

## Evidence Assessment: Summary of a Systematic Review

### Who is this summary for?

For Doctors and Health Personnel, Administrators, Managers of health facilities, and partners involved in non-communicable chronic disease control

## Fixed-dose combination therapy for the prevention of atherosclerotic cardiovascular diseases

### Key findings

- The effects of fixed-dose combination therapy on all-cause mortality or atherosclerotic cardiovascular disease (ASCVD) events are uncertain. A limited number of trials reported these outcomes, and the included trials were primarily designed to observe changes in ASCVD risk factor levels rather than clinical events.
- Fixed-dose combination therapy is associated with modest increases in adverse events compared with placebo, active comparators, or usual care which may result from improved adherence to a multidrug regimen.
- There were reductions in ASCVD risk factors: systolic and diastolic blood pressure and total and LDL cholesterol. These risk factor changes would have been expected to result in a reduction in ASCVD events if sustained, but the trials reporting changes in risk factors were generally too short to detect a potential difference by their design.

### Background

Atherosclerotic cardiovascular disease (ASCVD) is the leading cause of death and disability worldwide, yet ASCVD risk factor control and secondary prevention rates remain low. A fixed-dose combination of blood pressure- and cholesterol-lowering and antiplatelet treatments into a single pill, or polypill, has been proposed as one strategy to reduce the global burden of ASCVD.

### Questions

What is the effect of fixed-dose combination therapy on all-cause mortality, fatal and non-fatal ASCVD events, and adverse events? And also, what is the effect of fixed-dose combination therapy on blood pressure, lipids, adherence, discontinuation rates, health-related quality of life, and costs?

### Fixed-dose combination therapy for the prevention of atherosclerotic cardiovascular diseases in Cameroon:

In Cameroon, one of the major risk factors for cardiovascular diseases is arteriosclerosis which is secondary to excess LDL cholesterol. Clinical manifestations of arteriosclerosis are found in coronary artery disease, ischemic stroke, and peripheral vascular occlusive diseases. There exists a significant gap in population awareness about CVDs (Nanseu, 2016). Currently, there are no fixed dose combination therapies for ASCVD in Cameroon.

**Table 1: Summary of the systematic review**

	<b>What the review authors searched for</b>	<b>What the review authors found</b>
<b>Studies</b>	Randomised controlled trials (RCT).	Nine randomised controlled trials and four additional reports evaluated the effects of fixed-dose combination (FDC) therapy in populations without prevalent ASCVD.
<b>Participants</b>	Adults 18 years and older with no restriction regarding presence of ASCVD.	9059 participants. Middle-aged men with moderate elevations in blood pressure or cholesterol. Two studies specifically included ethnic Aboriginal or Maori minorities in half of the study participants. Mean age range 62 to 63 years; 30% to 37% women.
<b>Interventions</b>	A fixed-dose combination therapy, a combination of several active components into a single pill with the aim being to optimise ASCVD risk and reduce ASCVD fatal and non-fatal events. At least one statin and one antihypertensive agent should be included.	A fixed-dose combination pill was proposed in 2001 by a World Health Organization (WHO) and Wellcome Trust expert group and was subsequently specified as a combination of four drugs (beta-blocker, angiotensin-converting enzyme (ACE)- inhibitor, aspirin, and statin), which was estimated to reduce ASCVD events by 75% in people with clinical evidence of ASCVD. The fixed-dose combinations ranged from two to five drugs; all studies included at least one blood pressure-lowering and one cholesterol-lowering drug.
<b>Controls</b>	Trials were considered where the comparison group was usual care, placebo, or an active drug comparator.	placebo, usual care, or active drug comparator
<b>Outcomes</b>	<p><b>Primary outcomes</b></p> <ul style="list-style-type: none"> <li>Clinical outcomes including mortality (cardiovascular and all-cause); non-fatal ASCVD endpoints such as myocardial infarction, coronary artery bypass grafting (CABG), percutaneous transluminal coronary angioplasty (PTCA), angina or angiographically-defined ischaemic heart disease, stroke, transient ischaemic attack (TIA), carotid endarterectomy, or peripheral arterial disease (PAD). The previous version of the review included the broader outcome of CVD, but we have narrowed this definition for this update to include only ASCVD.</li> <li>Investigator-defined adverse events including the proportion of participants experiencing specific symptoms including: myalgias, cough, elevated liver enzymes, gastric irritation or dyspepsia.</li> </ul> <p><b>Secondary outcomes</b></p> <ul style="list-style-type: none"> <li>Systolic and diastolic blood pressure</li> <li>Total and LDL cholesterol</li> <li>Adherence</li> <li>Discontinuation rates</li> <li>Health-related quality of life, measured according to any well validated and adjusted scale concerning quality of life</li> <li>Costs of fixed-dose combination therapy</li> </ul>	<p><b>Primary outcomes</b></p> <ul style="list-style-type: none"> <li>All-cause mortality</li> <li>Adverse events</li> </ul> <p><b>Secondary outcomes</b></p> <ul style="list-style-type: none"> <li>Systolic and diastolic blood pressure</li> <li>Total and LDL cholesterol</li> <li>Adherence</li> <li>Discontinuation</li> <li>Health-related quality of life</li> <li>Costs</li> </ul>
<b>Date of the most recent search:</b> September 2016		
<b>Limitations:</b> This is a moderate quality systematic review, <b>AMSTAR = 9/11</b>		
<b>Citation:</b> Bahiru E, de Cates AN, Farr MRB, Jarvis MC, Palla M, Rees K, Ebrahim S, Huffman MD. <b>Fixed-dose combination therapy for the prevention of atherosclerotic cardiovascular diseases.</b> Cochrane Database of Systematic Reviews 2017, Issue 3. Art. No.: CD009868. DOI: 10.1002/14651858.CD009868.pub3.		

**Table 2: Summary of findings**

<b>Fixed-dose combination therapy for the prevention of atherosclerotic cardiovascular diseases (ASCVD)</b>					
<b>Patient or population:</b> adults older than 18 years, with no restriction regarding presence of ASCVD; participants generally had elevated risk of ASCVD (as estimated by the presence of at least one abnormal cardiovascular risk factor) without prevalent CVD (two studies included > 10% of participants with prior ASCVD)					
<b>Settings:</b> outpatient					
<b>Intervention:</b> fixed-dose combination therapy of varying drug combinations ranging from two to five drugs					
<b>Comparison:</b> usual care, placebo, or active drug therapy					
Outcomes	Illustrative comparative risks*(95%CI)		Relative effect (95%CI)	No. of participants (studies)	Quality of the evidence (GRADE)
	Assumed risk based on event rates or mean changes from baseline in the comparator group	Corresponding risk			
	Comparator group, including placebo, usual care, or active drug comparator	Fixed-dose combination therapy			
<b>All-cause mortality</b> Median follow-up range: 9 to 23 months	<b>Total</b>	<b>11 per 1000</b> (6 to 19)	RR = 1.10 (0.64 to 1.89)	5300 (5 studies)	Low
	10 per 1000				
<b>ASCVD event</b> , such as fatal or non-fatal myocardial infarction or stroke Median follow-up range : 6 weeks to 23 months	<b>Total</b>	<b>46 per 1000</b> (35 to 61)	RR = 1.26 (0.95 to 1.66)	4517 (6 studies)	Low
	37 per 1000				
<b>Any investigator-defined adverse event</b> Median follow up range: 6 weeks to 23 months	271 per 1000	<b>314 per 1000</b> (295 to 339)	RR = 1.16 (1.09 to 1.25)	6906 (11 studies)	Moderate
<b>Systolic blood pressure :</b> Median follow up range: 6 weeks to 12 months	The mean change in systolic blood pressure ranged across control groups from -17.9 mmHg to 0.9 mmHg	The mean difference in change in systolic blood pressure between the intervention and comparator groups was -6.34 mmHg (95% CI -9.03 to -3.64)		7638 (13 studies)	Moderate
<b>Total cholesterol, mmol/L</b> Median follow up range: 6 weeks to 23 months	The mean change in total cholesterol ranged across control groups from -1.6 mmol/ L to 0. 2 mmol/ L	The mean difference in change in total cholesterol between the intervention and comparator groups was -0.61 mmol/ L (-0.88 to -0.35)		6565 (11 studies)	Low
<b>LDL cholesterol, mmol/ L</b> Median follow up range: 6 weeks to 23 months	The mean change in LDL cholesterol ranged across control groups from -1.4 mmol/ L to 0.1 mmol/ L	The mean difference in change in LDL cholesterol between the intervention and comparator groups was -0.70 mmol/ L (95% CI - 0.98 to - 0.41)		7153 (12 studies)	Moderate
<b>Adherence, variable definitions</b> Median follow-up range: 9 to 23 months	<b>534 per 1000</b>	<b>769 per 1000</b> (673 to 882)	RR = 1.44 (1.26 to 1.65)	3835 (4 studies)	Moderate

\* The basis for the **assumed risk** (e.g. the median control group risk across studies) is the outcomes of the study control arms. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). **ASCVD** = atherosclerotic cardiovascular disease; **CI**: confidence interval; **RR**: risk ratio

## Applicability

These trials were performed in 32 countries, including 19 low- and middle-income countries, where the burden of ASCVD is greater than in high-income countries. This intervention is likely to be applicable in Cameroon.

## Conclusions

The effects of fixed-dose combination therapy on all-cause mortality or atherosclerotic cardiovascular disease (ASCVD) events are uncertain.

High-quality randomised controlled trials are needed to evaluate if the effect of fixed-dose combination therapies on risk factor levels translates into improvements in fatal and non-fatal events in both primary and secondary ASCVD-prevention settings.

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