JAMA Clinical Evidence Synopsis

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

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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.[1] This JAMA Clinical Evidence Synopsis summarizes a Cochrane review[2] 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.

Evidence Profile

No. of randomized clinical trials: 9 trials (7 primary prevention; 2 secondary prevention)

Study years: Conducted, 2006-2012; published, 2009-2013; end of literature search, July 19, 2013

No. of participants: 7047

Men: 4463 (63.3%) **Women:** 2584 (36.7%)

Race/ethnicity: Not available

Age range, mean (SD): 52.6 years (9.6) to 62.1 years (10.4)

Settings: Outpatient

Countries: International (5 continents)

Drug classes included: Aspirin, blood pressure–lowering drugs, and a lipid-lowering drug (exclusively statins)

No. of drug combinations: 2 drugs (3 trials), 4 drugs (5 trials), 5 drugs (1 trial)

Comparator groups: Usual care (3 trials), placebo (4 trials), active comparator (2 trials)

Follow-up: ≤12 weeks in 6 trials; 12-15 months in the remaining 3 trials

Primary outcomes: All-cause mortality; fatal and nonfatal cardiovascular disease events; adverse events

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

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] for polypill 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

Polypills are associated with lower blood pressure and cholesterol compared with usual care, active comparators, or placebo, which is

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

	Comparator[b]		Polypill					
	Total Participants	No. of Events (%)	Total Participants	No. of Events (%)	Relative Risk (95% CI)	No. of Participants (No. of Studies)	GRADE[c]	Rationale for Downgrading Quality of Evidence[d]
Categorical Outcomes								
All-cause mortality	1684	17 (1.0)	1781	22 (1.2)	1.26 (0.67 to 2.38)	3465 (2)	Low	Risk of bias; imprecision of effect
CVD event	1236	36 (2.9)	1243	50 (4.0)	1.38 (0.91 to 2.10)	2479 (2)	Low	Risk of bias; imprecision of effect
Any adverse event (6 wk-15 mo)	2379	576 (24.2)	2485	739 (29.7)	1.19 (1.09 to 1.30)	4864 (7)	Low	Risk of bias; indirectness of evidence
Discontinuation (for any reason)	1307	150 (11.5)	1116	156 (14.0)	1.26 (1.02 to 1.55)	2423 (6)	Low	Risk of bias; indirectness of evidence
Continuous Outcomes								
		Mean Change (Range)		Mean Change (Range)	Weighted Mean Difference (95% CI)			
Systolic blood pressure, mm Hg	2837	−6.3 (0 to −26.9)	2950	−13.4 (−3.7 to −28.8)	−7.02 (−10.18 to −3.87)	5787 (9)	Moderate	Risk of bias; unexplained heterogeneity
Total cholesterol, mg/dL	2636	−4.3 (7.0 to −38.7)	2933	−33.3 (−3.9 to −56.8)	−0.75 (−1.05 to −0.46)	5569 (9)	Low	Risk of bias; unexplained heterogeneity; funnel plot asymmetry
LDL cholesterol, mg/dL	2531	−1.2 (5.0 to −7.0)	2834	−32.1 (−5.8 to −54.1)	−0.81 (−1.09 to −0.53)	5365 (8)	Moderate	Risk of bias; unexplained heterogeneity

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

[a] Source: data adapted with permission from Wiley.[2]

[b] Comparator included usual care, placebo, or active comparator.

[c] Quality of the evidence: moderate quality, further research is likely to influence the confidence in the estimate of effect and may change the estimate; low quality, further research is very likely to influence the confidence in the estimate of effect and is likely to change the estimate.

[d] Rationale per GRADE methodology.[3]

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 a 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

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