Cardiovascular polypill rationale, evidence, and progress

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Disclosures

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Center for Medicare and Medicaid Innovation, significant
Cochrane Collaboration, significant

Travel
American Heart Association
World Heart Federation

Consultancy, speakers’ bureau, advisory board
None
Conclusions

Rather than being a panacea for all, polypills represent the most effective and scalable intervention for improving adherence to multi-drug therapy for initiation, step-up, or substitution indications.

Polypill trials have been generally designed to demonstrate bioequivalence rather than differences in clinical outcomes; high quality “usual care” seen in trials limits power.

Polypills meet criteria as essential medicines for secondary ASCVD prevention and the growth of polypill suggests an opening of the marketplace for these combinations.
Outline

Polypill background

Guide for use of polypills in future research and clinical activities

Contemporary evidence supporting polypill use

Polypills as essential medicines
Q: Can you name fixed-dose combinations that are used for other disease states?

For general wellness?
Polypill, c. 2001

Secondary Prevention of Noncommunicable Diseases
in Low- and Middle-Income Countries
through Community-Based & Health Service Interventions

Report of WHO-Wellcome Trust Meeting of Experts
1–3 August 2001, Hinxton, Cambridge, UK
Noncommunicable Diseases and Mental Health
World Health Organization

Richard Peto
Polypill research requirements, c. 2001

1) Stability testing (CMC)
2) Bioavailability testing (Pk)
3) Assessment of short-term effects on BP, LDL cholesterol, and platelet aggregation (Pd)
4) Assessment of safety and short-term side effects
5) Study of interactions and effects on combination of drugs on physiological mechanisms
6) Studies on adherence to treatment

Multiple polypills (at least 2 doses per drug) envisioned

WHO/Wellcome Trust were charged with partnering with industry for testing, including cost-effectiveness via RCTs or community demonstration projects (5-year timeline!)
Polypill, c. 2003
Estimated effects of polypills

Table 1: Effects of the Polypill on the risks of ischaemic heart disease (IHD) and stroke after two years of treatment at age 55-64

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Agent</th>
<th>Reduction in risk factor</th>
<th>% reduction in risk (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>IHD event</td>
</tr>
<tr>
<td>LDL cholesterol</td>
<td>Statin†</td>
<td>1.8 mmol/l (70 mg/dl) reduction in LDL cholesterol</td>
<td>61 (51 to 71)</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>Three classes of drug at half standard dose</td>
<td>11 mm Hg diastolic</td>
<td>46 (39 to 53)</td>
</tr>
<tr>
<td>Serum homocysteine</td>
<td>Folic acid (0.8 mg/day)</td>
<td>3 μmol/l</td>
<td>16 (11 to 20)</td>
</tr>
<tr>
<td>Platelet function</td>
<td>Aspirin (75 mg/day)</td>
<td>Not quantified</td>
<td>32 (23 to 40)</td>
</tr>
<tr>
<td>Combined effect</td>
<td>All</td>
<td></td>
<td>88 (84 to 91)</td>
</tr>
</tbody>
</table>

LDL—low density lipoprotein.

*95% confidence intervals include imprecision of the estimates of both the agent reducing the risk factor and the risk factor reduction decreasing risk.

†Atorvastatin 10 mg/day, or simvastatin or lovastatin 40 mg/day taken in the evening or 80 mg/day taken in the morning.
Expected harms of polypills

Table 3 Extracranial adverse effects of low dose aspirin (50-125 mg) from the meta-analysis of 15 randomised trials

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>No of events*</th>
<th>Aspirin group</th>
<th>Placebo group</th>
<th>Excess risk (treated minus placebo) (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>As prevalence per 100 people (%)</td>
</tr>
<tr>
<td>Extracranial haemorrhage:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatal bleed</td>
<td>13</td>
<td>15</td>
<td></td>
<td>-0.01 (-0.07 to 0.05)</td>
</tr>
<tr>
<td>Non-fatal major bleed (required transfusion or surgery)</td>
<td>51</td>
<td>28</td>
<td></td>
<td>0.4 (0.1 to 0.6)</td>
</tr>
<tr>
<td>Haematemesis or melaena</td>
<td>199</td>
<td>98</td>
<td></td>
<td>0.6 (0.4 to 0.8)</td>
</tr>
<tr>
<td>Any bleed</td>
<td>1049</td>
<td>710</td>
<td></td>
<td>2.3 (1.7 to 2.8)</td>
</tr>
<tr>
<td>Upper abdominal discomfort, including heartburn</td>
<td>689</td>
<td>621</td>
<td></td>
<td>1.6 (0.0 to 3.2)</td>
</tr>
<tr>
<td>Any symptom (any bleed and abdominal discomfort)</td>
<td>1738</td>
<td>1331</td>
<td></td>
<td>3.9 (2.2 to 5.6)</td>
</tr>
<tr>
<td>Adverse effects sufficient to stop taking the tablets</td>
<td>482</td>
<td>438</td>
<td></td>
<td>1.6 (0.7 to 2.5)</td>
</tr>
</tbody>
</table>

*Numbers of participants in the aspirin and placebo groups of each trial were almost identical (see web table B).
Polypill tensions after Wald & Law

Possibilities
80% reduction in CVD events (predicted)
Increased adherence
Less reliance on physicians
Lower cost

Potential problems
Primary vs. secondary prevention
Emphasis on pills >> lifestyle >> policies
Dose titration, side effects
Lower margins
Outline

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Contemporary evidence supporting polypill use

Polypills as essential medicines
Q: What is the problem that polypills are trying to solve?
Low secondary prevention rates: PURE

```
A Coronary heart disease

CHD

B Stroke


PURE: 153,996 participants in 17 countries (2003-9)
```
Low secondary prevention rates: NHANES

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin</td>
<td>4%</td>
<td>6.6%</td>
<td>13.9%</td>
<td>20.9%</td>
<td>15.7%</td>
<td>21.4%</td>
<td>28.0%</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Statin</td>
<td>36.3%</td>
<td>56.5%</td>
<td>46.1%</td>
<td>56.4%</td>
<td>48.6%</td>
<td>54.6%</td>
<td>72.9%</td>
<td>0.04</td>
</tr>
<tr>
<td>Beta-blocker</td>
<td>27.2%</td>
<td>47.0%</td>
<td>41.7%</td>
<td>63.6%</td>
<td>51.2%</td>
<td>57.0%</td>
<td>56.6%</td>
<td>0.12</td>
</tr>
<tr>
<td>ACE-I or ARB</td>
<td>32.9%</td>
<td>39.9%</td>
<td>41.9%</td>
<td>41.1%</td>
<td>47.5%</td>
<td>43.8%</td>
<td>46.3%</td>
<td>0.03</td>
</tr>
<tr>
<td>Aspirin, statin, and BP lowering drug</td>
<td>2.7%</td>
<td>4.9%</td>
<td>12.9%</td>
<td>18.2%</td>
<td>13.8%</td>
<td>19.6%</td>
<td>23.5%</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Indication</th>
<th>Current labelled indications for components</th>
<th>Key question</th>
<th>Relevant published trials</th>
</tr>
</thead>
<tbody>
<tr>
<td>Secondary prevention of atherosclerosis</td>
<td>Step-up</td>
<td>Does polypill-based care lead to better adherence than usual care?</td>
<td>CRUCIAL, IMPACT, Kanyini GAP, TIPS</td>
</tr>
<tr>
<td>Secondary prevention of atherosclerosis</td>
<td>Substitution</td>
<td>Do the products have bioequivalence?</td>
<td>UMPIRE, IMPACT, Kanyini GAP, FOCUS</td>
</tr>
<tr>
<td>High-risk primary prevention of atherosclerosis based on formal risk assessment</td>
<td>Initiation, step-up, or substitution</td>
<td>Are the benefits of polypills greater than the risks compared with individual components or usual care?</td>
<td>CUSP, Malekzadeh, OLSTA, PILL Pilot, Soliman, TIPS, TOGETHER</td>
</tr>
<tr>
<td>Primary prevention of atherosclerosis based on single risk factor measurement (eg, age) for mass treatment</td>
<td>Initiation, step-up, or substitution</td>
<td>Are the benefits of polypills greater than the risks compared with individual components or usual care?</td>
<td>Wald crossover</td>
</tr>
</tbody>
</table>

Initiation indication: individuals for whom all included drugs are recommended at included doses. Step-up indication: individuals for whom all included drugs are recommended at included doses but are not being taken (eg, because of non-adherence clinical inertia). Substitution indication: individuals who have already been stabilised on the same drugs at the same doses.

Table 1: Proposed guide for polypill uses

Outline

Polypill background

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Polypills as essential medicines
Q: How would you design a polypill trial for cardiovascular disease prevention and control?
Participants = Primary or secondary prevention population?

Intervention = Aspirin, statin, ACE-I, BB, CCB, diuretic, or combination?

Comparator = Individual drugs or usual care? Payment?

Outcomes = Adherence, risk factors, events, or all?

Time Course = 1, 3, or 5 years?

Setting = New York, Chicago, Delhi, or Tripoli—whose standard?
Participants = Primary and secondary prevention

Intervention = Polypill with at least 1 lipid lowering drug and 1 blood pressure lowering drug

Comparator = Any

Outcomes = Mortality, ASCVD events, adverse events, risk factors, adherence

Time Course/Setting = Any
2014 review: 9 trials, n=7,047 participants
2017 update: 4 new trials, n=2,012 additional participants
<table>
<thead>
<tr>
<th>Study</th>
<th>Polypill content</th>
<th>Comparator</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRUCIAL 2011</td>
<td>Atorvastatin, amlodipine</td>
<td>Usual care</td>
</tr>
<tr>
<td>CUSP 2009</td>
<td>Atorvastatin, amlodipine</td>
<td>Placebo</td>
</tr>
<tr>
<td>FOCUS 2014</td>
<td>ASA, simvastatin, ramipril</td>
<td>Individual components</td>
</tr>
<tr>
<td>IMPACT 2014</td>
<td>ASA, simvastatin, atenolol, lisinopril or</td>
<td>Usual care</td>
</tr>
<tr>
<td></td>
<td>ASA, simvastatin, lisinopril, HCTZ</td>
<td></td>
</tr>
<tr>
<td>Kanyini GAP 2014</td>
<td>ASA, simvastatin, atenolol, lisinopril or</td>
<td>Usual care</td>
</tr>
<tr>
<td></td>
<td>ASA, simvastatin, lisinopril, HCTZ</td>
<td></td>
</tr>
<tr>
<td>Malekzadeh 2010</td>
<td>ASA, atorvastatin, enalapril, HCTZ</td>
<td>Placebo</td>
</tr>
<tr>
<td>OLSTA 2016</td>
<td>Rosuvastatin, olmesartan</td>
<td>2 active drug groups or placebo</td>
</tr>
<tr>
<td>PILL 2011</td>
<td>ASA, simvastatin, lisinopril, HCTZ</td>
<td>Placebo</td>
</tr>
<tr>
<td>Soliman 2009</td>
<td>ASA, simvastatin, lisinopril, HCTZ</td>
<td>Usual care</td>
</tr>
<tr>
<td>TIPS 2009</td>
<td>ASA, simvastatin, atenolol, ramipril, HCTZ</td>
<td>8 other drug/combination groups</td>
</tr>
<tr>
<td>TOGETHER 2010</td>
<td>Atorvastatin, amlodipine</td>
<td>Amlodipine</td>
</tr>
<tr>
<td>UMPIRE 2013</td>
<td>ASA, simvastatin, atenolol, lisinopril or</td>
<td>Usual care</td>
</tr>
<tr>
<td></td>
<td>ASA, simvastatin, lisinopril, HCTZ</td>
<td></td>
</tr>
<tr>
<td>Wald 2012</td>
<td>Simvastatin, amlodipine, HCTZ, losartan</td>
<td>Placebo</td>
</tr>
</tbody>
</table>
Risk of bias across 13 RCTs

Figure 3. Risk of bias graph: review authors’ judgements about each risk of bias item presented as percentages across all included studies

Random sequence generation (selection bias)
Allocation concealment (selection bias)
Blinding of participants and personnel (performance bias)
Blinding of outcome assessment (detection bias)
Incomplete outcome data (attrition bias)
Selective reporting (reporting bias)
Other bias

Low risk of bias  Unclear risk of bias  High risk of bias

## Polypill: summary of findings

<table>
<thead>
<tr>
<th></th>
<th>Follow-up</th>
<th>Risk ratio or mean difference (95% CI)</th>
<th>Participants (studies)</th>
<th>Quality of evidence (GRADE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All cause mortality</td>
<td>9 to 23 months</td>
<td>1.10 (0.64, 1.89)</td>
<td>5300 (5 studies)</td>
<td>Low</td>
</tr>
<tr>
<td>ASCVD events</td>
<td>2 to 23 months</td>
<td>1.26 (0.95, 1.66)</td>
<td>4517 (6 studies)</td>
<td>Low</td>
</tr>
<tr>
<td>Adherence</td>
<td>9 to 23 months</td>
<td>1.44 (1.26, 1.65)</td>
<td>3835 (4 studies)</td>
<td>Moderate</td>
</tr>
<tr>
<td>SBP</td>
<td>1.5 to 12 months</td>
<td>-6.3 mmHg lower (-9.0, -3.6)</td>
<td>7638 (13 studies)</td>
<td>Moderate</td>
</tr>
<tr>
<td>LDL cholesterol</td>
<td>1.5 to 23 months</td>
<td>-0.7 mmol/L lower (-1.0, -0.4)</td>
<td>7153 (12 studies)</td>
<td>Moderate</td>
</tr>
</tbody>
</table>

## Polypill: summary of findings

<table>
<thead>
<tr>
<th></th>
<th>Usual care</th>
<th>Polypill</th>
<th>Risk ratio or mean difference (95% CI)</th>
<th>Participants (studies)</th>
<th>Quality of evidence (GRADE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All cause mortality</td>
<td>10 per 1000 (6, 19)</td>
<td>11 per 1000 (6, 19)</td>
<td>1.10 (0.64, 1.89)</td>
<td>5300 (5 studies)</td>
<td>Low</td>
</tr>
<tr>
<td>ASCVD events</td>
<td>37 per 1000 (35, 61)</td>
<td>46 per 1000 (35, 61)</td>
<td>1.26 (0.95, 1.66)</td>
<td>4517 (6 studies)</td>
<td>Low</td>
</tr>
<tr>
<td>Adherence</td>
<td>534 per 1000 (673, 882)</td>
<td>769 per 1000 (673, 882)</td>
<td>1.44 (1.26, 1.65)</td>
<td>3835 (4 studies)</td>
<td>Moderate</td>
</tr>
<tr>
<td>SBP Range: -17.9 to 0.9 mmHg</td>
<td>--</td>
<td>-6.3 mmHg lower (-9.0, -3.6)</td>
<td>7638 (13 studies)</td>
<td>Moderate</td>
<td></td>
</tr>
<tr>
<td>LDL cholesterol Range: -1.4 to 0.1 mmol/L</td>
<td>--</td>
<td>-0.7 mmol/L lower (-1.0, -0.4)</td>
<td>7153 (12 studies)</td>
<td>Moderate</td>
<td></td>
</tr>
</tbody>
</table>

# Polypill: summary of findings

<table>
<thead>
<tr>
<th></th>
<th>Usual care</th>
<th>Polypill</th>
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<th>Quality of evidence (GRADE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All cause mortality</td>
<td>10 per 1000</td>
<td>11 per 1000 (6, 19)</td>
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<td>Downgraded for imprecision and indirectness of evidence</td>
</tr>
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</tr>
<tr>
<td>SBP</td>
<td>Range: -17.9 to 0.9 mmHg</td>
<td>--</td>
<td>-6.3 mmHg lower (-9.0, -3.6)</td>
<td>Downgraded for heterogeneity</td>
</tr>
<tr>
<td>LDL cholesterol</td>
<td>0.1 mmol/L</td>
<td>--</td>
<td>-0.7 mmol/L lower (-1.0, -0.4)</td>
<td>Downgraded for heterogeneity</td>
</tr>
</tbody>
</table>

### Other outcomes

<table>
<thead>
<tr>
<th>Category</th>
<th>Effect Size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse events</td>
<td>RR=1.16 (1.09, 1.25)</td>
</tr>
<tr>
<td>Discontinuation</td>
<td>RR=1.24 (1.01, 1.51)</td>
</tr>
<tr>
<td>Quality of life</td>
<td>MD=0.22 (-1.02, 1.46)</td>
</tr>
<tr>
<td>Direct pharmacy costs</td>
<td>AUS$ -995 (-1366, -624)</td>
</tr>
</tbody>
</table>

### Subgroups

- **1° v 2° prevention**: No difference in events, risk factors
- **Number of drugs (2 v 3+)**: No difference in events, risk factors
- **Usual care v active comparator**: No difference in events, risk factors or adherence
Q: What instrument evaluates the quality of a systematic review?
AMSTAR – a measurement tool to assess the methodological quality of systematic reviews.

1. Was an 'a priori' design provided?
The research question and inclusion criteria should be established before the conduct of the review.

   Note: Need to refer to a protocol, ethics approval, or pre-determined/a priori published research objectives to score a "yes."

2. Was there duplicate study selection and data extraction?
There should be at least two independent data extractors and a consensus procedure for disagreements should be in place.

   Note: 2 people do study selection, 2 people do data extraction, consensus process or one person checks the other’s work.

3. Was a comprehensive literature search performed?
At least two electronic sources should be searched. The report must include years and databases used (e.g., Central, EMBASE, and MEDLINE). Key words and/or MESH terms must be stated and where feasible the search strategy should be provided. All searches should be supplemented by consulting current contents, reviews, textbooks, specialized registers, or experts in the particular field of study, and by reviewing the references in the studies found.

   Note: If at least 2 sources + one supplementary strategy used, select “yes” (Cochrane register/Central counts as 2 sources; a grey literature search counts as supplementary).
4. Was the status of publication (i.e. grey literature) used as an inclusion criterion?
The authors should state that they searched for reports regardless of their publication type. The authors should state whether or not they excluded any reports (from the systematic review), based on their publication status, language etc.

Note: If review indicates that there was a search for “grey literature” or “unpublished literature,” indicate “yes.” SIGLE database, dissertations, conference proceedings, and trial registries are all considered grey for this purpose. If searching a source that contains both grey and non-grey, must specify that they were searching for grey/unpublished lit.

5. Was a list of studies (included and excluded) provided?
A list of included and excluded studies should be provided.

Note: Acceptable if the excluded studies are referenced. If there is an electronic link to the list but the link is dead, select “no.”

6. Were the characteristics of the included studies provided?
In an aggregated form such as a table, data from the original studies should be provided on the participants, interventions and outcomes. The ranges of characteristics in all the studies analyzed e.g., age, race, sex, relevant socioeconomic data, disease status, duration, severity, or other diseases should be reported.

Note: Acceptable if not in table format as long as they are described as above.
7. Was the scientific quality of the included studies assessed and documented?  
'\textit{A priori}' methods of assessment should be provided (e.g., for effectiveness studies if the author(s) chose to include only randomized, double-blind, placebo controlled studies, or allocation concealment as inclusion criteria); for other types of studies alternative items will be relevant.

\textit{Note: Can include use of a quality scoring tool or checklist, e.g., Jadad scale, risk of bias, sensitivity analysis, etc., or a description of quality items, with some kind of result for EACH study ("low" or "high" is fine, as long as it is clear which studies scored "low" and which scored "high"; a summary score/range for all studies is not acceptable).}

8. Was the scientific quality of the included studies used appropriately in formulating conclusions?  
The results of the methodological rigor and scientific quality should be considered in the analysis and the conclusions of the review, and explicitly stated in formulating recommendations.

\textit{Note: Might say something such as "the results should be interpreted with caution due to poor quality of included studies." Cannot score "yes" for this question if scored "no" for question 7.}

9. Were the methods used to combine the findings of studies appropriate?  
For the pooled results, a test should be done to ensure the studies were combinable, to assess their homogeneity (i.e., $\chi^2$ test for homogeneity, $I^2$). If heterogeneity exists a random effects model should be used and/or the clinical appropriateness of combining should be taken into consideration (i.e., is it sensible to combine?).

\textit{Note: Indicate "yes" if they mention or describe heterogeneity, i.e., if they explain that they cannot pool because of heterogeneity/variability between interventions.}

10. Was the likelihood of publication bias assessed?  
An assessment of publication bias should include a combination of graphical aids (e.g., funnel plot, other available tests) and/or statistical tests (e.g., Egger regression test, Hedges-Olken).

\textit{Note: If no test values or funnel plot included, score "no". Score "yes" if mentions that publication bias could not be assessed because there were fewer than 10 included studies.}

11. Was the conflict of interest included?  
Potential sources of support should be clearly acknowledged in both the systematic review and the included studies.

\textit{Yes}  
\textit{No}
Polypill: larger effects among low adherers

## Strategies to improve adherence in 2° CVD prevention

<table>
<thead>
<tr>
<th>Non-personnel based strategies</th>
<th>OR/RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polypills</td>
<td>1.44 (1.26, 1.65)</td>
</tr>
<tr>
<td>Financial incentives</td>
<td>1.31 (1.20, 1.44)</td>
</tr>
<tr>
<td>Text messaging</td>
<td>0.94 (0.87, 1.01)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Personnel based strategies (largest effect study only)</th>
<th>OR/RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Collaborative care*</td>
<td>2.95 (1.46, 5.98)</td>
</tr>
<tr>
<td>Patient education</td>
<td>2.86 (0.95, 8.58)</td>
</tr>
<tr>
<td>Counseling*</td>
<td>2.95 (1.46, 5.98)</td>
</tr>
<tr>
<td>Intensified patient care*</td>
<td>2.95 (1.46, 5.98)</td>
</tr>
<tr>
<td>Medication aids*</td>
<td>2.95 (1.46, 5.98)</td>
</tr>
</tbody>
</table>


Outline

Polypill background

Guide for use of polypills in future research and clinical activities

Contemporary evidence supporting polypill use

Polypills as essential medicines
WHO Model List of Essential Medicines

Definition
Essential medicines are those that satisfy the priority health care needs of the population.

Criteria for selection of essential medicines
Essential medicines are selected with due regard to disease prevalence and public health relevance, evidence of clinical efficacy and safety, and comparative costs and cost-effectiveness.

Essential Medicines Lists
Essential medicines are intended to be available within the context of functioning health systems at all times in adequate amounts, in the appropriate dosage forms, with assured quality, and at a price the individual and the community can afford.

http://www.who.int/medicines/services/essmedicines_def/en/
WHO Model List of Essential Medicines

Individual components of cardiovascular polypills (aspirin, statin, blood pressure lowering drugs) are on the 19th Model List of Essential Medicines.

Previous fixed-dose combination applications for drugs to treat HIV, malaria, and TB have been listed on the WHO EML with phase 2 (or earlier) data.

2012 and 2014 polypill applications for 2° prevention indication → denied
• Bias demonstrated against drugs for non-communicable diseases

2016 polypill application for 2° prevention indication → importance of FDC acknowledged

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The Expert Committee considered that FDCs for NCDs may have advantages over the single medicines given concomitantly, including increased adherence and reduced pill burden. For this reason, the Committee recognized the potential value of FDCs of currently listed essential medicines, with regulatory approval and demonstrated bioavailability for the management of chronic NCDs. However, the Committee considered that many different combinations of cardiovascular medicines exist, with multiple permutations of components from different therapeutic classes, varying strengths and dosages. The Committee noted, for example, that currently at least 14 different combination products are in development (25), and that there does not yet appear to be consensus on the optimal components for a ‘universal FDC’. The Committee also agreed that there is a need to develop the evidence base for FDCs in low- and middle-income countries, including procurement, utilization, costeffectiveness and adherence (26). Given this complexity, the Committee was firmly of the view that it would not be appropriate to list individual FDCs for NCDs on the EML as this would not provide the required flexibility for choosing optimal combinations and doses of multi-drug therapy of cardiovascular disease.
HEARTS
Technical package for cardiovascular disease management in primary health care

- **HEALTHY LIFESTYLE**
  - Counselling on tobacco cessation, diet, physical activity, alcohol use and self-care

- **EVIDENCE-BASED TREATMENT PROTOCOLS**
  - Simple, standardized algorithms for clinical care

- **ACCESS TO ESSENTIAL MEDICINES AND TECHNOLOGY**
  - Access to core set of affordable medicines and basic technology

- **RISK-BASED MANAGEMENT**
  - Total cardiovascular risk assessment, treatment and referral

- **TEAM CARE AND TASK-SHARING**
  - Decentralized, community-based and patient-centred care

- **SYSTEMS FOR MONITORING**
  - Patient data collection and programme evaluation
“Use of (polypills) for 2° prevention and 1° prevention in high-risk individuals for CVD could close gaps in treatment of these conditions by reducing drug costs, improving adherence and simplifying the drug regimen for patients who take them and healthcare workers who prescribe them.”
## Barriers to polypills

**Q: What research questions address (some of) these barriers?**

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<th>Physician</th>
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<tr>
<td>• Perception that polypills limit autonomy of clinical decision making</td>
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<td>• Closer monitoring of risk factor levels is generally preferred with regular dose adjustments</td>
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<td>• Concern that only one combination will be available, which would limit choice of components</td>
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<th>Patient</th>
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<td>• Managing side-effects with use and risk of stopping the polypill</td>
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<td>• Uncertainty about cost</td>
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<th>Pharmaceutical manufacturers</th>
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<td>• Risks associated with new treatment strategy</td>
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<tr>
<td>• Influence of physician and patient barriers</td>
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<td>• Regulatory uncertainties with combination products, including patent protections</td>
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<td>• Challenges in forecasting of future sales</td>
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Could patents interfere with the development of a cardiovascular polypill?

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Abstract

\textbf{Background:} The Wellcome Trust, the World Health Organization, and cardiologists have advocated for the idea of a “polypill” containing multiple cardiovascular drugs to be co-formulated into a single pill for over a decade. Some cardiologists have asserted that the drugs commonly considered for inclusion into such a polypill are older and therefore free of patent protection. We tested this assertion. This project was requested by the World Heart Federation (WHF).

\textbf{Methods, data and materials:} Two cardiologists from the WHF provided a list of 48 cardiovascular drugs for evaluation. We designated the United States and Canada as the base jurisdictions for this patent study. We linked patent data from these countries’ national medicine patent registers to patent information in over 96 other countries using Derwent and INPADOC via Thomson Innovation. We expanded our study beyond the aforementioned data linkage through a systematic search of the World Intellectual Property Organization’s PatentScope, which was based primarily upon the drugs’ active ingredient names.

\textbf{Results:} In the United States and Canada, eight of the drugs were only available in the patent-protected, brand name formulation in one or both countries. Another 21 drugs had relevant patents, but generic equivalents were nevertheless available. Only 19 drugs (40\%) appeared entirely post-patent. Broadening the co-formulation searches globally, the overwhelming majority of drugs (40/48) were mentioned in patent applications for cardiovascular drug
Polypill patent landscape analysis

48 drugs in polypills.

Only 8 drugs in polypills are patented w/o any available generics; 19 (40%) are fully generic.

40/48 (83%) of active drugs or drug classes were listed in WIPO Patent Scope but is the glass half full or empty?

More, not fewer, polypills

Aspirin is now optional to capture 1st prevention population

Higher potency statins are increasingly included

More companies investing

- GSK3074477 (amlodipine, rosuvastatin), GlaxoSmithKline
- Livalo fixed combination drug (pitavastatin, valsartan), JW Pharmaceutical
- Polytorva A (ramipril, atorvastatin), USV
- Polytorva B (aspirin, ramipril, atorvastatin), USV
- Polycap (aspirin, ramipril, hydrochlorothiazide, atenolol, simvastatin), Cadila
- Polycap (ramipril, hydrochlorothiazide, atenolol, simvastatin), Cadila
- Ramitorva (aspirin, ramipril, atorvastatin), Zydus
- Starpill (aspirin, losartan, atenolol, atorvastatin), Cipla
- Trinomia (aspirin, ramipril, atorvastatin), Ferrer
- Trinomia (aspirin, ramipril, simvastatin), Ferrer
- Triveram (perindopril, amlodipine, atorvastatin), Servier
- Unnamed (irbesartan, atorvastatin), Sanofi
- Unnamed (valsartan, rosuvastatin), EMS
- Zycad (valsartan, ramipril, metoprolol, atorvastatin), Cadila

Q: What co-interventions would help potentiate the effects of polypills?
Large (n>1000) ongoing polypill trials

Step-up
SECURE
INTEGRATE (8 polypills; decision support + pharmacy support co-intervention)

High-risk primary prevention
TIPS-3
HOPE-4 (NPHW co-intervention)

Mass treatment
PolyIran
Conclusions

Rather than being a panacea for all, polypills represent the most effective and scalable intervention for improving adherence to multi-drug therapy for initiation, step-up, or substitution indications.

Polypill trials have been generally designed to demonstrate bioequivalence rather than differences in clinical outcomes; high quality “usual care” seen in trials limits power.

Polypills meet criteria as essential medicines for secondary ASCVD prevention and the growth of polypill suggests an opening of the marketplace for these combinations.
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