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Are polypills a viable option to improve health outcomes in those with cardiovascular disease?

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Are Polypills a Viable Option to Improve Health Outcomes in Those with Cardiovascular Disease?

Objective: Does the use of polypill therapy improve systolic blood pressure and low-density lipoprotein cholesterol (LDL-C) levels more than usual care in adults with established cardiovascular disease (CVD) or with 10-year atherosclerotic cardiovascular disease risk >10%. **Design:** Systematic literature review. **Methods**: Searches were performed in PubMed and UpToDate using the following search terms polypill and cardiovascular. Other limits included: randomized control trials, adults, published in the last 10 years, LDL-C and systolic blood pressure. **Results:** Analysis of articles to ensure similar design, intervention and fit with the other inclusion/exclusion criteria yielded three studies: Labefer et al, Muñoz et al, and Patel et al.[9,10,11] **Conclusion:** The polypill should be considered in all adults who have a 10-year ASCVD event risk >10% or those previously diagnosed with CVD. The polypill should particularly be considered in subgroups such as those taking fewer than two anti-hypertensive medications, patients who are failing to meet cholesterol goals with low potency statins or individuals that face challenges accessing medications. Price and production of the polypill in the United States remains to be seen and would have a significant impact on the clinical power of the polypill.

Introduction

Cardiovascular disease is the leading cause of death for men and women in the United States.[1] Nearly one in three deaths in the U.S each year is caused by heart disease or stroke.[2] The economic burden of cardiovascular disease was $219 billion dollars in 2014-2015, and its impact disproportionately affects minority and ethnic groups.[2,3]

One of the lesser discussed risk factors for development of a cardiovascular disease is a lack of medication compliance. The World Health Organization states adherence to medications can have more of an impact on patient outcomes than the specific treatment itself.[4] Among patients with chronic illness, approximately 50% do not take medications as prescribed.[5] As information from research provides new light about optimal dosing and drug to drug synergism, the burden of medication navigation becomes increasingly more complex. In response to increasing CVD prevalence and poor medication adherence, a fixed dose combination pill was developed which includes an aspirin, a statin, and two anti-hypertensive medications.[6]

Compliance is further exacerbated in underserved areas where individuals have inappropriate access to preventative medication and adherence is typically poor.[7] African Americans are 30% more likely to die from heart disease, twice as likely to have a stroke, 40% more likely to have high blood pressure, and 10% less likely to have their blood pressure under

control than their white counterparts. Mexican Americans have higher triglyceride levels, and Puerto Ricans have the highest rate of death related to hypertension.[7] Many minorities and underserved regions experience far greater health disparities— especially related to cardiovascular disease. Despite the potential benefits of the polypill, this pill is not yet available to the American consumer.

A potential disadvantage of polypill therapy is the inability to tailor doses to the individual, concomitantly, increasing the potential for adverse effects. Although studies have been completed in several European nations, this review provides a meta-analysis of current data to help evaluate the role and value the polypill could have in the United States.

A common guideline tool for stratifying patients is the Atherosclerotic Cardiovascular Disease (ASCVD) calculator. This is a predication based on certain risk factors such as age, sex, race, blood pressure, cholesterol levels, diabetes history, smoking history and if the individual is currently taking anti-hypertensive medications. The calculation creates a 10-year risk of having a cardiovascular related episode such as stroke or myocardial infarction and stratifies the risk by levels: low <5%, borderline 5%-7.5%, intermediate 7.5%-20% and high >20%. This analysis utilizes these stratifications to help with proper cross study patient comparison.

Clinical Question

In adults diagnosed with CVD or at a higher than borderline 10-year ASCVD risk who are already prescribed a multiple drug regimen, does administration of a polypill (one statin, two anti-hypertensive medications and an aspirin) show improved systolic blood pressure and LDL-C compared to usual care after one year.

Methods

Search engines utilized included PubMed, Cochrane Library and Google. An initial search was performed in September 2020 using MESH terms such as ‘polypill’ and ‘cardiovascular disease’ which yielded 396 records. Records that were excluded were non-randomized control trials, articles published before 2010, outcomes limited only to adverse events or did not include cardiovascular outcomes, this yielded 36 results. Results that did not compare intervention to usual care, included placebo control groups or did not trend LDL-C and blood pressure were excluded. The three studies selected were individually assessed and validated by comparing inclusion and exclusion criteria, funding and sample size. This process is depicted in Figure 1: PRISMA Search Strategy and Table 1: Inclusion and Exclusion Criteria.

Figure 1: PRISMA Search Strategy

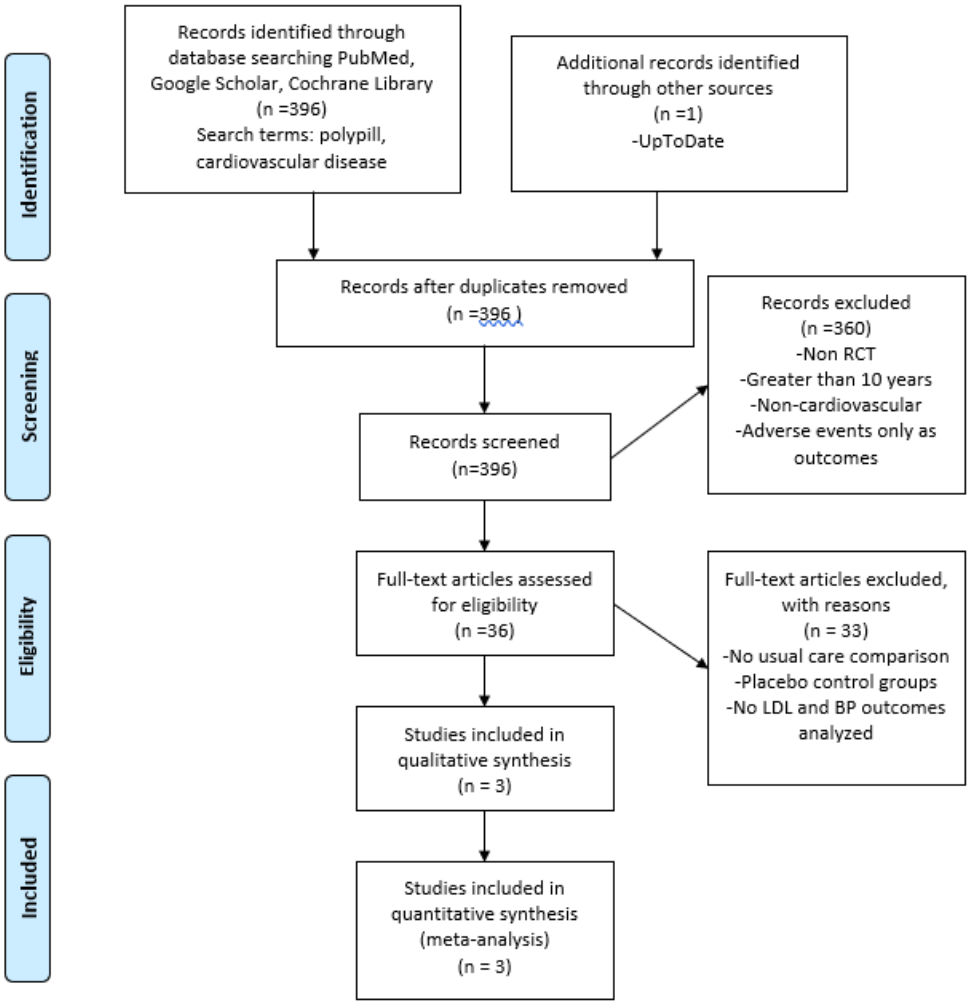

Table 1: Inclusion and Exclusion Criteria

Inclusion Criteria	**Exclusion Criteria**
Age > 18	Non-Randomized Control Trials
LDL-C and Systolic Blood Pressure measured as an outcome	Outdated research > 10 years of age
Polypill therapy that focused on cardiovascular disease treatment and risk factors	Only adverse events recorded as primary outcomes
	Polypill formulations that did not contain aspirin, two anti-hypertensive medications and a statin

Results

Study #1

Impact of switching from different treatment regimens to a fixed-dose combination polypill in patients with cardiovascular disease or similarly high risk.[9]

Objective: This study evaluated the impact of different polypill treatment regimens on cardiovascular risk factors.

Study Design

This is a post-hoc analysis of the UMPIRE trial which was a randomized, open label, blinded trail comparing a polypill-based treatment strategy against usual care in those with established cardiovascular disease or those at similar level of high risk; defined as a 5 year event risk > 15%. The study took place in India and three European countries England, Ireland, Netherlands. In total, 2004 participants were included in the study. Patients were randomized at a 1:1 ratio between the usual treatment group and polypill group. With 1002 of those participants assigned to the polypill. Further, broken down into 589 of those assigned to version one of the pill and 413 assigned to version 2 of the pill. The primary endpoint for the study looked at adherence to medication regimens and whether LDL-C and systolic blood pressure (BP) improved. The participants assigned to usual care continued to be seen by their routine doctor. Those assigned to the polypill group were prescribed one of the two polypill versions, at the discretion of the prescribing physician and as visualized in Table 2.

Table 2. Medications included in Polypill formulation

Version 1 Polypill	Aspirin 75 mg, Simvastatin 40 mg, Lisinopril 10 mg, Atenolol 50 mg
Version 2 Polypill	Aspirin 75 mg, Simvastatin 40 mg, Lisinopril 10 mg, Hydrochlorothiazide 12.5 mg

The end of study visit for all participants was scheduled to take place 12 months after the random assignment of the last participant. Telephone and clinic visits were conducted at 1 month and 6 months. Fasting lipids and BP were measured at baseline and at previously the stated visits.

The polypill medication potency was compared to those statin therapies that had LDL reductions of 32% to 40% were defined as equally potent to the polypill (Fluvastatin 80 mg, pravastatin 80 mg, simvastatin 40 mg, atorvastatin 10 mg and rosuvastatin 5 mg). The anti-hypertensive medications such as beta blockers, ACE-Inhibitors, angiotensin receptor blockers, calcium channel blockers at standard doses have all shown similar reduction in BP. The

reduction of LDL-C and systolic BP was calculated as the difference from baseline at follow -up. Data from 1, 6 month and 12 months were used in the analysis of BP and LDL-C for all participants who were required to attend these visits. Criteria for Study 1 is depicted below in Table 3.

Table 3 Study Population Criteria for Study 1

Inclusion Criteria	**Exclusion criteria**
Age > 18	Contraindications for medications
Cardiovascular disease dx or 5-year cardiac risk > 15% according to ASCVD calculator	Doctor considered changing the medications inappropriate
Had to have clear indications to take the medications	Patient was unlikely to complete study
	Medication may be altered for long period of time

Study Result*s*

Antiplatelet Therapy

Those in either polypill group saw an increase from baseline of 6% reported usage compared to 3% reported usage increase for the non-polypill group. This showed a relative risk of adherence of 1.08.

Antihypertensive medications

In those in the polypill group, there was a reduction mean BP of 5.4, 6.2, 3.3, 1.8 mmHg in those patients taking 0, 1, 2, or 3 BP lowering agents prior to the study respectively.

Statin Therapy

Those in the polypill group saw a 11% increase in adherence, self-reported at every visit, after randomization and there was a 7 % increase in adherence in the usual care group compared to baseline resulting in a RR of 1.05. There was a .37, .22, .14 and .07 mmol/L mean lowering difference from patients taking no statins, less potent, equipotent and more potent statins at baseline.

Overall cardiovascular risk

The overall estimated mean cardiovascular risk reduction was 12.6% in the polypill group than the usual care group, with a reduction of .15 LDL-C and 3.4 systolic BP points when compared to the usual care group.

Study Critique

Those who participated in the clinical trial were more motivated and may have resulted in a overestimation on the impact of the intervention compared to usual care. The individuals in the study receiving the polypill did not have to pay for the medication due to European regulations and this may have altered adherence; by as much as 5% as demonstrated by a large trial in the United State done by Choudhry NK et al.[13] The price of the polypill ranges from 0.23-23.12 dollars a day, which is within the range of the sum of the components. Thus, there is not a huge financial advantage to the polypill as relayed in this study.

Study #2

Polypill For Cardiovascular Disease Prevention in an Underserved Population.[10]

Objective: Evaluate if polypill-based therapy compared against usual care in economically vulnerable populations in the US produces cardiovascular disease benefit.

Study Design

This was an open label, randomized control trial with 303 adults who lived within 50-mile radius of the Franklin Primary Health Center in Mobile, Alabama. The average 10-year cardiovascular risk of participants in this study is 12.7%. Table 4 includes inclusion and exclusion criteria for study #2.

Table 4: Study Criteria for Study 2

Inclusion Criteria	**Exclusion Criteria**
Age: 45-75	Did not want to participate
Reported no history of coronary heart disease, stroke, cancer, liver disease, or insulin-dependent diabetes	Did not fill out questionnaire (as part of eligibility and screening)
Systolic BP between 120mmHg and 160mmHg	Did not complete clinical exam (as part of screening)
LDL-C level of less than 190 mg per deciliter	Did not meet inclusion criteria
An estimated glomerular filtration rate of at least 60 ml per minute per 1.73 m2 of body-surface area	
Normal potassium levels and hepatic aminotransferase levels of less than three times the upper limit of the normal range	
No contraindications to any polypill	

component	
Not pregnant	
Current use of no more than two antihypertensive medications	

*This upper limit was later removed following approval from the institutional review board and the data and safety monitoring board.

Of the 303 participants enrolled, 148 were allocated to polypill therapy and 155 participants were allocated to usual care. Over a 12-month period changes in systolic blood pressure, LDL-C and other cholesterol levels were measured and compared to baseline. Following randomization, all participants from both arms were scheduled for follow-up visits at 2 and 12 months. During the trial visits a clinical examination was conducted, blood pressure measured by a trial nurse utilizing appropriately sized cuff, and a fasting blood sample collected by a trained phlebotomist.

The polypill group received 90-day refillable supplies of daily trial medication. The polypill was a gelatin capsule containing four generic drug components: atorvastatin (10 mg), amlodipine (2.5mg), losartan (25mg), and hydrochlorothiazide (12.5mg). The initial polypill was shipped overnight to the participants residence and subsequent refills were filled at the Franklin Primary Health Center.

Blood-pressure data was calculated by the mean of two resting, manual, in-clinic measurements. The Martin-Hopkins equation was utilized to calculate the LDL-C level. At trial visits a trial coordinator performed pill counts to assess compliance to the polypill regimen.

Study Results

Adherence to the polypill regime was 86% based on unused pills counted at trial visits. In the polypill arm, 44% of participants had previous antihypertensives or lipid lowering medication reduced or discontinued by clinicians, with an escalation of therapy in 2% of patients. The usual care arm had no discontinuation or de-escalation of medication by clinicians, with a 10% escalation of therapy in participants.

The polypill group had a mean systolic decrease in blood pressure by 9mmHg, whereas the usual-care groups had a mean 2 mmHg decrease in blood pressure. (95% CI, P=.003) The mean LDL-C decreased in the polypill arm by 15mg per deciliter whereas the usual care arm had a mean decreased of 4 mg per deciliter. (95% CI, P<.001)

Study Critique

High compliance was a strength of the study- as 91% of the participants completed 12 months of the trial. There are few distinct aspects of this trail as 96% of the participants were black, thus these results may not be as applicable to white counterparts as patterns of cardiovascular disease risk factors may vary across different races. Second, the trial was conducted at a single federally qualified community health center and thus may be difficult to apply to differing settings.

The polypill group was not charged for the medication and thus introduced the possibility that lower costs impacted the results. Lastly, a large limit to this study was the open-label design. Although created for clinician flexibility to adjust medications, this likely altered the medication escalation and or de-escalation results.

Study #3

A pragmatic randomized trial of a polypill-based strategy to improve use of indicated preventive treatments in people at high cardiovascular disease risk.[11]

Objectives: This study aimed to determine whether fixed dose combinations of generic drugs would promote the use of cardiovascular disease risk reducing medications.

Study Design

The study was an open label randomized trial of 623 participants in general practices throughout Australia. Participants included had either an established CVD risk, an estimated 5-year ASCVD event risk >15% or has indications for combination therapy consisting of antiplatelet medication, statin and greater than or equal too anti-hypertensive medications. The study also included a 5% increment on the Framingham risk equation for those who identified as Aboriginals or Torres Strait Islander. The two versions of the polypill used and their formulations can be found in Table 5. Inclusion and exclusion criteria can be found in Table 6.

Computer based randomization to polypill strategy or usual care was completed and further stratified by primary healthcare center, type of indication, indigenous identification and level of preventative treatment at baseline. All patients were treated by their regular doctor regardless of group and no attempt was made to alter the treatment of the usual care patients.

Those in the polypill group received the medication as instructed by the provider. In either group, the provider could alter the polypill medication treatment with adding additional medications or withdraw the polypill. Out of pocket expenses for the polypill were identical to those any other drugs listed in the Pharmaceutical Benefits Scheme.

Participants had scheduled BP and cholesterol level checks at baseline, 12 months, 24 months and at the final visit. Self-reported use of all medications was reviewed at all visits. Primary endpoints included changes in systolic BP and total cholesterol from baseline. Secondary endpoints included renal events, serious adverse cardiovascular events among others.

Table 5. Medications included in study polypill formulation

Version 1 Polypill	Aspirin 75 mg, Simvastatin 40 mg, Lisinopril 10 mg, Atenolol 50 mg
Version 2 Polypill	Aspirin 75 mg, Simvastatin 40 mg, Lisinopril 10 mg, Hydrochlorothiazide 12.5 mg

Table 6. Study Criteria for Study 3

Inclusion Criteria	**Exclusion Criteria**
Age > 18	Contraindications for to any component of polypill
Established CVD (peripheral vascular, cerebrovascular or coronary ischemia)	Patient felt like it was clinically inappropriate to alter medications
5-year CVD risk greater than or equal to 15%	

Study Results

Primary measurement outcomes included medication use, systolic BP, and total cholesterol. 70.1% of participants in the polypill group reported compliance to medication regimen, 46.9% of participants in the usual care group reported compliance to their medication regime. (RR 1.49, CI 1.30- 1.72, p<.0001).

Mean baseline systolic BP for polypill arm was 143.4 mmHg and at end of study (30 months) the mean systolic BP was 139 mmHg. Mean baseline systolic BP for usual care was 142.5 mmHg, and the end of study results had a mean systolic BP of 140.3 mmHg.

Total mean cholesterol in the polypill group at baseline was 4.4mmol/l and at end of study was 4.39 mmol/l. Total mean cholesterol at baseline was 4.5mmol/l and at the end of the study was 4.31mmol/l.

Secondary endpoint of LDL-C levels showed no difference at the end of the study when comparing the usual care arm to the polypill treatment groups (p=.36).

Study Critique

Although a prominent finding was the difference in compliance in the polypill arms vs usual care, these measurements were self-reported and may not truly reflect compliance. Pill counts may have been a stronger measure. This study did not recruit as many participants as originally estimated due to resource limitations and is considered underpowered. This trial had an open label design and thus introduced the possibility that over-reporting could have differentiated in medication use.

Discussion

Cardiovascular disease is very common medical condition and can frequently result in fatal outcomes that could be prevented. When lifestyle modifications are not enough to prevent adverse complications of CVD, a multi-mediation regime becomes commonplace. Although there is benefit in tailoring a therapy to the individual within a multi-medication

regimen, it can be cumbersome. Especially for those facing disadvantages such as those who are economically challenged, living in rural areas, or identified as a minority, these factors independently or in combination can be barriers in adherence to multiple drug therapy. The purpose of this review is to determine if polypill-based therapy, a fixed dose combination of generic drugs in a single pill, compared against usual care would produce a cardiovascular disease benefit— with emphasis on application in underserved populations.

An overview of the studies is included in Table 7. Lafeber et al and Patel et al are similar to one another in that CVD inclusion criteria more closely mirrored each other such as sharing exactly similar polypill therapy and used similar interpretation measures.[9,11] More noteworthy was the interpretation measures used in Muñoz et al via manual BP taken by a nurse and pill counts to assess adherence rather than automated BP readings and self-reporting in the other two studies.[10]

All three studies were similar in that they were an open label design and shared similar age and gender demographics. All three studies differed in their length of trial, patient number and population.

Lafeber et al assessed a more diverse population, both through differing location and medical settings.[9] Whereas Muñoz et al assessed a largely all black population in a single rural setting. Patel et al assessed many locations (33 centers) in similar settings, all general practice settings in Australia.[10,11]

Table 7: Overview of Studies

	Lafeber et al	Muñoz et al	Patel et al
Patients, N	2004	303	623
Population	Adults living in England, Ireland, Netherlands and India recruited via clinics, hospitals, general practice and databases	Adults living within 50-mile radius of the Franklin Primary Health Center in Mobile, Alabama. 96% of participants are African American.	Adults in Australian general practice including a 5% increment for Aboriginal or Torres Strait Islander Identified
Gender/Age range	18% Women and 82% Men, $\geq$ 18 years	60% woman 40% men, age 45-75	Women and Men, $\geq$ 18 years
Average age of participants	61.85 years	56 years	63.55 years
CVD risk	Established CVD or those with high 5 year event risk > 15%	Average 10-year cardiovascular risk of participants is 12.7%	Established CVD or an estimated 5-year CVD risk >15%
Blinded	open label	open label	open label

Intervention (polypill contents)	Version 1: Aspirin 75 mg, Simvastatin 40 mg, Lisinopril 10 mg, Atenolol 50 mg. Version 2: Aspirin 75 mg, Simvastatin 40 mg, Lisinopril 10 mg, Hydrochlorothiazide 12.5 mg.	Atorvastatin 10 mg, Amlodipine 2.5mg, Losartan 25mg, and hydrochlorothiazide 12.5mg.	Version 1: Aspirin 75 mg, Simvastatin 40 mg, Lisinopril 10 mg, Atenolol 50 mg. Version 2: Aspirin 75 mg, Simvastatin 40 mg, Lisinopril 10 mg, Hydrochlorothiazide 12.5 mg.
Length of trial	24 months	12 months	30 months
Primary Interest	Adherence to polypill, systolic BP, and LDL-C compared to usual care	Adherence to polypill and mean systolic B/P, and LDL-C compared to usual care	Adherence to polypill, systolic B/P, and total cholesterol compared to usual care
Adherence to medication interpretation	Self-reported at visit	Trial Coordinator performed pill counts at visit	Self-reported at visit
Blood pressure interpretation	Electronic oscillometric BP monitor: Omron 705CP II	Manual B/P by Trial Nurse	Electronic oscillometric BP monitor: Omron 705CP II

Table 8: Overview of Results

	Lafeber et al	Muñoz et al	Patel et al
Overall adherence change in polypill arm	11% (using statin adherence values)	N/A	25.2%
Overall adherence change in usual care arm	7% (using statin adherence values)	N/A	-2.2%
Comparison	4%	N/A	27.4%
Significant?	Yes CI (1.04 to 1.07)	N/A	Yes CI (1.30-1.72)

Systolic BP change-polypill	-7.50 mmHg	-9mmHg	-4.4 mmHg
Systolic BP change-normal treatment	-4.12 mmHg	-2mmHg	-2.5 mmHg
Comparison	-3.38 mmHg	-7 mmHg	-1.9 mmHg
Significant?	Yes CI (-4.8--1.9)	Yes CI (-11--2) p=.002	No
Calculated LDL-C change-polypill	-.2 mmol/L	-.40 mmol/l	-0.07 mmol/l
Calculated LDL-C change normal treatment	-.01 mmol/L	-.10mmol/l	-.16 mmol/l
Comparison	-.19 mmol/dl	-.30mmol/l	.09 mmol/l
Significant?	Yes CI (-.21 to -.09)	Yes CI (-.30--.45, p<.001)	No

In those studies that included results analyzing adherence, the polypill treatment groups had a significant improvement. Two of three studies-Lafeber et al and Muñoz et al showed significant differences in BP levels. [9,10,11] Patel et al showed a BP decrease that was not considered clinically significant. The largest decrease in BP of 7 mmHg was seen in the Muñoz et al study. Both Lafeber et al and Muñoz et al saw decreases in LDL-C levels in the polypill arm as compared to usual care.[9,10] Conversely, Patel et al actually reported an increase in LDL-C compared to the usual care arm.[11] Which is a concerning finding as this study also reported adherence to combination therapy. Results can also be found in Table 8: Overview of Results.

APPLICATION IN CLINICAL SETTINGS

All three studies reported higher adherence in the polypill group as compared to the usual care group as the conclusion of the study. In regards to BP levels, two out of three studies reported a statistically significant decrease in the polypill arm as compared to usual care. With the largest decrease of 7mmHg in BP seen in the Muñoz et al study and thus could be considered clinically significant. Both Lafeber et al and Muñoz et al saw decreases in LDL-C levels in the polypill group as compared to usual care arm.[9,10] However, Patel et al reported an increase in LDL-C compared to usual care.[11]

The populations utilized in the studies are an important factor. Study two, Muñoz et al was conducted in a population in rural Alabama— highlighting the potential to be extended to

similar populations within the U.S. However, price is a component that none of these studies evaluated but is an important factor in adherence.[10]

Lastly, because the polypill contained preset medications, typically moderate statin intensity and two anti-hypertensive medications, it did not show improvement in SBP or LDL-C levels in individuals that were previously taking a more intense medication regime than what was in the polypill. Thus, a drawback to polypill therapy is its lack in ability to individualize care and would likely be less effective in more severe disease states which require high intensity statins or 2 or more anti-hypertensive medications.

Conclusion

In adults 18-65 with diagnosed CVD or higher than borderline ASCVD risk who are taking a multi-medication regimen, does administration of a polypill which includes a statin, 2 anti-hypertensive medications and aspirin opposed to usual medication regime improve blood pressure and LDL-C levels.

Polypill therapy improved LDL-C levels and BP in two out of three studies. As polypill therapy becomes available in the US, it could be considered as an alternative in patients taking a multiple medication regime particularly those who are on one or two anti-hypertensive medications, using a low potency statin and are also struggling with compliance or access to medication. There are many questions to be resolved; what the potential price of this pharmacological therapy would be, what concentrations of the components are best for differing subgroups, but at this time it appears further studies are warranted to confirm the most notable positive health findings as seen in Muñoz et al and Lafeber et al studies and whether similar results would occur in different populations.[10,9]

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