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The Polypill: A Proposed Global Solution to Cardiovascular Disease

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Abstract

Despite groundbreaking advances in healthcare, cardiovascular disease (CVD) remains the leading cause of death and disability worldwide, making it one of the most pressing global health issues to face the modern world. In 2002, Wald and Law proposed the concept of the polypill as a potential solution to this global health epidemic. The polypill represents a powerhouse pill that would consist of a combination of several key medications commonly prescribed for CVD prevention, such as a statin, diuretic, beta blocker, or ACE inhibitor, in one. It was suggested that it could be a novel, tactical measure in the approach to CVD prevention in that it greatly simplifies the healthcare delivery system. Not only does it increase medication compliance for those currently receiving healthcare, but it also has the potential to access those in underserved healthcare sectors of the world, primarily low- and middle- income countries, which have been identified as areas of highest CVD risk. A major drawback of the polypill is that there are limited data demonstrating its safety and efficacy in the prevention of CV morbidity and mortality. Thus far, research shows that the polypill has promise but needs to be approached with a few considerations, such as desired target patient population and formulation. This paper will examine the published and ongoing studies associated with the polypill, outline the advantages and disadvantages of utilizing the polypill as a global CVD prevention strategy, and discuss the design and availability of the polypill in the United States.

Key words: polypill, polycap, fixed dose compound, red heart pill, cardiovascular disease, global healthcare

According to the World Health Organization (WHO), cardiovascular disease (CVD) is the leading cause of death and disability worldwide, and is projected to remain so in decades to come.¹ CVD is a global health epidemic affecting individuals from all backgrounds, irrespective of socio-economic class, culture, gender, ethnicity, or geography. It is estimated that approximately half of the global population will develop CVD over their lifetime, with about 17.3 million patients dying from it annually, accounting for roughly 30% of all global deaths.^{1,2}

Clinically, CVD is approached from two standpoints, primary or secondary prevention. The probability of an individual developing CVD is predicted by the presence of non-modifiable or modifiable risk factors. The current standard of preventative care, primary or secondary, focuses on curbing an individual's modifiable risk factors, which is aligned to the worldwide findings that approximately 10 risk factors are responsible for 90% of the risk associated with having a myocardial infarction or stroke.^{3,4} Therefore, preventative care is targeted at behavioral modifications, namely weight management, minimizing alcohol consumption, tobacco cessation, and dietary adjustments, as well as pharmacotherapy targeting hypertension, hyperlipidemia, and diabetes.

At the present time, CVD is a global health crisis being micromanaged on an individual level by various clinicians. On the public health horizon, there lies a novel concept proposing that the approach to this global issue be reconstructed and broadened to embrace a macro-management, umbrella strategy. In other words, a global health issue would be addressed with a global health solution. The concept in question has been coined the polypill and was introduced in 2002 by Wald and Law.⁵ In essence, the polypill is a single powerhouse capsule containing a combination of several key, commonly prescribed medications targeting CVD, such as a statin, diuretic, beta blocker, or angiotensin converting enzyme (ACE) inhibitor. Wald and Law

postulated that the polypill could be used as a primary prevention means in patients 55 years of age or older due to their study's findings that the polypill strategy could prevent more than 80% of ischemic heart disease (IHD) events and strokes. There are a limited number of studies that have tested the polypill concept, in which the majority of them are ongoing. Thus far, there are only a few variations of the polypill concept available worldwide, notably the Polycap® in India and the Polypill® Heart Compound in the United States. This article will review the current literature analyzing the potential impact of the polypill against prevention of CVD morbidity and mortality, outline the advantages and disadvantages of utilizing the polypill as a global strategy to address CVD, and highlight the design and availability of the Polypill® Heart Compound in the United States.

Published Clinical Trials

To date, there are four trials studying the efficacy and safety of the polypill that have been completed and published: The Indian Polycap Study (TIPS), a study performed by Malekzadeh et al in Iran, a WHO international study, and an international study completed by the Program to Improve Life and Longevity (PILL) Collaborative Group.⁶⁻⁹ This section will discuss the design and results of each of these four published studies.

TIPS, published in 2009, was a crucial and significant landmark study because it was the first to assess the efficacy and safety of the polypill concept.⁶ The focus of the study was on the polypill for primary prevention and included participants 45-80 years of age without a history of CVD but with one CVD risk factor. In this double-blinded trial, a total of 2053 participants were randomized to one of 9 arms: the Polycap®, aspirin alone, simvastatin alone, hydrochlorothiazide alone, three combinations of two blood pressure-lowering medications, three blood pressure lowering medications, or three blood pressure-lowering medications plus aspirin. The

Polycap® was comprised of low dose ingredients, specifically hydrochlorothiazide 12.5mg, atenolol 50mg, ramipril 5mg, simvastatin 20mg, and aspirin 100mg. The medications and dosages used in the other arms were the same as those found in the Polycap® but in individual components or as different combinations. This study was designed to measure CVD risk level reductions in a 12-week study period. The primary endpoints included measurements of low-density lipoprotein (LDL)-cholesterol, blood pressure, heart rate, urinary 11-dehydrothromboxane B2 for the antiplatelet effect of aspirin, and rates of discontinuation of medications for safety.⁶

Results of this study showed that the Polycap® was non-inferior in primary outcome measurements when compared to the individual medications or combinations in other arms, except in the case of LDL-cholesterol lowering with simvastatin. The Polycap® and the three blood pressure lowering medications reduced systolic blood pressure (SBP) and diastolic blood pressure (DBP) comparably by 7.4 mmHg and 5.6 mmHg. Of note, an expected additive effect on blood pressure reductions with the increasing number of blood pressure medications was observed in this trial. The Polycap® decreased heart rate by 7bpm and 11-dehydrothromboxane B2 by 283.1 ng/mmol creatinine, similar to the beta blocker alone and aspirin alone arms. As stated previously, the only difference in primary outcome was seen with LDL-cholesterol reduction. Simvastatin alone reduced LDL cholesterol by 0.83 mmol/L, whereas the Polycap® had a smaller effect of 0.70 mmol/L (p=0.04). These results suggest that the effects of the Polycap® cannot be assumed to be the same as the combined effects of its individual components. Hence, the authors recommended that the pharmacological effects of every preparation of a polypill be tested prior to the start of future clinical outcomes studies.⁶

Tolerability and rate of discontinuation between the Polycap® and the 8 other arms were

similar, demonstrating that the higher number of ingredients in the Polycap® did not cause tolerability issues. Lastly, the TIPS authors used Wald and Law's approximations and estimated that the Polycap® could potentially reduce cardiovascular heart disease (CHD) by 62% and stroke by 48%. Although the reductions are lower than those projected by Wald and Law, they are still considered to be substantial.

In 2010, Malekzadeh et al published a double-blind, placebo-controlled trial, which took place in Golestan, Iran.⁷ Four hundred and seventy five participants 50-79 years of age without hypertension, hyperlipidemia, or CVD were randomized to receive either a low-dose polypill containing aspirin 81mg, enalapril 2.5mg, atorvastatin 20mg, and hydrochlorothiazide 12.5mg, or a placebo for 12 months. The primary endpoints were changes in LDL-cholesterol, blood pressure, and occurrence of adverse reactions. The authors reported that the polypill achieved modest results. Specifically, SBP was lowered by 4.5 mmHg ($p < 0.001$), DBP by 1.6 mmHg ($p < 0.032$), and LDL-cholesterol by 0.46 mmol/L ($p < 0.001$) in the polypill arm compared to the placebo arm. Also, the authors found that there was not a statistically significant difference in the rate of adverse events between the two arms, signifying that the polypill was well-tolerated.

The third completed study was sponsored by the WHO and sought to assess the feasibility of the polypill for primary prevention of CVD for three months.⁸ It was an open-label, parallel-group, randomized clinical trial performed in Sri Lanka with 216 patients. The study compared the polypill (Red Heart pill 2b containing aspirin 75mg, simvastatin 20mg, lisinopril 10mg, and hydrochlorothiazide 12.5mg) to standard practice in participants ≥ 40 years of age with an estimated 10-year total CVD risk score $\geq 20\%$. Primary outcomes focused on reduction of SBP, total cholesterol, and estimated 10-year CVD risk. Patient and physician acceptability of the polypill was also assessed.

There were no significant differences in primary outcomes between the patients taking the polypill and those being treated by standard practice. Furthermore, 90% of the patients who completed the study stated that they would take the polypill for life if it was proven to be effective in lowering CVD risk. In addition, an overwhelming majority of physicians agreed that they would support the use of the polypill in primary (86%) and secondary prevention (93%).⁸

The Pill Collaborative group published the fourth completed study of the polypill in 2011.⁹ This international trial was held in seven countries: Australia, Brazil, India, the Netherlands, New Zealand, the United Kingdom, and the United States. Individuals were included if they were ≥ 18 years of age with an estimated 5-year CVD risk of at least 7.5% based on the Framingham risk score. A total of 378 participants were randomized to placebo or the Red Heart Pill, comprised of aspirin 75mg, lisinopril 10mg, hydrochlorothiazide 12.5mg, and simvastatin 20mg. Primary outcomes included reductions in SBP, LDL-cholesterol, and tolerability measured after a 12-week study period.

Results of this study were positive in terms of efficacy and feasibility but questionable for tolerability. The Red Heart Pill reduced SBP by 9.9 mmHg (95% CI: 7.7 to 12.1) and LDL-cholesterol by 0.8 mmol/L (95% CI: 0.6 to 0.9). The results supported the feasibility and tolerability of the Red Heart Pill in that the discontinuation rates between the two arms was not statistically significant; rates were 23% and 18% in the Red Heart Pill group and the placebo arm, respectively (RR 1.33, 95% CI 0.89 to 2.00, $p=0.2$). However, a notable finding from the study was that side effects were more prevalent in the Red Heart Pill arm compared to the placebo group (58% vs 42%, $p=0.001$). It was estimated that 1 out of 20 participants had to stop the treatment due to an adverse event, such as aspirin-induced gastric irritation. Gastric bleeding tendency was also reported as a side effect of aspirin in the Red Heart Pill, but it did not

necessitate discontinuation of treatment in this study. Nevertheless, these findings question whether aspirin should be included in a polypill formulation due to bleeding risks.

The authors concluded that an approximate 60% reduction in CHD and ischemic stroke risk could be achieved with the polypill, which was similar to the reductions reported by the TIPS study. They predicted that about 1 in 18 individuals could avoid a major CV event if they were on polypill treatment for 5 years; this ratio could increase to 1 out of 4 individuals if addressing only the high-risk population. However, in terms of adverse effects, this was the first study to conclude that the benefits of the polypill could possibly be impeded by an excess amount of side effects. They estimated that there could be about a 50% increase in risk for extracranial bleeding due to aspirin. The authors argued that previous trials had a higher final follow-up loss (16% in TIPS vs. 27% in Malekzadeh et al vs. 1% in this trial), which could explain a lack of excess side effect findings on their end. In summary, the authors supported the efficacy of the polypill but recommended that the target population should consist solely of high-risk patients due to a significant side effect profile.

Ongoing Clinical Trials

A number of the ongoing studies of the polypill are continuations of previous trials. For instance, TIPS-K and TIPS-3 are extensions of the TIPS trial, and the POLYIRAN trial succeeds the study performed by Malekzadeh et al. TIPS-K is awaiting publication and is different from TIPS in that it questions the role of the polypill in secondary prevention, the polypill dose strength, and the polypill formulation.¹⁰ The study includes participants ≥ 40 years of age with stable chronic CVD. Patients are either randomized into one arm to receive one low-dose Polycap® daily or another arm to receive 2 doses of Polycap® daily, equivalent to a full dose. Patients in the double Polycap® arm are also randomized to either receive or not receive oral

potassium to determine if it would be a beneficial component of a polypill formulation. The logic being that potassium supplementation would balance diuretic potassium wasting. The authors will seek to determine whether the double dose of the Polycap® is safe and more effective than the original low-dose Polycap® in controlling blood pressure and cholesterol in patients with a history of CVD or uncontrolled diabetes. For TIPS-3, the principal investigator of TIPS, Salim Yusuf, told the European Society of Cardiology Congress News in 2011 that the trial will study the Polycap® minus aspirin on a larger scale (5000 patients over a 5-year period) to assess the efficacy, safety, and benefits of the Polycap® in primary prevention.¹¹ This will be the first trial to directly measure the rate of CV events and not the surrogate markers of risk factor level reduction.

The POLYIRAN trial seeks to determine the efficacy of the polypill in primary and secondary prevention of CVD in Iranians 50 to 79 years of age.¹² The trial period is expected to run 5 years and include 7000 participants. The three arms are defined as: 1) minimal care and POLYIRAN1 (aspirin 81 mg, enalapril 5 mg, atorvastatin 20 mg, and hydrochlorothiazide 25 mg) or POLYIRAN 2 (aspirin 81 mg, valsartan 40 mg, atorvastatin 20 mg, and hydrochlorothiazide 12.5 mg); 2) minimal care; and 3) usual care. Minimal care consists of a health education pamphlet, education from a physician and community health worker, and biannual follow-up. Primary outcomes include time to first major CV event and rate of CV-specific mortality.

A unique organization, the Single Pill to Avert Cardiovascular Events (SPACE), is a collaboration sponsored by the George Institute of Global Health that is comprised of investigators conducting various trials around the world testing the Red Heart Pill.¹³ Currently, three major trials are underway: Use of a Multidrug Pill In Reducing Cardiovascular Events

(UMPIRE), Kanyini Guidelines Adherence with the Polypill Study (Kanyini-GAP), and Improving Adherence through Combination Therapy (IMPACT).¹⁴⁻¹⁶ Additionally, they have just received funding from the Brazilian government's Ministry of Health to recruit 2000 patients for a trial to take place at Hospital do Coracao in Sao Paulo. Furthermore, they are planning to have future trials in Canada, South Africa, and China.¹³

The UMPIRE trial enlisted 1000 participants from the United Kingdom, The Netherlands, and Ireland and 1000 patients in India.¹⁴ The purpose of the 18-month, open-label UMPIRE study is to determine whether medications delivered via a single polypill enhances adherence and is comparable in efficacy to its individual medication components in primary and secondary prevention. Patients ≥ 18 years of age with established atherothrombotic CVD or high CV risk, defined as a history of CHD, ischemic cerebrovascular disease, or peripheral vascular disease, or a calculated 5-year CVD risk $\geq 15\%$ were included. The experimental arm consists of those getting the polypill, either the Red Heart Pill Version 1 (aspirin 75mg, simvastatin 40mg, lisinopril 10mg, and atenolol 50mg) for those with a history of CHD, or Version 2 (aspirin 75mg, simvastatin 40mg, lisinopril 10mg and hydrochlorothiazide 12.5mg) for those with a history of stroke or cerebrovascular disease. The comparator arm will be treated with usual care. Primary outcome measures include adherence at the end of the trial follow-up, which will be analyzed by self-reported use of anti-platelet, statin, and blood pressure-lowering therapy. In addition, the changes in blood pressure and LDL-cholesterol levels will be reported.

The design, inclusion criteria, interventions, and endpoints of the IMPACT and Kanyini-GAP study are similar to those of the UMPIRE study. However, the IMPACT study had 600 participants from New Zealand, and the Kanyini-GAP study recruited 1000 participants from Australia.^{15,16}

The FOCUS study is a randomized, open-label, two phase trial that seeks to identify and analyze the factors contributing to a lack of medication adherence in secondary CVD prevention and demonstrate that the polypill is a viable solution to the issue of adherence as a whole.¹⁷ In the first phase of the trial, questionnaires will be used to identify medication non-compliance factors. The questionnaires will be distributed to populations with varying degrees of socio-economic characteristics to determine associations between factors and socio-economic class. The second phase will study the primary outcome of adherence between patients receiving a Fixed Dose Combination (FDC) pill, comprised of 100 mg aspirin, 40 mg simvastatin, and 2.5, 5, or 10 mg ramipril, vs. the medications individually. Patients were only enrolled into the study if they were ≥ 40 years of age with a history of ST elevation myocardial infarction within the last 2 years. This ongoing study has a trial period of 18 months.

Lastly, the Heart Outcomes Prevention Evaluation-3 (HOPE-3) trial will evaluate the concept of the polypill.¹⁸ In this trial spanning 20 countries, investigators will compare the reduction in CVD and stroke risk among rosuvastatin 10mg, candesartan 16mg/ hydrochlorothiazide 12.5mg, and the combination of both these arms. Enrollment is estimated to target 11,000 participants, with inclusion criteria of women > 60 years of age and men > 55 years of age without established CVD but at least one CVD risk factor. This study is expected to be completed in May 2013.

Potential Benefits of the Polypill

The polypill possesses several exciting advantages that enable it to have the potential of changing the landscape of public health in the modern world. Its core advantages include the capability of being able to provide a blanket solution to a devastating and deadly public health concern, simplifying healthcare delivery, improving cost-effectiveness, increasing medication

adherence, and enhancing completeness of evidence-based prescribing. Moreover, there is a growing professional support for the polypill in the healthcare field.

The public health benefits of the polypill could have worldwide influence, making it a viable solution to a debilitating global health concern. CVD does not affect the world uniformly; in reality, approximately 80% of CVD cases occur in low- to middle- income countries¹. The issue with combating CVD in these countries is that their healthcare systems do not allow for robust healthcare; oftentimes, there are a lack or complete absence of physicians, healthcare practitioners, financial means, clinics, medicine, and follow-up care.¹⁹ The promise of the polypill is that it can function in these minimalistic settings due to the ease of which a patient can be assessed to receive the polypill, the ease in which the polypill can be prescribed, and that a patient can manage the polypill independently. At present, there is no consensus as to which patient population the polypill should be prescribed. However, it has been suggested that the consensus should consist of only a few selected criteria for either primary or secondary prevention. By avoiding complex therapy algorithms, assessment would be far simpler and a greater majority of patients at risk could be treated.¹⁹ The polypill is given as a simple one pill a day regimen with no substantial tolerability issues, need for titration, or need to monitor, which makes follow-up unnecessary.¹⁹ In this scenario, the healthcare systems of low- to middle-income countries, which do not have the means to ensure adequate patient services, can adopt the polypill strategy because patients are able to manage it autonomously.

Another feature of the polypill that gives it the potential to be successful worldwide is its cost-effectiveness. The polypill would be cost-effective primarily for two reasons: low cost of production and costs savings from CVD event avoidance. The WHO chronic diseases report estimated that a patent would not protect the polypill because it is made up of generic drugs.

Therefore, the polypill could be produced for as little as approximately \$1 per month.²⁰ Cost-effectiveness is especially important considering that a 1-month supply of standard generic secondary prevention medications can cost a government worker in a low-income country about 1.6 to 18.4 days of work wages.²¹ Furthermore, there will be additional savings associated with the polypill because there will be reduced costs in packaging, distribution, marketing, physician visits, and lab tests associated with it.¹⁹ In the United States alone, it was estimated that CVD costs account for roughly \$450 billion annually and are projected to more than double by 2030.²² Therefore, the significant reduction of CVD events predicted with the polypill would make a substantial fiscal impact. As for low- and middle-income countries, the WHOCHOICE project and the study by Gaziano et al. have demonstrated that multi-drug regimens are cost-effective strategies for the prevention of CVD.^{21,23}

It is estimated that about one-third to one-half of patients are not being properly managed for their disease states due to medication non-compliance.^{24,25} Non-compliant patients in turn make up of about one- to two-thirds of all patients being admitted to hospitals for medication-related causes.²⁴ Two of the major causes of medication non-compliance are pill burden and polypharmacy confusion. The polypill has the potential to resolve these issues, leading to improved adherence and better management of disease states.²⁵ The effect of reducing pill burden and improving adherence has already been demonstrated in the use of combination pills for maintenance of tuberculosis, malaria, asthma, and HIV.¹⁹ In addition, a simplified one pill a day dosing regimen can help to eliminate confusion from taking multiple dosages of medications, especially in the elderly population.²⁶ Another potential advantage of the polypill is that patients would receive all the evidence-based medications that they require.²⁶ It was shown that only about 27% of dyslipidemic individuals receive lipid-lowering therapy, and of these

patients, only 6.2% to 8% and 17.3% to 21.3% of patients reached their LDL-cholesterol goal of <100 mg/dl for primary prevention and secondary prevention, respectively.²⁷ From these findings, it is evident that a greater number of patients need to receive the medications they require. Current CVD guidelines recommend multiple medications for primary and secondary prevention. Giving these patients a polypill ensures that all the necessary medications are being administered so that more patients are able to reach goal.

Due to the many potential benefits offered by the polypill, there is a solid and growing healthcare support for the use of this approach for more effective health management. In the previously aforementioned WHO trial performed in Sri Lanka, an overwhelming majority of physicians and patients supported the use of the polypill.⁸ Moreover, in a study published in the International Journal of Pharmacy Practice, it was reported that 73.6% and 79.2% of pharmacists surveyed agreed that a polypill would simplify treatment and reduce patient costs, respectively.²⁸ Results of this survey showed that a majority of pharmacists viewed the polypill as a potentially valuable strategy in improving patients adherence to long-term cardiovascular therapy.

Potential Disadvantages and Unresolved Issues of the Polypill

There is no doubt that the polypill delivers an impressive array of possible advantages, but it is a controversial concept because there are also quite a number of challenges associated with it. Notable concerns include lack of direct evidence that the polypill reduces the rate of CVD morbidity and mortality, registration, cost, formulations issues, acceptability, and effect on patient's perspective of health maintenance.^{19, 26}

Thus far, polypill trials have only used surrogate markers, such as changes in blood pressure or LDL-cholesterol, as primary endpoints to measure CVD risk factor reduction. At this time, there is a lack of concrete evidence reporting that the polypill is effective at decreasing the

rate of morbidity and mortality attributed to CVD or safe in primary CVD prevention.¹⁹ There have been no large-scale morbidity and mortality trials completed with the polypill. The TIPS-3 trial will be the first to venture into this necessary territory.¹¹ Another challenge facing the polypill is the need for it to be registered as any other new medication. Typically, in order for any new medication to gain approval from regulatory bodies, large-scale morbidity and mortality trials are needed to demonstrate its efficacy and safety. Since the polypill is made up of well-studied medications already on the market, it may be feasible that existing trials for the individual components provide sufficient evidence for the regulatory bodies. However, there is still a possibility that the regulatory bodies will require large-scale morbidity and mortality trials to definitively prove the polypill's efficacy and safety.^{19,26} This concern, in turn, may add in a possible cost challenge. Additional costs, such as those from pharmaceutical development and research and registration, need to be considered because they may make the polypill more expensive than expected.²⁶

Other complications that need to be considered are those of pharmaceutical formulation: physiochemical compatibility, ensuring expected bioavailability, and ideal composition. For one, the high number of medications in the polypill must be physiochemically compatible with one another to ensure a well-tolerated and stable product.²⁶ Secondly, it is important that all of the medications in the polypill provide the expected bioavailability. This concern was raised by the unexpected lower LDL-reduction of simvastatin in the polypill in the TIPS trial.⁶ Lastly, there are currently a few forms of the polypill available, but there has been no consensus as to what the ideal composition of a worldwide polypill would be. Several issues need to be addressed when formulating the ideal polypill composition. First, all the ingredients need to be stable with one another to prevent drug-drug interactions or changes in pharmacokinetics.¹⁹

Secondly, only the medications, which are proven to have benefits outweighing the risks should be included in the polypill. Therefore, aspirin's risk profile should be assessed to determine if it should be included. Special populations, such as asthma patients, need to be considered when designing an ideal formulation because they may not be tolerant to specific ingredients, such as non-selective beta blockers. Another concern that the TIPS-2 trial will address is whether the ingredients should be low-dose or high-dose.¹⁰ All of these concerns are especially important when considering that the majority of these patients will not be monitored. It has been suggested that there should be multiple variations of the polypill to account for different populations and that one pill most likely will not be suitable for every patient.

An additional challenge of the polypill is acceptability by prescribers and patients. Prescribers are trained to follow complex algorithms to treat their patients. In practice, when a medication is not tolerated or effective, a prescriber will exercise their clinical judgment to titrate the dose or choose an alternative. Prescribers will not have the ability to employ this common practice with the polypill, thus rendering their clinical judgment unnecessary. Instead, they will be forced to practice minimally and unconventionally with the polypill, which may cause prescriber resistance toward the polypill.

Another way the polypill could cast a negative view is its affect on standard practice. It is well-known that healthy lifestyle choices in exercise, diet, smoking, and alcohol consumption can play a major role in CVD prevention and treatment. If patients adopt a glorified outlook of the polypill in that it will cure them of all their ailments, they may feel that they have leeway to make poorer lifestyle choices. Therefore, in a way, the polypill could serve as a hindrance to health maintenance in patients who choose the polypill in lieu of lifestyle modifications. This could prove frustrating to physicians who are unable to get their patients to goal due to this issue.

Polypill® Heart Compound in the United States

The Polypill® Heart Compound is presently made in the United States by a Florida-based company, Polypill of America.²⁹ According to the president of the company, Mark Blake, the primary mission of Polypill of America is to proudly offer a solution to a pressing healthcare issue, medication non-compliance, through the availability of a combination pill containing a complete therapy regimen customized to each patient.³⁰ Prescribers throughout the nation can phone or fax in prescriptions to their Polypill pharmacy detailing what medications and strengths they would like their patient's Polypill® Heart Compound to contain. In India, the Polycap® has a standard composition, whereas the Polypill® Heart Compound in America is customized. The ingredients are entirely dependent on the prescriber, but commonly prescribed ingredients include ACE inhibitors, angiotensin receptor blockers, beta blockers, calcium channel blockers, diuretics, and statins. Prescribers may write separate morning and evening Polypill® Heart Compound recipes in the case where certain medications should only be taken at night or in the morning. Moreover, depending on the prescriber, additional medications can be included, such as Diovan®, Plavix®, and Prilosec®, as long as the maximum number of 6 ingredients per pill is abided by. Brand and generic ingredient preference is also indicated by the prescriber's orders.³⁰

The Polypill pharmacy compounds each Polypill® Heart Compound from the powder form of FDA-approved ingredients ordered from FDA-approved manufacturers.³⁰ The Polypill® Heart Compound is only available in capsules and generally has a 1-year expiration date. The cost of a 30-day supply of the medication is \$40. However, according to the company, over 200 insurance companies currently cover the Polypill® Heart Compound, including Aetna, United, and Blue Cross Blue Shield. Medicare does not cover it. Typically, once a prescription is received, orders are sent out to patients via Mail Order UPS with an expected delivery time of 5-

7 business days. The company currently is able to service forty four states but not the entire fifty due to licensing requirement differences between states.³⁰

Conclusion

Despite groundbreaking advances in healthcare, CVD remains a prevalent global health issue affecting millions throughout the world. It has been a decade since Wald and Law proposed the concept of the polypill as a potential solution to a deadly global health epidemic. Since 2002, there have only been a handful of trials that have been completed and published to assess the efficacy and safety of this innovative concept. The results of these trials have supported the viability of the polypill in CVD prevention and management but with a few reservations.

The polypill has a growing professional and consumer support base because of the several advantages that it offers. The polypill has the potential to curb a global health epidemic by reaching underdeveloped corners of the world, simplifying healthcare delivery, improving cost-effectiveness, increasing medication compliance, and supporting completeness of evidence-based prescribing. However, there are concerns with the polypill. The most important being that there are a lack of clinical trials studying the polypill. Furthermore, the trials that have been completed have all measured surrogate markers as primary outcomes. The highly anticipated TIPS-3 trial will be the first to address the effect of the polypill on morbidity and mortality in patients with CVD. Other concerns of the polypill include registration, cost, formulations issues, acceptability, and effect on a patient's perspective of health maintenance.

The polypill is an exciting concept on the forefront of global health. Studies are being done around the world as investigators unite to determine whether it is a viable solution to an epidemic facing every country, race, and community. Further research of the polypill is much

needed with the collective results having the potential power to change the face of healthcare across the world.

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