

Cardiovascular Polypill

Current and Evolving Landscape for
Primary and Secondary Prevention

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This report was commissioned by the Wellcome Trust and conducted by Globe Life Sciences, and presented at the Third Cardiovascular Combination Pharmacotherapy Global Summit, convened by the World Heart Federation on the 8th June 2016, Mexico City, Mexico.



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Executive summary

Wellcome commissioned Global Life Sciences to assess and report on the current landscape for the polypill in the primary and secondary prevention of cardiovascular diseases (CVD), with the key aim of providing an update on the accumulated evidence in this field. The assessment was conducted based on secondary sources - reviewing the current literature and primary sources – through qualitative interviews with eight key opinion leaders. The scope of the report included commercial, competitor, regulatory, ethical, and clinical dimensions, and an assessment of current hurdles to the adoption of the polypill. The report findings were presented and discussed by the attendees of the Third Cardiovascular Combination Pharmacotherapy Global Summit, Mexico City, 8 June 2016, hosted by the World Heart Federation.

The report showed that since the polypill concept was introduced in 2001, opinion still remains divided on whether the polypill is a viable public health tool for the prevention of cardiovascular incidence, and only a handful of polypill products have been approved.

Based on a survey of the current literature and qualitative interviews, the key barriers identified for the polypill in the primary and secondary prevention settings overlap and ranged from: current lack of clinical data on cardiovascular outcomes, safety concerns from healthcare provider (HCP) if treatment dosages were not individually tailored to patients, poorly defined regulatory approval pathway, and economic costs to the payor. Some of these key hurdles are higher in the primary prevention setting, such as: a lack of clinical outcomes data, safety concerns in medicating a large proportion of the population and cost-effectiveness for the payor.

Of note is the approval of Trinomia (Ferrer) in 2014 across a broad range of geographies in 15 EU and eight Latin American countries, albeit within a defined secondary prevention substitution role in patients already controlled on its components – demonstrate that these hurdles can be overcome, and the roll-out of Trinomia provides the opportunity to reconsider the current HCP and payor perceptions of the polypill. Indeed, further emerging developments since the completion of this report indicates that the momentum for change is increasing.*

In addition, new data from studies such as HOPE-3 and in future, further outcome-based studies, will provide the much-needed evidence on the benefits of the polypill in both primary and secondary prevention settings. Nonetheless, engrained barriers in the minds of HCPs which could take time to erode.

The analyses indicate that a key challenge is the need for continued education around the polypill, as new data and information emerge. Central to this is the struggle in moving away from the individualised / tailored approach to treatment, to a broader preventative approach. While some HCPs and stakeholders are beginning to recognise the need to ‘compromise’ based upon realism of patients not achieving goals on multiple different therapies, others may not be comfortable in making this change – particularly in the absence of compelling data and supportive guidelines. In addition, clear definitions – particularly of the target population for primary prevention – could play a key role for increasing polypill usage.

The increasing recognition of secondary prevention as a viable option for certain patients who could benefit from improved adherence, will serve to build confidence and understanding of the pros and cons of the polypill – and drive its use in primary prevention. There could then be a natural evolution into specific populations for primary prevention, as the evidence base develops.

*: On 23rd May 2016, the 2016 European Guidelines on cardiovascular disease prevention in clinical practice by the European Society of Cardiology, advised that the polypill could be considered as an treatment option, as part of integral part of a comprehensive CVD prevention strategy in certain patients. Eur Heart J (2016) 37 (29): 2315-2381 DOI: <http://dx.doi.org/10.1093/eurheartj/ehw106>.

On 19th June 2016, Trinomia was approved for reimbursement for Mexico's public markets.

Objectives and Methodology

Wellcome commissioned Global Life Sciences to provide an assessment report on the current landscape for the polypill for the primary and secondary prevention of cardiovascular diseases (CVD), with the key aim of providing an update on the available evidence in this field. The report focused on the barriers facing the polypill concept, covering commercial, competitor, regulatory, ethical, and clinical dimensions.

The methodology combined a review of published sources with the outputs of qualitative interviews with eight selected key opinion leaders (KOLs). The profiles of interviewees were as follows:

- Geographic spread; EU (3), US (4), India (1)
- Known advocates and critics of the polypill approach; including triallists / authors involved in key studies as well as KOLs with more neutral / negative views
- Cardiologists involved in developing guidelines, have a breadth of publications, and designing and running clinical trials
- KOLs with regulatory experience with the polypill in US / Europe
- KOLs with payor expertise on the evaluation of polypills

Background

Polypill Definition

There is no single definition of the cardiovascular (CV) polypill, and the concept has evolved since it was first introduced as an idea. A fixed-dose combination (FDC) pill was first proposed in a meeting hosted by the WHO and the Wellcome Trust in 2001, described as consisting of a combination of four drugs: a beta-blocker, an angiotensin converting enzyme (ACE) inhibitor, aspirin and a statin¹. In 2003 Wald and Law proposed the combination of folic acid, aspirin, three low-dose anti-hypertensives, and a low-dose statin (i.e. six components) into a once-a-day polypill². Inherently, these proposed polypills were targeting multiple risk factors. Moving forward, the definition of the polypill became more flexible but the general consensus in the literature was that a CV polypill would contain an anti-hypertensive, a lipid-lowering medication and aspirin. It should be noted however, that several reviews centred on the clinical data of polypills have a looser definition – some of which exclude aspirin.

In the interviews, it was confirmed that there is no ‘standard’ definition of a polypill – although there was agreement that it should be targeting multiple risk factors in one treatment. There was also some debate as to what really differentiates a polypill from a simple fixed-dose (which was generally viewed as just containing two complementary components). It was also recognised that the composition of a polypill will also inherently vary depending on the target population and objectives. However, there was general consensus that the polypill should target lipid lowering (statin) and blood pressure (ACE inhibitor, beta blocker), and potentially contain aspirin – although aspirin was clearly identified as a ‘controversial’ component, particularly if looking at a broad primary prevention role. Indeed, the inclusion of aspirin was often identified as a key area for debate when defining a polypill.

In summary, the definition of a polypill has evolved from its first description encompassing numerous therapies – some of which were not well validated – to a core group of drugs with clearly defined benefits. The previous flux around the definition is potentially one of the factors that has divided opinions on the polypill amongst specialists.

Rationale for Use – Primary / Secondary Prevention

Whilst the original concept of a polypill focused particularly on its potential in primary prevention, there is increasing recognition of its potential in a secondary prevention role. In primary prevention, the polypill would be given to subjects over a certain age who are not necessarily indicated for all of its individual components. This strategy could either target whole populations (the ‘vaccination’ approach) or those in risk-associated populations but without cardiovascular disease (CVD), in order to reduce the incidence of CVD. In secondary prevention the pill would act more as a replacement therapy for patients indicated for the individual components, in order to increase adherence and reduce costs.

Based on our interviews, there was strong debate over the relative value in these two settings. Some KOLs commented that the real value of the polypill is in the primary prevention setting – in line with the positioning proposed by Wald and Law. Whilst these KOLs recognised that there could be some adherence (and potentially cost) benefits in the secondary prevention setting, the issues raised were around gaining consensus on the polypill composition (given greater tailoring of treatment in this population), and the ability to adhere to guideline recommendations. However, an increasing number of KOLs are beginning to view secondary prevention as an attractive target setting – and potentially with lower barriers to entry. Indeed, secondary prevention was viewed as the most likely to gain initial approval for polypills, particularly in developed markets.

The key potential benefits identified by the KOLs for the polypills were:

- **Adherence:** Due to improved simplicity for patients taking multiple medicines
- **Cost:** Potential to be more cost-effective than the individual components, and also potentially to deliver overall cost savings from reduced CV events
- **Accessibility:** Providing a simple option in LMIC countries, which has the potential to enable broad target populations access to preventative therapy, whether as secondary or primary prevention
- **Public Health Benefit:** All of the above could reduce CV risk at a lower cost in a broader population than the current approach

These benefits were seen to apply in both primary and secondary prevention.

Current Polypill Products

Overview of Approved Products

Despite the launch of the polypill concept consisting of a combination of marketed cardiovascular products almost 15 years ago, progress in the area has been glacial, with only one product approved across a reasonably wide geography (Ferrer's Trinomia). The products listed in the table below adhere to the definition of polypill that includes the aspirin component, a lipid-lowering medication and an anti-hypertensive.

Overview of Currently Approved Polypills Which Contain Aspirin, a Statin and an Anti-hypertensive

Product	Company	Composition	Geography	Indication
Trinomia / Sincronium / Iltria	Ferrer *	Aspirin (100mg), ramipril (2.5mg, 5mg or 10mg) and either simvastatin (40mg) or atorvastatin (20mg)	<ul style="list-style-type: none"> Latin America: Guatemala, Honduras, Dominican Republic, El Salvador, Nicaragua, Argentina, Chile, Paraguay, Ecuador, Mexico Europe: Belgium, Bulgaria, Germany, Finland, France, Greece, Ireland, Italy, Austria, Poland, Portugal, Romania, Spain, Sweden, Czech Rep. 	Secondary prevention
Polycap	Cadila Pharma	Aspirin (100mg), atenolol (50mg), thiazide (12.5mg), ramipril (5mg) and simvastatin (20mg)	<ul style="list-style-type: none"> India and Zambia 	Primary prevention
Zycad-4	Zydus CND	Aspirin (75mg), atorvastatin (10mg) ramipril (5mg) and metoprolol (50mg) (metoprolol is supplied as separate tab)	<ul style="list-style-type: none"> India 	Secondary prevention
Ramitorva	Zydus Cardiva	Aspirin (75mg), atorvastatin (10mg) and ramipril (5mg)	<ul style="list-style-type: none"> India 	Secondary prevention
Polytorva	USV	Aspirin (75mg), atorvastatin (5mg) and ramipril (10mg)	<ul style="list-style-type: none"> India 	Secondary prevention
Red Heart Pill	Dr Reddy's	Aspirin (75mg), lisinopril (10mg), simvastatin (40mg), and atenolol (50mg) or hydrochlorothiazide (12.5mg)	<ul style="list-style-type: none"> No market approval 	Secondary prevention

Databases, Company Sources; accessed Mar 2016

* Note that Sincronium is marketed by Hexal (a subsidiary of Sandoz) in Germany; † Dr Reddy's product has not yet sought market approval
Note: Other CV fixed dose combinations – such as Novartis; Exforge – are launched

Trinomia – Status and Regulatory Process

Trinomia – which comprises aspirin, ACE inhibitor and statin – is approved in 15 European countries (to date) ⁷, as well as in 10 Latin American countries (including Argentina and Mexico). The product has been commercialised in 6 of the European countries (Spain, Portugal, Germany, Bulgaria, Romania and Greece) and 8 of the Latin American countries. The product first gained approval around 2014/15, and is clearly in its roll-out phase.

In Europe the product was approved in a decentralised fashion, co-ordinated by the Spanish Medicine Agency ⁸. Sources suggest that the key factor required for approval was demonstrating bioequivalence to the three individual components. The company has been seeking to gain inclusion on the WHO essential medicines list.

Trinomia is approved in Europe as a secondary preventative treatment and is recommended as a substitution therapy in patients adequately controlled with its three active components ⁹.

In Latin American countries, the marketed product consists of aspirin, ramipril and simvastatin, whilst in European geographies, a version containing atorvastatin rather than simvastatin is marketed. The doses of ramipril include 2.5mg, 5mg and 10mg, to allow for titration.

Trinomia – Messaging

Hexal – who market the product in Germany – have initiated a marketing campaign called ‘hand on heart’, which focuses on the benefit to patient compliance through a reduced number of tablets to be taken (and emphasises that it is targeted for a specific segment of patients) ¹⁰.

Trinomia – Price

The price varies across regions and countries, but is competitively priced. Trinomia has a laboratory sale price of ~€14 – €17 a month in Latin America (which is reportedly 30 – 50% cheaper than the LSP of the three APIs acquired separately) ¹¹. In Germany, where the product is marketed under the name Sincronium by Hexal (a subsidiary of Sandoz), the list price is €37.95 for a month’s supply (28 tablets) ⁴. In Spain, the drug is priced at the equivalent level to the three generic components (c. €10). Sources suggest that the product will become available to other lower income countries at a low price ¹².

Trinomia – Impact

In Latin America the product is predominantly restricted to the private market, and has been regarded as a more limited opportunity.* In Europe, interviews conducted suggest that Trinomia is generating interest and debate, particularly regarding the appropriate target populations for the drug. A recent roundtable of Spanish physicians debated the potential role for Trinomia ⁵. In secondary prevention, the group concluded the following patients would be suitable:

- Patients with a history of or at risk of poor adherence, or who are not well controlled with equivalent doses and have problems of adherence
- Patients well controlled on the individual drugs, or patients with comorbidities and receiving several drugs (to improve simplicity and therefore adherence)

The panel found that the polypill would also be suitable in patients with subclinical CVD, and specifically either hypertensive patients at high CV risk, or patients with diabetes, hypertension, and microalbuminuria / proteinuria (provided they are not at risk of bleeding). In the primary prevention role however, the group concluded that whilst there was some evidence of efficacy, the evidence was not robust enough for to reach a consensus recommendation. The panel also recognised that the dose of statin may not be high enough to control LDL levels in some patients, and in this case Trinomia would not be suitable.

Trinomia – Ongoing Activities

The company has plans to enter further markets in 2016, including the rest of Europe and some countries in the Middle East. In 2017 it hopes to receive marketing authorisation in the US and has reportedly met with the FDA to discuss requirements for approval ¹⁶.

In September 2015, Ferrer announced plans to build a cardiovascular manufacturing site in Mexico, through which it hoped to produce supply for the Latin American markets, including the public sector in Mexico. The company stated the production site could also potentially supply the US market ¹⁷.

Moving forward, a consortium of partners (including Ferrer), with funding from the European Commission, are in the process of initiating the Secondary prEvention of CardiovasCular disease in the Elderly (SECURE) trial – which will evaluate whether Trinomia can reduce the rate of CV events (as well as explore adherence rates and cost effectiveness). The trial will evaluate Trinomia with usual care as a comparator and, importantly, the primary outcome for this trial will be major adverse cardiac events (MACE), rather than just CV risk factors, meaning that the trial will be powered for real cardiac outcomes in this population.

Trinomia – Summary

Trinomia appears to be spearheading the introduction of the polypill usage in the secondary prevention setting, in both developed and developing markets. The product has successfully navigated the regulatory pathway in Europe, as well as Latin America, and has the commercial support of organisations including Hexal and Ferrer. The ongoing outcomes-based SECURE trial could be a pivotal milestone in further supporting the uptake of Trinomia in this setting.

* Since the conclusion of the study, on 19th June 2016, Trinomia was approved for reimbursement for Mexico’s public markets. A key challenge identified for Trinomia was gaining consensus from physicians on the value of improved adherence, and changing established practices.

Current Polypill Situation in India

Whilst a number of cardiovascular polypills have been approved in India, based on our interviews it was suggested that the uptake of these products has been modest, primarily as many specialist physicians still favour tailoring the individual components of therapy. The Indian KOL interviewed suggested that the key opportunity was for polypills to gain inclusion in the universal healthcare coverage system, which would provide the potential for much wider application.

Future Polypill Products

Overview of Products in Development

Based on secondary sources, a number of polypills are being actively developed by commercial organisations. One development appears to be CardioPharma's CardiaPill, which claims to be seeking FDA approval, although there is limited up-to-date information on its progress.

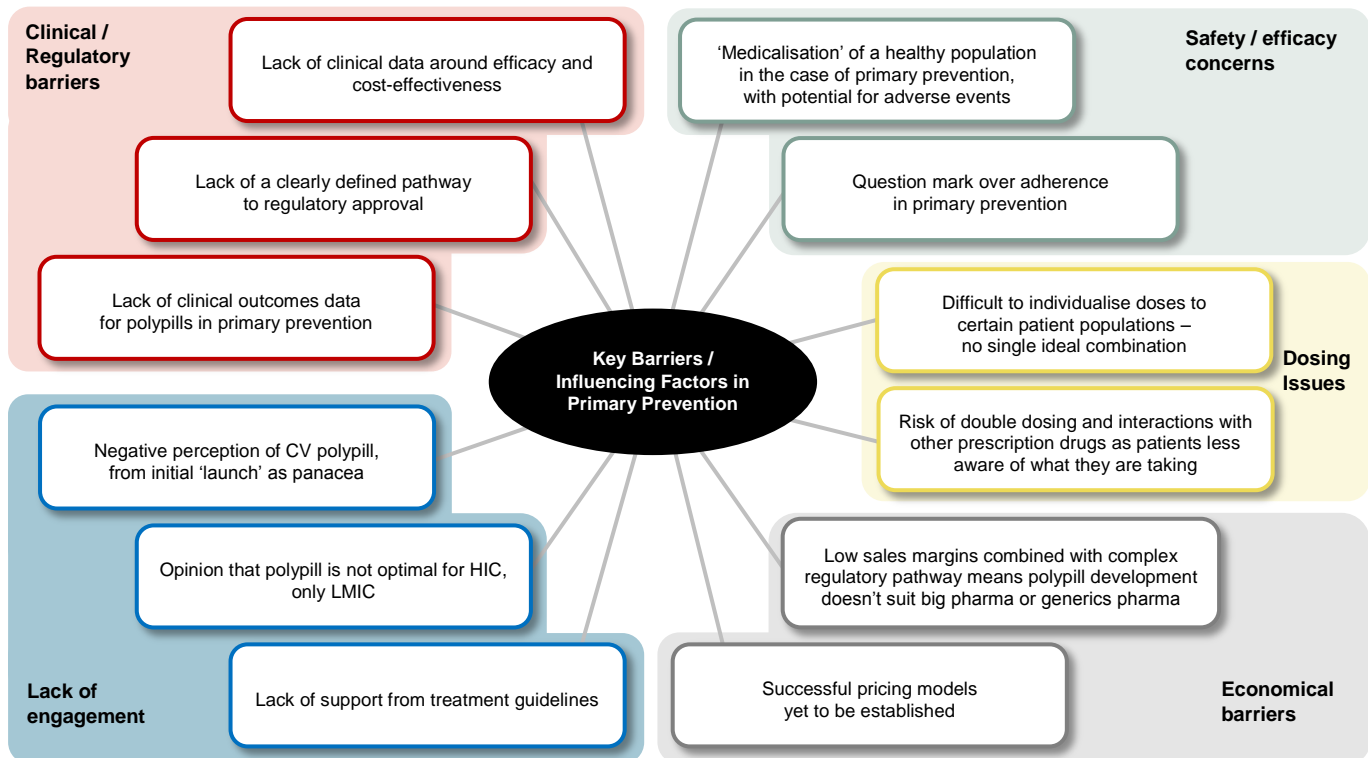
Examples of Polypill Products in Development Which Contain Aspirin, a Statin and an Anti-hypertensive

Product	Company	Composition	Status	Comments
CardiaPill (CP-101)	CardioPharma	Aspirin + simvastatin + lisinopril	<ul style="list-style-type: none"> PK study completed PD study planned Q1 2016 	<ul style="list-style-type: none"> Pharmacokinetic study reportedly completed in Nov 2013, showing bioequivalence to its individual components Company announced in Dec 2015 that it planned to initiate a pivotal PD study in Q1 2016 Appears to be positioned for use in the secondary prevention setting initially
Poly Pill 4-2	Tehran University / Alborz Darou	Aspirin + enalapril / valsartan + atorvastatin + hydrochlorothiazide	<ul style="list-style-type: none"> Large ongoing Phase III study in Iran (PolyIran) 	<ul style="list-style-type: none"> The PolyIran study was initiated in Feb 2011 and is being conducted by the University of Tehran, evaluating a single polypill (manufactured by Alborz Darou) in patients over 50 years of age The study appears to be assessing the product as both a primary and secondary prevention method It is not clear whether the Poly Pill 4-2 product is currently being marketed in Iran by Alborz Darou

Sources: R&D Databases, Company Sources, ClinicalTrials.gov; accessed Mar 2016

Key Barriers

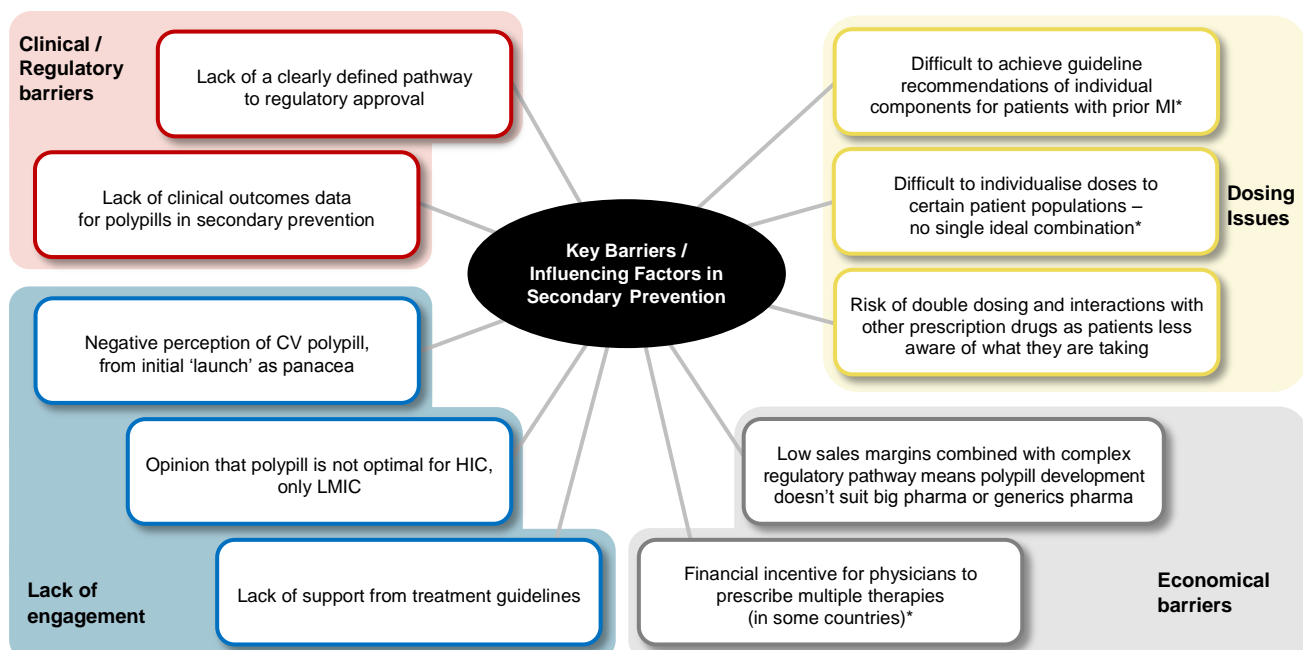
Overview – Primary Prevention



Based on an analyses of the information obtained, a number of potential barriers against polypill usage in the primary prevention role is outlined in the following diagram.

Overview – Secondary Prevention

These barriers are slightly different in secondary prevention, and a number of these are evolving by recent developments in this field.



* Barriers specific to secondary prevention

Key Barriers – Clinical Data

Various publications have modelled the potential impact of polypills on reducing cardiovascular risk, which has clearly stimulated the interest of several investigators and institutions to conduct clinical studies in this field.

Despite this activity, a key barrier which is often cited is the lack of supporting clinical data. This section reviews the data in both primary and secondary prevention patients, and KOLs perceptions of the strength of this supporting evidence. Completed trials have focussed on CV risk surrogates such as low density lipoproteins (LDL) and blood pressure (BP) and generated data to support improved adherence on polypills. Trials looking at hard outcomes in primary and secondary prevention patients are underway. The HOPE-3 study has just reported – while not a “polypill” it has reinforced the need to further evaluate the polypill concept.

Primary Prevention Trials

There have been several relatively short-term trials evaluating the effects of polypills on risk factor surrogates in primary prevention in patients who are either healthy or who carry a small CVD risk. The studies captured in the table below evaluated products containing at least one anti-hypertensive and one statin, as well as aspirin.

Selected Trials in Primary Prevention

Trial	Polypill Composition	Inclusion Criteria	Trial Design	Key Results
The Indian Polycap Study ‘TIPS’ – 2009 (India)	Polycap • hydrochlorothiazide (12.5mg) • atenolol (50mg) • ramipril (5mg) • simvastatin (20mg) • aspirin (100mg)	• ≥ 1 cardiovascular risk factor • 45 – 80 years old	• Multi-arm study using individual components as comparators • N=2,053 • 12 week study	• Systolic blood pressure reduced by 7.4mmHg (95% CI 6.1-8.1) • Reduced LDL cholesterol by 0.7mmol/L (95% CI 0.62-0.78)
PolyIran Pilot Study – 2010 (Iran)	Poly Pill 4-2 • hydrochlorothiazide (12.5mg) • enalapril (2.5mg) • atorvastatin (20mg) • aspirin (81mg)	• No prior CVD • 50 – 79 years old	• Placebo-controlled • N=468 • 12 months duration of follow up	• Systolic blood pressure reduced by 2.4mmHg • Reduced LDL cholesterol by 0.5mmol/L
PILL Collaborative – 2011 (Global)	Red Heart Pill 2b • aspirin (75mg) • simvastatin (20mg) • lisinopril (10mg) • hydrochlorothiazide (12.5mg)	• No indication for any component of the polypill • 5-year CVD risk of over 7.5%	• Placebo-controlled • N=378 • 12 week study	• Systolic blood pressure reduced by 9.9mmHg (95% CI 7.7-12.1) • Reduced LDL cholesterol by 0.8mmol/L (95% CI 0.6-0.9)
Sri Lanka Polypill Study – 2011 (Sri Lanka)	Red Heart Pill 2b • aspirin (75mg) • simvastatin (20mg) • lisinopril (10mg) • hydrochlorothiazide (12.5mg)	• No established CVD, but 10-year total CV risk score $\geq 20\%$ • Over 40 years old if male, over 50 if female	• Randomised study vs. standard practice • N=216 • 3 month duration of follow up	• No significant differences in systolic blood pressure, cholesterol or 10-year CVD risk vs. comparator group
Wald – 2012 (UK)	• hydrochlorothiazide (12.5mg) • amlodipine (2.5mg) • losartan (25mg) • simvastatin (40mg)	• No prior CVD • Aged over 50 years old	• Placebo-controlled randomised crossover trial [patients already controlled on individual components] • N=86 • 12 week study	• Systolic blood pressure reduced by 17.9mmHg (95% CI 15.7-20.1) • Reduced LDL cholesterol by 1.4mmol/L (95% CI 1.2-1.6)

Secondary Prevention Trials

In secondary prevention, in addition to trials around Polycap and Trinomia, there have been three key studies on Dr Reddy's Red Heart Pill – a product for which the company has not sought regulatory approval.

Selected Trials in Secondary Prevention

Trial	Polypill Composition	Inclusion Criteria	Trial Design	Key Results
The Second Indian Polycap Study 'TIPS-2' – 2012 (India)	Polycap (double dose) plus K+ supplementation • hydrochlorothiazide (25mg) • atenolol (100mg) • ramipril (10mg) • simvastatin (40mg) • aspirin (200mg)	• Prior CVD or diabetes mellitus • Aged 40 years or older	• Randomised trial vs. single dose Polycap • N=518 • 8 week study	• Systolic blood pressure reduced by 2.8 mmHg further than in half dose arm • Reduced LDL cholesterol by 0.2 mmol/L further than in half dose arm
UMPIRE – 2013 (EU / India)	Red Heart Pill • aspirin (75mg) • lisinopril (10mg) • simvastatin (40mg) • atenolol (50mg) / hydrochlorothiazide (12.5mg)	• Established CVD or CVD risk of >15% over 5 years • Indicated for the polypill components	• Randomised, open-label study vs. usual care • N=2,004 • Minimum 12 month follow up	• Improved adherence by 33% (95% CI 26%-41%) • Systolic blood pressure reduced by 2.6 mmHg (95% CI 1.1-4.0) • Significantly improved cholesterol
IMPACT – 2014 (New Zealand)	Red Heart Pill • aspirin (75mg) • lisinopril (10mg) • simvastatin (40mg) • atenolol (50mg) / hydrochlorothiazide (12.5mg)	• Established CVD or CVD risk of >15% over 5 years • Indicated for the polypill components	• Randomised, open-label study vs. usual care • N=513 • Minimum 12 month follow up	• Improved adherence by 75% (95% CI 52%-103%) • No significant differences in risk factors at 12 months
Kanyani-GAP – 2014 (Australia)	Red Heart Pill • aspirin (75mg) • lisinopril (10mg) • simvastatin (40mg) • atenolol (50mg) / hydrochlorothiazide (12.5mg)	• Established CVD or CVD risk of >15% over 5 years • Indicated for the polypill components	• Randomised, open-label study vs. usual care • N=623 • Minimum 12 month follow up	• Improved adherence by 49% (95% CI 30%-72%) • No significant differences in risk factors at 12 months
FOCUS – 2014 (EU / Argentina, Brazil, Paraguay)	Trinomia • aspirin (100mg) • simvastatin (40mg) • ramipril (2.5, 5, 10mg)	• Acute MI within the past 2 years • Aged 40 years or older	• Randomised trial vs. individual components • N=4,000 (Phase I) • N=1,340 (Phase II) • 9 month follow up	• Improved adherence by 24% • No significant differences in risk factors

Reviews of Data:

Cochrane Review – Effect on Blood Pressure

A 2014 Cochrane review compiled data from 9 trials dating from 2009 to 2013 evaluating fixed dose combination (FDC) products containing at least one anti-hypertensive and one lipid-lowering medication (in both primary and secondary prevention)¹. The study reported weighted mean reductions in systolic and diastolic blood pressure of 7.02mmHg and 3.65mmHg respectively. The study concluded however, that there was substantial heterogeneity in the results, and as such they should be interpreted with caution.

Cochrane Review – Effect on Lipids

Looking at the effect on cholesterol, the study reported mean reductions in LDL levels of 0.81mmol/L. However, once again the authors highlighted significant heterogeneity between studies. The authors proposed that the heterogeneity likely arose from differing doses of active ingredients, differing comparison groups and differing patient characteristics.

Cochrane Review – Effect on CVD, Mortality and Adverse Events

The review found no differences in mortality and CV events between fixed-dose combination and comparator groups, but highlighted that only two out of the nine studies reported these outcomes and each had a risk of bias, and as such the results may not be representative. Across the seven studies which measured adverse events, it was found that no serious adverse events were reported. Adverse Events (AE) were common in both FDC and comparator arms, with those randomised to FDC approx. 20% more likely to report an event.

Cochrane Review – Effect on Adherence

The review found that trials demonstrated a 26% increased risk of discontinuing an FDC compared with either usual care, placebo, or a single drug (e.g. aspirin, statin or thiazide in the case of TIPS 2009). However, it is important to note that only one of the six trials that reported adherence was evaluating a polypill against a usual care arm, and this trial (UMPIRE), actually showed an improvement in adherence. Therefore the discontinuation increase quoted is not based on an assessment of a polypill versus a true comparator.

Cochrane Review – Conclusion and Limitations

It was concluded that the effects of polypills on mortality or CVD events are uncertain, reduction in blood pressure and lipid parameters were lower than those previously reported, and that polypills may be associated with modest increases in adverse events vs. placebo. The authors stated however, that the review was limited by presence of bias, imprecision of results for the effects of all-cause and CVD mortality and the heterogeneity of effects on CV risk factors.

Huffman Review – Adherence

A review by Mark Huffman, published in 2015¹⁸, consolidated data on adherence from the key studies on Dr Reddy's Red Heart Pill and Ferrer's Trinomia (for these studies the comparator arm was either usual care or the individual component). Huffman concluded that polypills have shown a consistent improvement in adherence across diverse settings, and that whilst not a 'panacea', polypills offer a promising strategy to improve this measure.

Webster et al. Review – Adherence

A review which combined individual patient data across the three trials of Dr Reddy's product (the SPACE collaboration) was published in 2015¹⁹. Importantly, this review found that an improvement in adherence was significantly more common in patients who had a low level of baseline adherence, which improved from 17% to 74%, compared with 86% to 90% in patients adherent at baseline.

Chrysant Review – Risk Factors

Another recent review analysed data from 15 polypill trials and grouped CV risk factor data into primary and secondary prevention²⁰. The authors concluded that the clinical data to date clearly demonstrates the ability of polypills to reduce CV risk factors, which thus indicates their usefulness in the primary and secondary prevention of CVD and stroke.

Impact of HOPE-3 Trial

A key new trial in the field that has recently released results is the HOPE-3 study – which enrolled 12,705 at medium risk of heart attack (primary prevention), and used hard clinical outcomes. The trial had four arms: rosuvastatin / candesartan / Hydrochlorothiazide (HTZ) combination, rosuvastatin alone, candesartan / HTZ combination and placebo.

Overview of the HOPE-3 Trial

Title	• Heart Outcomes Prevention Evaluation-3 (HOPE-3)
Sponsor	• Population Health Research Institute
Location	• 21 countries in North America, South America, Europe, Asia, and Australia
Design	• Randomised, double-blind trial with a 2x2 factorial design
Patients	• 12,705
Primary Endpoints	• First co-primary outcome: composite of death from CV causes, non-fatal myocardial infarction, or non-fatal stroke • Second co-primary outcome: additionally included revascularization, heart failure, and resuscitated cardiac arrest
Key Secondary Endpoints	• Second co-primary outcome plus angina with evidence of ischemia, all-cause death, incidence of diabetes, adverse events
Inclusion Criteria	• Men ≥55 years old and women ≥65 years old who had at least one of the following cardiovascular risk factors: elevated waist-to-hip ratio, history of a low level of HDLs, current or recent smoker, dysglycemia, family history of premature coronary disease and mild renal dysfunction [Note: Two-thirds were not hypertensive and people were not specifically chosen to have elevated LDL-C]
Treatment Arms	• Arm 1: rosuvastatin 10mg/day and candesartan 16mg/day plus hydrochlorothiazide 12.5mg/day • Arm 2: rosuvastatin 10mg/day • Arm 3: candesartan 16mg/day plus hydrochlorothiazide 12.5mg/day • Arm 4: placebo
Timeline	• Start date: May 2007 • Primary completion date: Oct 2015 • Completion date: Mar 2016

Source: Yusuf et al., New Eng. J. Med. 2016; DOI: 10.1056/NEJMoa1600176

The results of the trial were announced in April 2016²¹, with the investigators focusing on the benefit of statins in reducing CV events vs. placebo in this population.* The results showed that 3.7% of those on 10mg of the statin had heart attacks, strokes or heart-related deaths, compared to 4.8% of those on placebo, a statistically significant 24% reduction in risk. The BP lowering arm showed no significant reduction in CVD. In a prespecified subgroup analysis, the effects of BP lowering lead to a significant reduction in CVD in those with the highest third of BP, ie the hypertensives (both statistically vs placebo as well as a test of interaction), in those with the highest third of BP, the combination of BP lowering and statins decreased the risk of CVD by 40% but in the remaining two thirds, the effects were entirely due to the benefits of statins.

In the interviews, the data was viewed as a significant advance, which is going to reignite the debate on the potential for polypills in primary prevention (in intermediate-risk patients) – although clearly does also raise some questions. Some articles in the medical literature have suggested that this is starting to challenge strong-held beliefs amongst some physicians regarding the dangers of a broad preventative approach versus individualised treatment. Indeed, one such article was titled ‘HOPE-3: Is It Time to Hate the Polypill Concept Less?’

* Results now published in the NEJM.

Ongoing Key Trials

Further outcome-based trials will add to the evidence base in the future, as shown in the table below:

Key Ongoing Trials of Polypills

Trial	Polypill Composition	Inclusion Criteria	Trial Design	Timeline
PolyIran Study (Iran) n=7,000 [Primary / Secondary]	Poly Pill 4-2 • thiazide (12.5mg) • enalapril (5mg) or valsartan (40mg) • atorvastatin (20mg) • aspirin (81mg)	<ul style="list-style-type: none"> • ≥50 years old • With or without prior CVD • Prior enrolment in Golestan cohort study 	<ul style="list-style-type: none"> • Randomised trial vs. minimal care • Primary endpoint: time to first major CV event (up to 5 years) 	<ul style="list-style-type: none"> • Start: Feb 2011 • Completion: Apr 2018
The International Polycap Study 3 (TIPS-3) (Worldwide) n=5,000 HI RISK [Primary]	Polycap • Thiazide (25mg) • atenolol (100mg) • ramipril (10mg) • simvastatin (40mg)	<ul style="list-style-type: none"> • No heart disease or prior stroke • Interheart risk score ≥10 • Women aged ≥60 years old, men aged ≥55 years old 	<ul style="list-style-type: none"> • 2x2x2 factorial study where patients will receive Polycap +/- 75mg aspirin, +/- monthly vitamin D supplementation • Subjects will be monitored for 5 years • Primary endpoint: CVD and CV events, risk of fractures in vitamin D arms 	<ul style="list-style-type: none"> • Start: Jun 2012 • Primary completion: Jun 2019 • Completion: Mar 2020
Heart Outcomes Prevention and Evaluation 4 (HOPE-4) Canada, Colombia, Malaysia n=30 community clusters of approximately 50 participants each [Primary]	• Combination blood pressure lowering medication (2-3 components) plus a statin (provided separately) purchased locally within each participating country	<ul style="list-style-type: none"> • ≥50 years old • SBP≥160 mmHg; or SBP 140-159 mmHg and diagnosis of hypertension or taking anti-HTs or on two separate visits; or SBP≥130 mmHg and diagnosis of diabetes or taking diabetes medication 	<ul style="list-style-type: none"> • Open-label, parallel, cluster randomized controlled pragmatic trial evaluating an intensive CV risk detection and control programme supported by non-physician health workers or to care as usual for 12 months • Primary endpoint: Framingham Risk Score 	<ul style="list-style-type: none"> • Start: 2015 • Completion: Aug 2018
Secondary Prevention of Cardiovascular Disease in the Elderly (SECURE) (Europe) n=3,206 [Secondary]	Trinomia • aspirin (100mg) • atorvastatin (40 or 20mg) • ramipril (2.5, 5, 10mg)	<ul style="list-style-type: none"> • ≥65 years old • Type I MI within the previous 8 weeks, with at least one additional risk factor 	<ul style="list-style-type: none"> • Randomised trial vs. standard care • Primary endpoint: MACE at 6, 12, 18 and 24 months 	<ul style="list-style-type: none"> • Start: Jan 2016 • Primary completion: Oct 2019 • Completion: Jan 2020

Source: ClinicalTrials.gov; Trial publications, accessed Apr 2016

Clinical Data Barriers: Summary

Overall, despite the range of trials that have now been conducted with polypills, reviews of the data conclude that there is a lack of clear supporting evidence, particularly around CV outcomes. There is evidence to support the improvement in adherence that can be achieved with polypills.

The perception of KOLs was that the data is currently strongest around secondary prevention, but uncertainty around the primary prevention role still exists. However, the field is clearly in a dynamic state. The release of the HOPE-3 data provides new data to support the use in primary prevention (especially those with hypertension), which is generating strong debate. The data supporting the use of polypills could also become stronger over the coming years with the completion of further trials focusing on hard clinical endpoints with a variety of agents (TIPS-3, SECURE etc), as well as from the 'real-life' use of products such as Trinomia.

Key Barriers – Regulatory Position

Approval of a polypill has yet to be granted by the FDA, although the FDA's Cardiovascular and Renal Drugs Advisory Committee met publicly in September 2014 to discuss the use of FDC of aspirin, statins and anti-hypertensives for the secondary prevention of cardiovascular disease. It is reported that the FDA offered cautious support to polypills in this setting. However, the panel did not discuss use in primary prevention as it was seen as outside of the FDA remit due to it being 'so far off approvability'²². As a potentially positive move, it appears that recently the FDA set up a Combination Products Policy council to develop a unified position on the requirements for approving combination therapies²³. KOLs commented that the US regulatory environment is also now more accepting of the polypill, and the expectation is that products could gain approval in a secondary prevention role in the near future.

In general, there is a lack of a clearly defined pathway to regulatory approval, particularly outside of a 'straight substitution' indication based on bioequivalence data, where polypills are used in patients already stabilised on individual component medicines.

Another issue which has been identified is that current regulatory guidelines do not incorporate adherence into their metrics. Real-world factors such as cost, complexity and patient preference are not taken into account²⁴. However, as evidenced by Trinomia – the regulatory environment is clearly supporting the entry of polypill products in the secondary prevention setting (albeit with a specific role and target population) – in Europe and other markets. India is a further country which has shown the potential for more polypills to gain approval.

Key Barriers: Economic and Pricing Issues

The low potential sales margins and complex and expensive regulatory pathway are seen by some as a key reason for so few approved polypills in the market. Big pharma has the budget and regulatory expertise required, but lacks the incentive, whilst generics companies (and government research agencies) have the incentive but lack the budget²⁵. Commentators believe the transfer of licensure for Dr Reddy's Red Heart Pill in 2012 was a clear sign that pharma companies have not developed successful pricing models¹⁸. However, the progress of Ferrer with Trinomia is an indicator that this barrier can potentially be overcome. In the interviews it was suggested that other commercial organisations are interested in this opportunity.

Key Barriers: Concerns of HCPs

It is widely reported that there are a number of 'concerns' that HCPs (particularly specialists) have with the use of polypills. These concerns are particularly evident in primary prevention, where issues have been raised around low potential adherence, the potential for 'medicalising an entire population' (particularly if considering low risk elements of the population)²⁶, dosing risks due to 'hiding' components²⁷, and also the composition of the polypill (particularly around the use of aspirin). Indeed, US KOLs in particular highlighted concerns with the use of a polypill containing aspirin in primary prevention patients, given the unproven risk benefit.

In the secondary prevention setting, whilst there are still concerns, they appear to be much lower than in primary prevention (e.g. the use of aspirin is more accepted). The key issue however hinges on the continued belief of the need to tailor treatment to each individual in order to optimise outcomes. At present, the relative benefits of improving adherence do not appear to outweigh this perceived loss of control in managing each patient individually. The fact that polypills are not included on guidelines adds weight to the argument for tailoring treatment (and will also be an influencing factor on regulators such as the FDA).

A perceptual issue surrounding polypills has emerged following the high profile 'launch' of the concept – which has polarised views. A challenge moving forward will be to manage some of this engrained negativity.

Interestingly, in the primary research patients were viewed as a potential key stakeholder group which could influence the HCPs. The perception was that the reaction of patients to the polypill has been very positive.

Key Barriers: Payors

A further barrier identified has been the potential resistance from payors towards the potential cost implications of the polypill, particularly in primary prevention. However, interviewees highlighted that there is an increasing body of data demonstrating the impact of adherence in reducing the overall costs to the healthcare system, which could support the polypill usage amongst payors. One US KOL also commented on the shift in the US where some payors are incentivised financially from reducing total healthcare costs, which could be a strong boost for using polypills in a more primary prevention role. The overall cost effectiveness of the polypill – particularly if priced appropriately – could be a positive factor supporting their uptake.

* On 23rd May 2016, the 2016 European Guidelines on cardiovascular disease prevention in clinical practice by the European Society of Cardiology, advised that the polypill could be considered as an treatment option, as part of integral part of a comprehensive CVD prevention strategy in certain patients. Eur Heart J (2016) 37 (29): 2315-2381 DOI: <http://dx.doi.org/10.1093/eurheartj/ehw106>.

Key Barriers: Summary of Situation

Overall across the board, a number of these barriers are being lowered, particularly for secondary prevention – but there are still a number of challenges still remain.

The regulatory barriers are clearly lowering, as seen by the European approval of Trinomia, and also the perception that the FDA is potentially open to the concept (in a secondary prevention role). However, this was still viewed as a complicated hurdle, particularly if looking to move into primary prevention.

KOLs also commented that there are a number of concerns which are holding back the usage of the polypill – such as lack of outcomes data, ongoing preference for tailored treatment etc. As a result, the view is that there is a continued negative perception of polypills by HCPs, as well as other key stakeholders. Some of these negative perceptions appear to have been a result of the initial fanfare surrounding the polypill concept, which acted to polarise opinions. However, the critical underlying struggle is moving away from the individualised / tailored approach to treatment, to a broader preventative approach (particularly amongst specialists).

For the polypill to be indicated for a primary prevention role, it was suggested that there needs to be stronger data generated in a well-defined (risk stratified) population. The perception is that there are lower barriers for the polypill in secondary prevention.

Further data from the outcomes studies would be key to overcoming the barriers to the polypill. Patients were also identified as a key stakeholder who could drive the use of polypills in future.

Overall, the consensus was that the use of polypills will start to take hold in Europe and US – initially in the secondary prevention setting, and potentially within certain populations. In India, it was suggested that there are very similar barriers to the uptake of polypills, with concerns around the preference to tailor treatment, and some inherent scepticism. The key factor which could increase support for the wide-spread use of the polypill in India would be listing in the public procurement list for universal treatment.

The key drivers that were identified as supporting this move were:

- Outcome-based clinical trial results
- Positive influence of acceptance of polypills in US and Europe
- Positive move by the WHO to add to the essential drug list.

Across all interviews, the view was that polypills were most likely to gain initial usage in a secondary prevention role, and could then migrate into specific populations for primary prevention.

Below is outlined a summary of the current and evolving situation for the barriers facing the CV polypill:

Regulatory Barriers	<ul style="list-style-type: none"> • European (and broader geographic) approval of polypills demonstrate that regulatory barriers for secondary prevention are lowering and can be overcome. • Statements suggest FDA may be accepting of a polypill for secondary prevention with only PK and PD data. • Hurdles still remain for primary prevention
Clinical Barriers	<ul style="list-style-type: none"> • Breadth of data now demonstrating the benefits of adherence of the polypill in secondary prevention • Key gap is lack of hard CV outcomes data • Data from HOPE-3 is catalysing debate on the future role of polypills in primary prevention • Over time increasing outcomes-based data will become available for primary and secondary prevention from studies such as TIP-3 and SECURE
Economic Barriers	<ul style="list-style-type: none"> • The apparent successful commercialisation of Trinomia demonstrates that economic barriers are potentially becoming surmountable
HCP Barriers	<ul style="list-style-type: none"> • Evidence that many healthcare physicians are recognising the potential benefits of the polypill on improving adherence, particularly in certain patient types for secondary prevention (but for many there are still concerns in moving from tailored treatment) • Lack of universal support in guidelines remains an issue, although is being challenged as products such as Trinomia become discussed • Some engrained negativity appears to remain, in part as a reflex to the previous 'fanfare' around the potential benefits of a polypill • Continued question marks around the optimum primary prevention role, and concerns with medicalising a population (as well as the use of aspirin when considering a low risk population)

Summary and Conclusions

Whilst progress with polypills has been slow since the concept was first raised in 2001, new developments are emerging that has the potential to start challenging and change the perceptual barriers against the polypill concept.

The introduction of Trinomia across a broad range of geographies in a defined secondary prevention substitution role in patients already controlled on its components, has demonstrated that regulatory and economic hurdles can be overcome. The roll-out of Trinomia provides the opportunity to challenge the perceptions of HCPs and payors and improve their understanding of the polypill as a potential public health tool for cardiovascular disease management.

New data from studies such as HOPE-3 and other outcome-based studies, will provide additional evidence on pros and cons of the polypill in both primary and secondary prevention settings. A key challenge is the need for continued education around polypills, as the critical barriers appear to be based partly on an inherent mistrust of the polypill. Central to this is the struggle in moving away from the individualised / tailored approach to treatment, to a broader preventative approach. Many HCPs and stakeholders are beginning to recognise the need to 'compromise' based upon realism of patients not achieving goals on multiple different therapies, but are not comfortable in making this change – particularly in the absence of compelling data and supportive guidelines. Clear definitions – particularly of the target population for primary prevention – could play a key role for increasing polypill usage.

There is increasing recognition that the polypill is a treatment option in secondary prevention for certain groups of patients that could benefit from improved adherence, and could evolve into usage by specific populations for primary prevention, as the evidence base develops. This would also require a holistic approach, ensuring all aspects of the health system are addressed to provide the basis for adoption.

Appendix

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Declaration of Interest

Wellcome has provided funding for clinical trial studies of two cardiovascular polypill innovations: i) the Red Heart Polypill, resulting in a publication - *An International Randomised Placebo-Controlled Trial of a Four-Component Combination Pill ("Polypill") in People with Raised Cardiovascular Risk*, PLoS ONE 6(5): e19857. doi:10.1371/journal.pone.0019857; ii) the PolyCap - *The International Study 3 (TIPS-3), a Randomised Double-blind Placebo-controlled Trial for the Evaluation of PolyCap, Low Dose Aspirin and Vitamin D Supplementation in Primary Prevention*, which is still ongoing at the time of writing.

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