Huffman, MD; de Cates, AN; Ebrahim, S (2014) Fixed-dose combination therapy (polypill) for the prevention of cardiovascular disease. JAMA, 312 (19). pp. 2030-1. ISSN 0098-7484 DOI: https://doi.org/10.1001/jama.2014.13616

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DOI: 10.1001/jama.2014.13616

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Fixed-Dose Combination Therapy (Polypill) for the Prevention of Cardiovascular Disease

Mark D. Huffman, MD, MPH; Angharad N. de Cates, BMBCh, BA; Shah Ebrahim, DM

CLINICAL QUESTION Is fixed-dose combination therapy (polypill) that combines antiplatelet, blood pressure-lowering, and cholesterol-lowering medications into a single pill associated with improved cardiovascular disease (CVD) risk factors or reduced all-cause mortality or fatal and nonfatal CVD events? Is the polypill associated with an increase in adverse events?

BOTTOM LINE Polypills are associated with greater reductions in systolic blood pressure and total cholesterol compared with usual care, placebo, or active comparators, but also with a 19% higher risk of any adverse event. Due to limited power from available evidence, the association of polypills with all-cause mortality or fatal and nonfatal CVD events is uncertain.

Fixed-dose combination therapy (polypill) combines low-dose blood pressure- and cholesterol-lowering medications with or without aspirin into a single pill for cardiovascular disease (CVD) prevention. A polypill has potential utility in low-resource settings because it increases adherence at potentially lower cost. This JAMA Clinical Evidence Synopsis summarizes a Cochrane review assessing the association of polypills on cardiovascular diseases.

Summary of Findings
The 9 trials (N = 7047) included 6 different drug combinations. The 3 largest trials included 78% of all participants across the studies.

<table>
<thead>
<tr>
<th>Evidence Profile</th>
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</thead>
<tbody>
<tr>
<td>No. of randomized clinical trials:</td>
<td>9 trials (7 primary prevention; 2 secondary prevention)</td>
</tr>
<tr>
<td>Study years: Conducted, 2006-2012; published, 2009-2013; end of literature search, July 19, 2013</td>
<td></td>
</tr>
<tr>
<td>No. of participants: 7047</td>
<td></td>
</tr>
<tr>
<td>Men: 4463 (63.3%); Women: 2584 (36.7%)</td>
<td></td>
</tr>
<tr>
<td>Race/ethnicity: Not available</td>
<td></td>
</tr>
<tr>
<td>Age range, mean (SD): 52.6 years (9.6) to 62.1 years (10.4)</td>
<td></td>
</tr>
<tr>
<td>Settings: Outpatient</td>
<td></td>
</tr>
<tr>
<td>Countries: International (5 continents)</td>
<td></td>
</tr>
<tr>
<td>Drug classes included: Aspirin, blood pressure-lowering drugs, and a lipid-lowering drug (exclusively statins)</td>
<td></td>
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<tr>
<td>No. of drug combinations: 2 drugs (3 trials), 4 drugs (5 trials), 5 drugs (1 trial)</td>
<td></td>
</tr>
<tr>
<td>Comparator groups: Usual care (3 trials), placebo (4 trials), active comparator (2 trials)</td>
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</tr>
<tr>
<td>Follow-up: ≤ 12 weeks in 6 trials, 12-15 months in the remaining 3 trials</td>
<td></td>
</tr>
<tr>
<td>Primary outcomes: All-cause mortality; fatal and nonfatal cardiovascular disease events; adverse events</td>
<td></td>
</tr>
<tr>
<td>Secondary outcomes: Change in total and low-density lipoprotein (LDL) cholesterol concentration, change in systolic and diastolic blood pressure, adherence, health-related quality of life, and costs</td>
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</table>

The follow-up period was 12 weeks or less in 6 trials, and 12 to 15 months in the remaining 3 trials. Only 2 trials reported rates of all-cause mortality (n = 3465) and fatal and nonfatal CVD events (n = 2479). Two trials included at least 10% of participants with prevalent CVD at baseline.

The intervention group was associated with decreases in systolic blood pressure of 13.4 mm Hg vs 6.3 mm Hg in the comparator group (Table). The intervention group was associated with a 33.3 mg/dL decrease in mean total cholesterol vs a decrease of 4.3 mg/dL in the comparator group. One secondary prevention trial (n = 2004) reported differences in adherence at 15 months (86% for intervention vs 65% for comparator; relative risk [RR], 1.33 [95% CI, 1.26-1.41]).

The polypill was associated with a higher adverse event rate compared with the comparator group. Seven trials (n = 4864) reported adverse events. Adverse event rates were higher in participants randomized to the polypill compared with comparator (29.7% [739/2485 participants] vs 24.2% [576/2379] for comparator; RR, 1.19 [95% CI, 1.09-1.30]). The 3 most commonly reported adverse events in the intervention and comparator groups were increased liver chemistries (7.8% for intervention vs 7.6% for comparator, P = .91), cough (6.4% for intervention vs 3.5% for comparator, P = .002), and myalgias (4.0% for intervention vs 3.6% for comparator, P = .55).

All-cause mortality was low in both study groups (1.2% [22/1781] for intervention compared with 1.0% [17/1684] for comparator), and there was no association of decreased mortality in the intervention group compared with the comparator group (RR, 1.26 [95% CI, 0.67-2.38]). Fatal and nonfatal CVD event rates were 4.0% [50/1243] in the intervention group vs 2.9% [36/1236] in the comparator group (RR, 1.38 [95% CI, 0.91-2.10]). No differences in serious adverse events were reported. There was no difference in quality of life (1 trial, n = 2004). No trials reported cost outcomes.

Discussion
Polyills are associated with lower blood pressure and cholesterol compared with usual care, active comparators, or placebo, which is
likely to be driven by increased adherence, particularly when compared with active comparators or usual care. The trials were not planned with statistical power to evaluate effects on all-cause mortality and fatal and nonfatal CVD events. Polypills are associated with greater adherence in patients with low baseline adherence compared with patients who already have high adherence.4 Rather than replace usual care for CVD prevention, polypills will likely be useful adjunct.

Limitations
Five of the included trials had a moderate to high risk of bias, which reduces the overall quality of evidence. Long-term adherence and clinical event rates remain to be determined. There was substantial heterogeneity that was not explained by either a single trial, the number of drugs in the intervention group, or primary vs secondary prevention trials. Pooled results should be viewed with caution.

Comparison of Findings With Current Practice Guideline
Clinical practice guidelines have adopted blood pressure–lowering combination therapy for hypertension management,5 but we do not know of any guidelines that recommend polypills for CVD prevention. Polypills are not part of the World Health Organization’s Model List of Essential Medicines to date.6

Areas in Need of Future Study
Ongoing trials of polypills will likely inform end points of all-cause mortality, fatal and nonfatal CVD events, quality of life, and costs, which may inform future regulatory decisions and guidelines.

ARTICLE INFORMATION

Author Affiliations: Department of Preventive Medicine, Northwestern University, Chicago, Illinois (Huffman); Division of Health Sciences, Warwick Medical School, University of Warwick, Coventry, United Kingdom (de Cates); Department of Noncommunicable Disease Epidemiology, London School of Hygiene and Tropical Medicine, Camden, United Kingdom (Ebrahim).

Corresponding Author: Mark D. Huffman, MD, MPH, Cochrane Heart Group US Satellite, Department of Preventive Medicine, Northwestern University Feinberg School of Medicine, 680 N Lake Shore Dr, Ste 1400, Chicago, IL 60611 (m-huffman@northwestern.edu).

Conflict of Interest Disclosures: All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr Huffman reports grant funding from the World Heart Foundation. Dr de Cates reports grant funding from the National Institute of Health Research. No other disclosures were reported.

Additional Contributions: We thank our coauthors for their work to produce this systematic review.

REFERENCES


Table. Summary of Findings of Fixed-Dose Combination Therapy (Polypill) vs Usual Care, Active Comparator, or Placebo (Comparator) by Outcome

<table>
<thead>
<tr>
<th>Comparatorb</th>
<th>Polypill</th>
<th>Relative Risk (95% CI)</th>
<th>No. of Participants (No. of Studies)</th>
<th>GRADEc</th>
<th>Rationale for Downgrading Quality of Evidenced</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Participants</td>
<td>No. of Events (%)</td>
<td>Total Participants</td>
<td>No. of Events (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>1684</td>
<td>17 (1.0)</td>
<td>1781</td>
<td>22 (1.2)</td>
<td>1.26 (0.67 to 2.38)</td>
</tr>
<tr>
<td>CVD event</td>
<td>1236</td>
<td>36 (2.9)</td>
<td>1243</td>
<td>50 (4.0)</td>
<td>1.38 (0.91 to 2.10)</td>
</tr>
<tr>
<td>Any adverse event</td>
<td>2379</td>
<td>576 (24.2)</td>
<td>2485</td>
<td>739 (29.7)</td>
<td>1.19 (1.09 to 1.30)</td>
</tr>
<tr>
<td>Discontinuation</td>
<td>1307</td>
<td>150 (11.5)</td>
<td>1116</td>
<td>156 (14.0)</td>
<td>1.26 (1.02 to 1.55)</td>
</tr>
</tbody>
</table>

Continuous Outcomes

<table>
<thead>
<tr>
<th>Mean Change (Range)</th>
<th>Weighted Mean Difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>2837</td>
</tr>
<tr>
<td>Total cholesterol, mg/dL</td>
<td>2636</td>
</tr>
<tr>
<td>LDL cholesterol, mg/dL</td>
<td>2531</td>
</tr>
</tbody>
</table>

Abbreviations: CVD, cardiovascular disease; GRADE, Grading of Recommendations Assessment, Development, and Evaluation; LDL, low-density lipoprotein.

Source: data adapted with permission from Wiley.2

Comparator included usual care, placebo, or active comparator.