerns above, along with general disapproval for a shotgun method of treatment rather than individualized approaches. However, a recent review in JAMA concluded that associations between the polypill and an inflexible or shotgun method or useful only in low-middle income populations are all misconceptions refuted by the literature and recent polypill formulations, and the review endorsed a closer look at polypills in the context of larger high-powered studies.

Studies comparing the clinical benefits of the polypill to placebo pills are unsurprising in their positive results since the individual components of the polypill have already been well-studied and shown to improve CVD risk factors such as SBP and LDL-C. In fact, many patients are already on the exact medication combinations being trialed in polypills precisely for their synergistic clinical benefits. Studies comparing the polypill to “usual care” such as the PolyIran study are more valuable for supporting the implementation of polypills in clinical practice. However, improved adherence has not consistently led to significantly improved clinical outcomes compared to usual care, which Bramlage et al. suggest is the result of insufficient statistical power coupled with insufficient trial lengths. I would be interested in taking a closer look at the value of the polypill compared to usual care by studying a much larger population of patients in the U.S. with CVD or a 10yr ASCVD >7.5%, including individuals of different ages, races, and socioeconomic status.

I recommend standardizing the “usual care” group by establishing algorithms for medications/dosing based on clinical measures (eg. 10yr ASCVD risk, SBP, LDL-C) with support from the literature, and with minor adjustments allowed for adverse effects and patient response. All recommended lifestyle and diet modifications should be encouraged for both groups in conjunction with pharmacotherapy. The polypill group should also have a standardized treatment algorithm, and should be prescribed medication from 4-6 different polypill compositions per their physician, to allow for a realistic level of flexibility. The two groups would not necessarily need to be dosed equivalently, since composing polypills with relatively smaller doses of individual medications may highlight whether improvements in adherence allow for smaller doses with the same outcome, and potentially an improved safety profile. Patients would be seen monthly for 24 months and assessed for clinical outcome measures, adherence, adverse effects, cardiovascular events, lifestyle modifications, and patient satisfaction. In the event of missed doses, missed appointments or discontinuation of therapy in either group, a brief questionnaire could be used to record the reason for discontinuation or poor adherence (eg. cost, side effects, availability, convenience, transportation, etc). The strengths of the study would include addressing the insufficient statistical power of past studies, standardizing treatment groups for easier study comparison and replication, and addressing physician concerns regarding the inflexibility of monotherapy. The results of the study may support or refute existing data regarding the polypill’s impact on adherence, and determine whether the polypill is more likely to discourage individuals from pursuing lifestyle modifications compared to usual care, is associated with more adverse effects than its usual care counterparts, results in fewer cardiovascular events in the course of 24 months, and/or is associated with better patient satisfaction and quality of life. A potential weakness of the study would be the exclusion from the polypill group any participants who have contraindications to any one of the polypill’s components, which may artificially improve adherence in that group and affect the study’s
generalizability. The study will be limited by the number of participants, and the number of physicians willing to cooperate with the standardized treatments in the study, which may once again lead to statistically underwhelming differences as with past studies. Differences in baseline clinical measures between the two groups at the start of the study may also affect the results, and variability in the treatment options for both groups will make the study challenging to replicate.

As a sub-study to the study described above, or perhaps a separate investigation, a multi-center survey of physicians and their preferences/concerns regarding the polypill may be useful. Goals of the study would include delineating major concerns to be addressed, explaining the failure of the polypill to take off commercially even in countries where it is approved and available, and predicting its reception among physicians in the U.S. were it to be cleared as an alternative to the current “usual care”. The survey could begin with questions about physician education, whether they’ve heard of the polypill, and true/false questions regarding the current literature. It could continue with questions regarding physician concerns for the polypill, their current preferred approach to CVD, how likely they are to participate in a clinical trial for the polypill, and how likely they would be to incorporate it into their practice if results were promising. In order to emphasize a patient-centered approach, a similar survey of patients with CVD would be conducted in tandem to estimate patient interest in monotherapy and assess self-reported symptoms, health attitudes and compliance factors, with full disclosure of the known risks and benefits. The survey could include questions related to interest in a single-pill regimen, concerns, and potential obstacles for acquiring treatment, along with assessing satisfaction with their current regimen. Such an investigation could greatly inform adjustments to and future studies on the polypill and its potential role in routine CVD prophylaxis.

Challenges in a survey study such as this include limited participation, variations in survey interpretation, and incomplete surveys. In addition, physicians most likely to complete the survey may be those who are already well-versed in the polypill literature and already have strong feelings one way or another, which is likely to affect the results. A similar conundrum may be faced with the patient survey.

An additional study could compare the side effect profile of several polypill formulations to the side effects experienced by patients receiving usual care. The cessation of therapy in response to adverse effects is a common concern cited for fixed-dose combination therapy, which would result in discontinuation of all its therapeutic components. Patients would be randomized into two groups to receive either usual care or one of several polypills depending on their clinical presentation, and they would be seen in clinic bi-weekly for 4 months to assess for adverse effects of their therapy and adherence to their regimen. Although the polypill is likely to demonstrate similar adverse effects to those already observed in its individual components, the polypill is often constructed with lower doses compared to its usual care counterparts, and this investigation would seek to discover whether those doses would allow for improved tolerance with comparable therapeutic results. Study design would likely exclude those with known contraindications to any component of the polypill from being in that group, which may bias the results favorably, however the availability of several formulations may allow for greater flexibility and personalization of therapy. This variation in treatment may subsequently result in difficulties reproducing the study in the future or generalizing the results.

Optimizing the prevention and treatment of cardiovascular disease is an incredibly rich field of study which still offers much to be discovered, particularly in the realm of polypill research which may hold the answer to a breakthrough in affordable and accessible CVD prophylaxis and management, particularly in high-risk populations.
References


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