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Polypill: Can Mass-Prevention without Precision Promote Cardiovascular Health?

Cardiovascular disease is the leading cause of death and disability in the world.[1] Three-quarters of these deaths occur in low- and middle-income countries. Risk factors for cardiovascular disease are similar throughout the world, and include tobacco use, hypertension, dyslipidemia, diabetes, lack of physical activity, and obesity. Similarly, the strategies to prevent heart disease are universal - healthier diets, regular exercise, no tobacco use, and management of risk factors through lifestyle changes and medication. These are similar to interventions recommended to prevent other noncommunicable diseases (NCDs) like diabetes and cancer. However, inequities in health care resources, income, and access to healthy food are associated with marked risk disparities and worsening cardiovascular disease outcomes, particularly in lower-resource regions. Poverty is correlated with later detection and earlier death from cardiovascular disease, contributing to a cycle of lower future economic productivity. Poverty, in essence, increases the risk of cardiovascular disease, and in turn, cardiovascular disease increases the risk of poverty.[2] For this reason, cardiovascular disease not only presents a formidable health care challenge, but it also stands in the way of economic development.

In an effort to break this cycle of poverty and heart disease, the World Health Organization has proposed a *"Global action plan for the prevention and control of NCDs 2013-2020"* - two of the plan's nine global targets address cardiovascular disease, through a recommended reduction in hypertension, which disproportionately impacts low- and middle-income countries, and through focused medical therapy and behavioral counseling to prevent heart attacks and strokes, which is a similar strategy used in higher-income countries. While these are admirable goals, challenges to success include identifying the optimal strategy to accomplish them, funding to support them, logistics to organize them, and implementation to bring them to the world's population. The World Health Organization recognizes these challenges, and has commented,

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[1] Cardiovascular diseases fact sheet, World Health Organization Cardiovascular diseases (CVDs) (who.int)

[2] Gheorghe A, Griffiths U, Murphy A, Legido-Quigley H, Lamptey P, Perel P. The economic burden of cardiovascular disease and hypertension in low- and middle-income countries: a systematic review. BMC Public Health. 2018 Aug 6;18(1):975. doi: 10.1186/s12889-018-5806-x. PMID: 30081871; PMCID: PMC6090747.

"Achieving this target will require strengthening key health system components, including health-care financing to ensure access to basic health technologies and essential NCD medicines."[3] As of this writing, no updates to this plan are currently available.

The purpose of this review is to explore and evaluate one potential solution: the polypill. A polypill is a fixed-dose combination medication which is intended to prevent or treat a medical condition. These are commonly used in the United States to treat hypertension, and are used worldwide to help manage tuberculosis and HIV. But a mass-prevention polypill strategy has yet to be accepted in the global cardiovascular health landscape. Since 2001, the World Health Organization has considered the potential value of this strategy to prevent heart disease, by using lipid-lowering and anti-hypertensive medications in combination to lower cardiovascular disease risk.[4] And during the past twenty years, multiple research studies have examined the effectiveness of the polypill with respect to patient compliance, improvements in blood pressure and lipid profiles, and most importantly in improvement in cardiovascular outcomes. However, obvious challenges to implementation exist, which include cost, compliance, safety, tolerability, and logistics. There is also the ethical concern of whether it is appropriate to deliver a treatment globally that is not the current standard of care in higher-resource settings. The global polypill experience so far, in the context of global health history, may ultimately inform the recommendation to adopt a polypill prevention strategy worldwide.

Cardiovascular Disease is the Leading Cause of Death in the World

During the past several decades, great strides have been taken toward advancing global health, with significant improvements in vaccinations, medical treatment of HIV infection, and management of multidrug resistant tuberculosis. But during this time period, the world has also experienced a steady increase in the burden of noncommunicable diseases - particularly cardiovascular disease. Even as trauma, motor vehicle accidents, and infectious diseases maintain their profound impacts on disability and years of potential life lost in younger populations, cases of heart disease have nearly doubled in mature populations from 271 million worldwide in 1990 to 523

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[3] Cardiovascular diseases fact sheet, World Health Organization Cardiovascular diseases (CVDs) (who.int)

[4] Secondary Prevention of Noncommunicable Disease in Low- and Middle-Income Countries through Community Based and Health Service Interventions: Report of WHO–Wellcome Trust Meeting of Experts – August , Hinxton, Cambridge, Noncommunicable Diseases and Mental Health W H O https://www.who.int/cardiovascular_diseases/media/en/615.pdf

million in 2019.[5] The number of cardiovascular deaths, years of life lost, and disability-adjusted life years have all increased significantly. But what hasn't changed is the role and contribution of widely recognized cardiovascular disease risk factors toward this increasing tide of morbidity and mortality. Hypertension, unhealthy diets, and elevated LDL cholesterol continue to be important modifiable risk factors for heart disease, and they have become even more impactful as the world becomes further industrialized and food systems have become increasingly reliant upon highly processed foods, which include corn syrup, trans fats and sodium among their ingredients.

The prevalence of high blood pressure has increased worldwide, now impacting approximately nine in ten adults.[6] While it is conceivable that the increased prevalence may reflect an increase in screening, the disproportionately higher rates in lower- and middle-income countries are notable. There appears to be a higher prevalence of hypertension in Central Asia, North and Sub-Saharan Africa, and the Middle East, all regions with limited primary care resources to screen for hypertension and treat it adequately with medications. The global trend for elevated LDL cholesterol has also increased throughout the world, and appears to be correlated with obesity and unhealthy diets, both more common in lower- and middle-income countries.[7] Given the limited primary care infrastructure in most of these settings, public health leaders have historically championed a focus on the potential role of healthy lifestyles, including healthier diets and increased exercise, in preventing cardiovascular disease. But the medical evidence would suggest that this approach may be neither achievable nor even successful, even if it were embraced.[8]

Behavior Change is Neither a Feasible Nor Effective Strategy to Prevent Cardiovascular Disease Worldwide

Educational public health campaigns and targeted behavioral counseling to improve diet quality and increase physical activity are a cornerstone of heart disease prevention strategies in environments with well established primary care infrastructures.

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[5] Cardiovascular diseases fact sheet, World Health Organization Cardiovascular diseases (CVDs) (who.int)

[6] Roth GA et al. Global Burden of Cardiovascular Diseases and Risk Factors, 1990–2019: Update From the GBD 2019 Study. *J Am Coll Cardiol.* 2020 Dec, 76 (25) 2982–3021.

[7] Roth GA et al. Global Burden of Cardiovascular Diseases and Risk Factors, 1990–2019: Update From the GBD 2019 Study. *J Am Coll Cardiol.* 2020 Dec, 76 (25) 2982–3021.

[8] Patnode CD, Evans CV, Senger CA, Redmond N, Lin JS. Behavioral Counseling to Promote a Healthful Diet and Physical Activity for Cardiovascular Disease Prevention in Adults Without Known Cardiovascular Disease Risk Factors: Updated Systematic Review for the U.S. Preventive Services Task Force [Internet]. Rockville (MD): Agency for Healthcare Research and Quality (US); 2017 Jul. Report No.: 15-05222-EF-1. PMID: 29364620.

By extension, a potential strategy for cardiovascular disease prevention in lower- and middle-income countries might be to incorporate the best of these initiatives into current care paradigms, even with their known limitations. But surprisingly to some proponents of this approach, the research unfortunately suggests that even in high-resource settings, these campaigns have limited effectiveness and durability.

In 2017, the United States Preventive Services Task Force published a meta-analysis of 88 primary prevention trials that studied the effectiveness of behavioral counseling to promote healthy diets and physical activity in general populations, without targeting individuals with known cardiovascular disease risk factors.[9] The majority of these studies took place in primary care settings in the United States, and interventions included “low-intensity” strategies such as mailed printed materials, as well as “medium- and high-intensity” tactics which included one-on-one or group counseling, including during primary care office visits.. All of these interventions required significant infrastructure, including content creation and distribution as well as established primary care-based health systems to deliver counseling, which varied in duration from minutes to hours.

Unfortunately, despite the considerable investment in these efforts, there was no discernible effect on health outcomes. High-intensity, diet-only interventions reported no differences in all-cause or cardiovascular mortality at 3 to 15 years of follow-up. There were no consistent findings for the effects on cardiovascular events over 8 to 15 years of follow-up. Physical activity intervention trials did show general improvement in quality of life for up to a year among intervention groups, but without consistent benefits compared to controls. There were limited benefits of behavioral interventions on blood pressure (less than 2 mm Hg), LDL cholesterol (less than 3 mg/dl), and body mass index (-0.41 kg/m2) at 6 to 12 months, but the effects beyond 12 months were even less clear. More importantly, these small benefits did not translate into improvements in clinical outcomes.

This data does have some limitations with respect to its generalizability. It is mostly based upon a population with greater access to primary health care than most communities in lower- and middle-income countries. And this meta-analysis focuses on a primary prevention public health model, rather than targeting higher-risk individuals with established cardiovascular disease risk factors with behavioral interventions to

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[9] Patnode CD, Evans CV, Senger CA, Redmond N, Lin JS. Behavioral Counseling to Promote a Healthful Diet and Physical Activity for Cardiovascular Disease Prevention in Adults Without Known Cardiovascular Disease Risk Factors: Updated Systematic Review for the U.S. Preventive Services Task Force [Internet]. Rockville (MD): Agency for Healthcare Research and Quality (US); 2017 Jul. Report No.: 15-05222-EF-1. PMID: 29364620.

modify diet and physical activity. Targeted interventions may be more impactful in higher-risk populations. However, they may also be less realistic in low-resource settings with less access to primary care and widespread underdiagnosis of hypertension, dyslipidemia, and diabetes. Additionally, there may be less access to healthier diets in low-resource settings characterized by poverty and easier access to foods with poor nutritional quality. Finally, this data does not imply that true behavior change is not effective. Eating healthier and exercising regularly have been shown to reduce cardiovascular risk.[10] But this data does suggest that behavioral counseling and health education have limited effectiveness. For these reasons, education and awareness campaigns would be expected to have limited benefits on a global scale, and effective behavioral interventions are not likely on a population level. Given that behavioral interventions would not be expected to be effective in preventing cardiovascular disease, it is even more important to seriously consider a pharmacologic approach to primary prevention - the polypill.

Polypill: From Theory to Trial

In 2001, the World Health Organization and The Wellcome Trust came together to discuss future directions for the prevention and management of non-communicable diseases, including heart disease.[11] The concept of fixed-dose combination pills including aspirin, blood pressure medications and a statin was explored as a means of improving adherence to treatment plans and reducing medication costs. The WHO Annual Report outlined the potential public health benefit and overall cost-effectiveness of implementing a combination medication prevention or treatment plan.

The polypill moniker was then introduced in a landmark 2003 *British Medical Journal* article titled, *"A strategy to reduce cardiovascular disease by more than 80%."*[12]

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[10] Arnett DK, Blumenthal RS, Albert MA, Buroker AB, Goldberger ZD, Hahn EJ, Himmelfarb CD, Khera A, Lloyd-Jones D, McEvoy JW, Michos ED, Miedema MD, Muñoz D, Smith SC Jr, Virani SS, Williams KA Sr, Yeboah J, Ziaeian B. 2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease: Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation. 2019 Sep 10;140(11):e563-e595. doi: 10.1161/CIR.0000000000000677. Epub 2019 Mar 17. Erratum in: Circulation. 2019 Sep 10;140(11):e647-e648. Erratum in: Circulation. 2020 Jan 28;141(4):e59. Erratum in: Circulation. 2020 Apr 21;141(16):e773. PMID: 30879339.

[11] Secondary Prevention of Noncommunicable Disease in Low- and Middle-Income Countries through Community Based and Health Service Interventions: Report of WHO–Wellcome Trust Meeting of Experts – August , Hinxton, Cambridge, Noncommunicable Diseases and Mental Health W H O https://www.who.int/cardiovascular_diseases/media/en/615.pdf

[12] Wald NJ, Law MR. A strategy to reduce cardiovascular disease by more than 80%. BMJ 2003; 326: 1419-23.

The authors proposed that the current pharmacologic approach to cardiovascular disease prevention has been overly restricted to the highest risk groups, with a narrow focus on individual risk factors rather than global risk. They argued,

> *"Drug treatment to prevent ischemic heart disease events and stroke has generally been limited to single risk factors, to targeting the minority of patients with values in the tail of the risk factor distribution, and to reducing the risk factors to "average" population values. This policy can achieve only modest reductions in disease. A large preventive effect would require intervention in everyone at increased risk irrespective of the risk factor levels; intervention on several reversible causal risk factors together; and reducing these risk factors by as much as possible."*

The authors suggested that combining six different medications (aspirin, three anti-hypertensives, a statin, and folic acid) might be expected to reduce cardiovascular disease risk by 80% if given to everyone over 55 years of age. Folic acid was added to more traditional heart disease prevention medications due to its purported benefits in reducing homocysteine levels; however, this supplementation strategy is not currently supported by the medical evidence.[13]

During the subsequent decade, dozens of opinion articles, cost-effectiveness analyses, and review papers were published that lauded, debated, and decried this concept, without the benefit of randomized trial data to support or refute its efficacy. Meanwhile, combination anti-hypertensive medications and combination statin/anti-hypertensive drugs slowly entered the marketplace and have become socialized into medical practice to varying degrees, focusing on secondary prevention of heart disease through treatment of hypertension and dyslipidemia, rather than as a larger scale primary prevention public health program.[14] [15] [16] [17]

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[13] Li Y, Huang T, Zheng Y, Muka T, Troup J, Hu FB. Folic Acid Supplementation and the Risk of Cardiovascular Diseases: A Meta-Analysis of Randomized Controlled Trials. J Am Heart Assoc. 2016 Aug 15;5(8):e003768. doi: 10.1161/JAHA.116.003768. PMID: 27528407; PMCID: PMC5015297.

[14] Law MR, Wald NJ, Morris JK, Jordan RE. Value of low dose combination treatment with blood pressure lowering drugs: analysis of 354 randomised trials. BMJ 2003;326: 1427-31.

[15] Law MR, Wald NJ, Rudnick AR. Quantifying the effect of statins on low density lipoprotein cholesterol, ischaemic heart disease, and stroke: systematic review and meta-analysis. BMJ 2003; 326: 1423-7.

[16] Rosenthal T. Can a polypill one single tablet combat different cardiovascular risk factors? J Am Soc Hypertens. 2018 May;12(5):335-339. doi: 10.1016/j.jash.2018.02.008. Epub 2018 Mar 2. PMID: 29573975.

[17] Luteijn M, Wald NJ. The NHS Health Checks programme: a better alternative.J Med Screen 2016;23:57-58.

In the next several years, multiple studies were published that demonstrated that a polypill was not only a feasible intervention from a biochemical and safety standpoint, but was also effective in reducing blood pressure and LDL cholesterol in settings with adequate primary care support structures.[18] [19] Some heterogeneity in treatment effects were noted, and were attributable to the varying components of the different polypill formulations, as well as variations in medication compliance and baseline characteristics of the study populations. Accordingly, there was widespread variation with respect to the degree of side effects and drop-out rates.

For example, a 2011 randomized, double-blind placebo-controlled trial involving 378 individuals found that a polypill containing aspirin, lisinopril, hydrochlorothiazide, and simvastatin was effective in reducing systolic blood pressure by 9.9 mmHg, and LDL cholesterol by 21%.[20] Baseline blood pressures averaged 143/86. The discontinuation rates in the polypill group were 23% vs 18% compared to placebo. There was an excess of side effects related to the polypill medications (58% vs 42%), which was mostly apparent within a few weeks and usually did not warrant cessation of trial treatment. These primarily included muscle aches, and did not include hypotension.

In a 2012 randomized, double-blind crossover trial, 84 participants took a combination pill containing amlodipine, losartan, hydrochlorothiazide and simvastatin for twelve weeks.[21] The average age of participants was 59. Compliance with the regimen was greater than 85%. No one dropped out of the study due to side effects. The researchers found that this polypill formulation lowered systolic blood pressure by an average of nearly 18 mmHg, diastolic pressure by nearly 10 mmHg, and LDL cholesterol by 39%.

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[18] Indian Polycap Study (TIPS), Yusuf S, Pais P, Afzal R, Xavier D, Teo K, Eikelboom J, Sigamani A, Mohan V, Gupta R, Thomas N. Effects of a polypill (Polycap) on risk factors in middle-aged individuals without cardiovascular disease (TIPS): a phase II, double-blind, randomised trial. Lancet. 2009 Apr 18;373(9672):1341-51.

[19] Malekzadeh F, Marshall T, Pourshams A, Gharravi M, Aslani A, Nateghi A, Rastegarpanah M, Khoshnia M, Semnani S, Salahi R, Thomas GN, Larijani B, Cheng KK, Malekzadeh R. A pilot double-blind randomised placebo-controlled trial of the effects of fixed-dose combination therapy ('polypill') on cardiovascular risk factors. Int J Clin Pract. 2010 Aug;64(9):1220-7.

[20] PILL Collaborative Group, Rodgers A, Patel A, Berwanger O, Bots M, Grimm R, Grobbee DE, Jackson R, Neal B, Neaton J, Poulter N, Rafter N, Raju PK, Reddy S, Thom S, Vander Hoorn S, Webster R. An international randomised placebo-controlled trial of a four-component combination pill ("polypill") in people with raised cardiovascular risk. PLoS One. 2011;6(5):e19857. doi: 10.1371/journal.pone.0019857. Epub 2011 May 25. Erratum in: PLoS One. 2019 Nov 25;14(11):e0225924. PMID: 21647425; PMCID: PMC3102053.

[21] Wald DS, Morris JK, Wald NJ. Randomized Polypill crossover trial in people aged 50 and over.PLoS One 2012;7:e41297.

Having demonstrated that a polypill could improve surrogate endpoints of blood pressure and LDL cholesterol, polypill researchers would then evaluate the polypill with respect to clinical endpoints. The PolyIran study enrolled more than 6800 rural 50-75-year-old participants and followed them for five years.[22] The polypills included aspirin, statin, hydrochlorothiazide, and angiotensin-converting enzyme inhibitors or angiotensin receptor blockers. The intervention was associated with an overall 34% reduction in cardiovascular events, which increased to 57% among those with high adherence. There was a 40% reduction in events among participants without a known history of cardiovascular disease. The number needed to treat in the high adherence care arm to prevent a major cardiovascular event was 21. This number-needed-to-treat would suggest comparable effectiveness to many accepted pharmacological interventions in the United States, including the use of aspirin and statins to reduce cardiovascular events among individuals with a history of a prior heart attack.[23] [24]

The *New England Journal of Medicine* then published a small trial designed to prove whether a polypill prevention strategy was feasible in an underserved American population, using a combination pill of low-dose atorvastatin, amlodipine, hydrochlorothiazide and losartan.[25] Adherence to the polypill regimen was an impressive 86%, and during the twelve-month study, the mean systolic blood pressure decreased by 9 mm Hg and the mean LDL cholesterol level decreased by 15 mg/dL in the polypill group. The study authors estimated that based upon prior meta-analyses of cardiovascular outcomes trials in primary prevention, these changes, if continued long-term, would be associated with a 25% reduction in the incidence of cardiovascular events over time.

The most recent large polypill study is notable for its impressive results in a multinational participant population. Published in the *New England Journal of Medicine* in 2021, the TIPS-3 study was a placebo-controlled, double-blinded study of over 5000 individuals from nine countries during nearly five years.[26] The study examined the

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[22] Rosandel 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 394 672-683.

[23] Antithrombotic Trialists Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. BMJ. 2002 Jan 12;324(7329):71-86.

[24] CTT Collaborators. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90 056 participants in 14 randomised trials of statins. Lancet. 2005; 366: 1267-1278.

[25] Munoz D et al, Polypill for Cardiovascular Disease Prevention in an Underserved Population N Engl J Med 2019; 381: 1114-1123.

[26] Yusuf S et al, Polypill with or without Aspirin in Persons without Cardiovascular Disease. N Engl J Med 2021; 384: 216-228.

impact of a polypill with or without aspirin on clinical outcomes. Individuals at intermediate risk (men over 50, women over 55) without known cardiovascular disease were included. During the follow-up period, the polypill was found to reduce cardiovascular outcomes by 31%. An accompanying editorial remarked, “The findings of TIPS-3 support the inclusion of multidrug therapy for cardiovascular disease prevention in the World Health Organization ‘best buys’ for noncommunicable disease prevention and control as the lone health-system approach that is potentially highly cost-effective.”[27]

In summary, the polypill has been demonstrated in multiple randomized placebo-controlled prevention trials to improve blood pressure and LDL cholesterol in women and men at intermediate baseline cardiovascular risk. And even more importantly, the polypill is associated with a reduction in cardiovascular events. Discontinuation and nonadherence are variable among the different research studies, as are the exact components of the polypills studied. It is notable that the degree of risk factor improvement and outcome reduction are generally less impressive in real-world trials as compared to the original predictions in the landmark 2003 *British Medical Journal* editorial. And while the overall effectiveness of the polypill has been demonstrated in a research setting, real-world experience is lacking as to whether a polypill is a viable public health strategy, particularly in resource-limited environments. Although one polypill formulation called Trinomia (aspirin, atorvastatin, ramipril) is licensed in 21 countries, it is not widely used.

Ironically, the World Health Organization itself may be one obstacle to implementation. Despite three applications to include the cardiovascular polypill on the WHO Model List of Essential Medicines, the WHO has refused. This list is used by the majority of countries to define what safe and essential medicines will be made available on a national scale. The absence of the polypill makes its implementation less likely. Dr. RIchard Smith, former editor of the *British Medical Journal*, noted,

> *“The first application was rejected for being unclear on the indication (both primary and secondary prevention); the second for being a concept with too many variants of three and four drug combinations; and the third for having neither a guideline nor an adequate strategy to support its widespread use. The rejections strike enthusiasts for the polypill as deeply unfair as polypills (fixed dose combinations) for HIV, TB, and malaria have all been allowed onto the list with what the cardiovascular polypill enthusiasts see as much less evidence.”*[28]

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[27] Huffman MD, Patel A. Polypills - A Central Strategy for Improving Cardiovascular Health. N Engl J Med. 2021 Jan 21;384(3):288-289. doi: 10.1056/NEJMe2033310. PMID: 33471983.
[28] https://blogs.bmj.com/bmj/2018/08/08/richard-smith-polypill-long-journey-major-impact/

While the World Health Organization may create some momentum toward widespread use of the polypill if it becomes included on the Essential Medicines List, there will still be multiple challenges ahead.

Barriers to Polypill Implementation

The barriers to implementing a polypill prevention strategy - beyond inclusion by the World Health Organization - are considerable, and include concerns regarding acceptance, safety and tolerability, cost, and overall logistics. Acceptability is always a concern when considering a prevention strategy. Even in high-resource settings, it is often challenging to convince asymptomatic individuals to aggressively manage their hypertension, dyslipidemia, or even diabetes. It is therefore important to consider issues related to acceptability for a polypill primary prevention strategy for otherwise asymptomatic adults in low-resource settings.

Acceptability

We unfortunately have limited data as to whether a population in a low-resource community would accept the opportunity to take a daily preventive medication and continue it over the long term, in a non-research setting. But we do know that long-term compliance with prescribed medications for hypertension and dyslipidemia is limited. For example, adherence to hypertension medication beyond one year is less than 50%.[29] [30] Among older adults taking statins for primary prevention, adherence after two years is closer to 25%.[31] Reasons for discontinuation are complex, and may include personal preference, tolerability, side effects, and cost. These discontinuation rates are reflective of the experience in more highly resourced environments with more established primary care infrastructures. This raises concerns about the long-term viability of a daily polypill program in a less resourced setting. For example, while a short-term feasibility study in Sri Lanka involving 216 patients during three months suggested a high rate of patient acceptability, it is unclear whether patients would

[29] Vrijens B et al. Adherence to prescribed antihypertensive drug treatments: longitudinal study of electronically compiled dosing histories. *British Medical Journal 2008*; 336: 1114-1117.
[30] Hill MN et al. American Society of Hypertension Writing Group. Adherence and persistence with taking medication to control high blood pressure. J Am Soc Hypertens. 2011; 5: 56-63.
[31] Maningat P, Gordon BR, Breslow JL. How do we improve patient compliance and adherence to long-term statin therapy?. *Curr Atheroscler Rep*. 2013;15(1):291. doi:10.1007/s11883-012-0291-7.

continue the polypill during a period of years that would be required to significantly impact the incidence of heart disease.[32]

Trust

Trust is another factor that is related to acceptance. Trust in government, science, and healthcare have never been more tenuous in light of the coronavirus pandemic, and are especially relevant when considering a polypill medication recommendation. While medication side effects are commonly described as reasons for noncompliance in highly resourced settings, one cannot underestimate the role of distrust in lower-resourced settings. Historically, outside entities have defined access to medical care or public health care; trust has therefore been a central component of varying degrees of treatment success throughout the AIDS epidemic,[33] in the international response to Ebola,[34] and even today as coronavirus vaccines are not made widely available throughout the world, even though they are accessible to nearly everyone in the United States. The uneven power relationship among countries with unequal resources could understandably have an impact on how individuals might perceive a recommendation to take a lifelong daily medication with negligible monitoring and follow-up, while limited resources are made available to help build a primary care infrastructure or address basic nutrition, water and sanitation needs, and multinational corporations push tobacco products and low-quality processed food and beverages into these very same communities.

Tolerability

Even if accepted, would a polypill strategy be tolerated? In the various research studies cited earlier, dropout rates due to side effects were generally low, but these

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[32] Soliman EZ, Mendis S, Dissanayake WP, Somasundaram NP, Gunaratne PS, Jayasingne IK, Furberg CD. A Polypill for primary prevention of cardiovascular disease: a feasibility study of the World Health Organization. Trials. 2011 Jan 5;12:3.

[33] Dawson-Rose C, Cuca YP, Webel AR, Solís Báez SS, Holzemer WL, Rivero-Méndez M, Sanzero Eller L, Reid P, Johnson MO, Kemppainen J, Reyes D, Nokes K, Nicholas PK, Matshediso E, Mogobe KD, Sabone MB, Ntsayagae EI, Shaibu S, Corless IB, Wantland D, Lindgren T. Building Trust and Relationships Between Patients and Providers: An Essential Complement to Health Literacy in HIV Care. J Assoc Nurses AIDS Care. 2016 Sep-Oct;27(5):574-84. doi: 10.1016/j.jana.2016.03.001. Epub 2016 Mar 22. PMID: 27080926; PMCID: PMC5207494.

[34] Richards P, Mokuwa E, Welmers P, Maat H, Beisel U. Trust, and distrust, of Ebola Treatment Centers: A case-study from Sierra Leone. *PLoS One*. 2019;14(12):e0224511. Published 2019 Dec 2. doi:10.1371/journal.pone.0224511.

individuals were followed during a relatively short period of time.[35] Given that years of treatment are required to impact clinical effectiveness, it is unclear how many individuals would discontinue a polypill due to side effects.[36] [37] Based upon adherence rates for hypertension medications and statins, long-term adherence might be expected to be lower than 25% in a non-research setting.[38] It is also worth considering the potential impacts of inevitable side effects related to a universal primary prevention strategy on future trust of the healthcare system and the likelihood of adopting future medical recommendations, whether related to cardiovascular disease, AIDS, tuberculosis, or even a coronavirus vaccine.

Safety

Safety is another important concern. It would not be feasible to check liver function tests or a basic metabolic panel on every candidate for a polypill formulation that includes a statin, a diuretic, or an angiotensin receptor blocker. Laboratory testing is the standard of care for monitoring these medications in a more highly resourced environment. Is it ethical to withhold the same standard of monitoring from a population taking the polypill? For example, approximately one out of 250 individuals taking a statin might be expected to develop statin-associated diabetes;[39] should this be communicated to polypill users, and should routine glucose monitoring be

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[35] Soliman EZ, Mendis S, Dissanayake WP, Somasundaram NP, Gunaratne PS, Jayasingne IK, Furberg CD. A Polypill for primary prevention of cardiovascular disease: a feasibility study of the World Health Organization. Trials. 2011 Jan 5;12:3.

[36] Anushka Patel, Alan Cass, David Peiris, Tim Usherwood, Alex Brown, Stephen Jan, Bruce Neal, Graham S Hillis, Natasha Rafter, Andrew Tonkin, Ruth Webster, Laurent Billot, Severine Bompoint, Carol Burch, Hugh Burke, Noel Hayman, Barbara Molanus, Christopher M Reid, Louise Shiel, Samantha Togni, Anthony Rodgers, for the Kanyini Guidelines Adherence with the Polypill (Kanyini GAP) Collaboration, A pragmatic randomized trial of a polypill-based strategy to improve use of indicated preventive treatments in people at high cardiovascular disease risk, European Journal of Preventive Cardiology, Volume 22, Issue 7, 1 July 2015, Pages 920–930.

[37] PILL Collaborative Group, Rodgers A, Patel A, Berwanger O, Bots M, Grimm R, Grobbee DE, Jackson R, Neal B, Neaton J, Poulter N, Rafter N, Raju PK, Reddy S, Thom S, Vander Hoorn S, Webster R. An international randomised placebo-controlled trial of a four-component combination pill ("polypill") in people with raised cardiovascular risk. PLoS One. 2011;6(5):e19857. doi: 10.1371/journal.pone.0019857. Epub 2011 May 25. Erratum in: PLoS One. 2019 Nov 25;14(11):e0225924. PMID: 21647425; PMCID: PMC3102053.

[38] Maningat P, Gordon BR, Breslow JL. How do we improve patient compliance and adherence to long-term statin therapy?. *Curr Atheroscler Rep*. 2013;15(1):291. doi:10.1007/s11883-012-0291-7.

[39] Collins R, Reith C, Emberson J, Armitage J, Baigent C, Blackwell L, Blumenthal R, Danesh J, Smith GD, DeMets D, Evans S, Law M, MacMahon S, Martin S, Neal B, Poulter N, Preiss D, Ridker P, Roberts I, Rodgers A, Sandercock P, Schulz K, Sever P, Simes J, Smeeth L, Wald N, Yusuf S, Peto R. Interpretation of the evidence for the efficacy and safety of statin therapy. Lancet. 2016 Nov 19;388(10059):2532-2561.

recommended? A polypill strategy suggests a new standard of care in primary prevention; if this is to be implemented broadly in lower-resource settings, it should meet safety standards in all settings.

Cost

Cost is another potential obstacle to funding a successful and sustainable polypill program. Daily cost estimates currently range from 1-2 USD per participant.[40] A primary prevention strategy relies on large population adoption in order to bring about a significant clinical effect or future cost-savings. One argument for recommending a polypill strategy is that low resource settings do not offer adequate access to cardiologists, cardiac testing, or cardiac interventions such that there are limited opportunities to care for individuals with heart attacks or heart failure. Therefore, prevention is not only clinically sound, but should be cost-effective, as it will reduce the need for future resources to care for people with heart disease.[41] [42] A cost-benefit analysis of a national polypill prevention program in the United Kingdom assumed a substantial cost, but with an acceptable cost per year of life gained:

> *"If the cost of the Polypill Prevention Programme were £1 per person per day, the total cost would be £4.76 bn and, given the savings (at 2014 prices) of £2.65 bn arising from the disease prevented, there would be a net cost of £2.11 bn representing a net cost per year of life gained without a first MI or stroke of £2120."*[43]

But it is unclear who would be paying for it. Given the low amount of health care spending per individual in low-resource settings by their own governments, it seems unlikely that polypills would be supplied domestically. The World Health Organization and international nongovernmental organizations could provide funding, but it would seem overly optimistic to assume that funding for primary prevention of cardiovascular disease would supersede funding for the current medical treatment of HIV, tuberculosis, and diarrheal illnesses. Similarly, it appears unlikely that polypill funding would be

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[40] Wald NJ, Luteijn JM, Morris JK, Taylor D, Oppenheimer P. Cost-benefit analysis of the Polypill in the primary prevention of myocardial infarction and stroke.Eur J Epidemiol 2016; DOI 10.1007/s10654-016-0122-1.

[41] Wald NJ, Luteijn JM, Morris JK, Taylor D, Oppenheimer P. Cost-benefit analysis of the Polypill in the primary prevention of myocardial infarction and stroke.Eur J Epidemiol 2016; DOI 10.1007/s10654-016-0122-1.

[42] Wald NJ, Morris JK. Quantifying the health benefits of chronic disease prevention: a fresh approach using cardiovascular disease as an example. Eur J Epidemiol 2014;29:605-612.

[43] Wald NJ, Luteijn JM, Morris JK, Taylor D, Oppenheimer P. Cost-benefit analysis of the Polypill in the primary prevention of myocardial infarction and stroke.Eur J Epidemiol 2016; DOI 10.1007/s10654-016-0122-1.

sustained. The short-term return on investment for treatment of diarrheal illnesses or common infectious diseases is quite attractive to funding organizations; the potential benefits of a polypill strategy might not be realized for years in most settings. In our current economic environment, is it realistic to expect large funding organizations to invest in a decades-long strategy when health care crises are ubiquitous and requests for emergency funding are quotidian? While a polypill prevention strategy may eventually become cost-effective,many funding organizations may not have the patience or resources to realize the benefit given the years-long investment.

Logistics

Finally, the logistics of providing daily medication to an asymptomatic population are incredibly complex. For example, awareness of hypertension is less than 50% in many lower-resourced countries, and control with medications is only 10%.[44] It is heartening to learn of examples in which there have been some successes - such as the treatment of multidrug-resistant tuberculosis in Peru, or HIV in Haiti by Partners in Health. But is it possible to expect similar successes for implementing a daily cardiovascular care program for asymptomatic individuals? Arguably, some of the success in treatment implementation for infectious diseases is fueled by the rapid clinical course of these illnesses. Daily treatment programs save lives in the short-term, and can improve quality of life almost immediately. Would it feel equitable to recommend the same level of financial and human resources to be successful for an intervention with a significantly lower number-needed-to-treat to achieve clinical effectiveness? Accessing medication and health care is already a challenge for most people in low-resource settings - supplying rural and poor people with a steady supply of daily medication over years would seem to be insurmountable.

Conclusion

In the classrooms of medical schools and hallways of teaching hospitals, it is common to hear the phrase “academic exercise” - typically stated in a pejorative fashion. It is often used to describe something theoretical, overly intellectualized, and often lacking in practical application. An academic exercise may represent fact or truth, but it may also not be very useful.

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[44] Lloyd-Sherlock P, Beard J, Minicuci N, Ebrahim S, Chatterji S. Hypertension among older adults in low- and middle-income countries: prevalence, awareness and control. Int J Epidemiol. 2014 Feb;43(1):116-28. doi: 10.1093/ije/dyt215. Epub 2014 Feb 6. PMID: 24505082; PMCID: PMC3937973.

The argument for a comprehensive polypill strategy for the prevention of cardiovascular disease began twenty years ago as an academic exercise, a moonshot strategy for consideration. And the academy responded in kind, with multiple research studies that have ultimately supported the benefit of blood pressure treatment and LDL reduction to prevent heart disease, and the success of polypill formulations to deliver effective medications in combination. Impressively, polypills have even been proven to prevent heart disease. But is this enough?

Can scientific evidence move this academic exercise into the real world of global health, with all of its financial, logistical, and social challenges? In a health landscape where multiple interest groups compete for limited resources, how can we know whether a polypill prevention strategy is the right choice when compared to the other opportunities to improve global health? The title of this review poses the question, “Can mass-prevention without precision promote cardiovascular health?” The published scientific evidence would suggest it can. The next step is to determine how.

Prevention-based medical approaches are challenged by issues of acceptability and trust, tolerability and safety, cost and logistics. The academy has shown that a polypill can be clinically effective, but we need to better understand how a polypill *program* can be effective. Public health experts should now focus on different strategies to safely deploy a polypill program in different communities to better understand real-world issues around acceptance, side-effects, and feasibility. We need to better understand supply chains and the logistics around delivering large quantities of medication to rural locations on a consistent basis. And finally, we need to recognize the role of community health workers and local leaders with respect to communicating this strategy and maintaining trust. The coronavirus pandemic has taught us that public health needs improved public relations - this will be essential to successfully delivering a polypill program.

Once we better understand the “can” and the “how,” we cannot neglect the “should.” Health care ethicists and economists alike might help us explore perhaps the most profound and challenging questions of all: Should limited healthcare resources be used to fund a polypill program? Should we prioritize mass-prevention rather than invest in more personalized primary care? Should we implement a polypill strategy in environments with fewer resources even as we drive toward precision medicine in higher-resource settings?

The first steps toward answering these questions can be taken if the World Health Organization creates a taskforce to explore adding a cardiovascular polypill to its Essential Medicines List. Twenty years ago, the WHO identified the potential public

health benefits and cost-effectiveness of this strategy. We now need the leadership of the WHO to put this into action. We need head-to-head comparisons of different fixed-dose medication formulations to determine the most efficacious, well-tolerated, and cost-effective polypill. We need the collaboration of public health experts, ethicists, and economists to guide the right strategy. And we need to partner with organizations like Partners in Health who have experienced success with long-term daily medication interventions with HIV and TB to better understand the logistics and education required to create a successful polypill program on the local level. This is indeed no longer just an academic exercise. The WHO should bring the polypill from the halls of the academy out into the homes of our communities, where it is desperately needed to help prevent cardiovascular disease throughout the world.