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Fixed-dose combination therapies with and without aspirin for primary prevention of cardiovascular disease: an individual participant data meta-analysis

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Summary

Background In randomised controlled trials, fixed-dose combination treatments (or polypills) have been shown to reduce a composite of cardiovascular disease outcomes in primary prevention. However, whether or not aspirin should be included, effects on specific outcomes, and effects in key subgroups are unknown.

Methods We did an individual participant data meta-analysis of large randomised controlled trials (each with ≥1000 participants and ≥2 years of follow-up) of a fixed-dose combination treatment strategy versus control in a primary cardiovascular disease prevention population. We included trials that evaluated a fixed-dose combination strategy of at least two blood pressure lowering agents plus a statin (with or without aspirin), compared with a control strategy (either placebo or usual care). The primary outcome was time to first occurrence of a composite of cardiovascular death, myocardial infarction, stroke, or arterial revascularisation. Additional outcomes included individual cardiovascular outcomes and death from any cause. Outcomes were also evaluated in groups stratified by the inclusion of aspirin in the fixed-dose treatment strategy, and effect sizes were estimated in prespecified subgroups based on risk factors. Kaplan-Meier survival curves and Cox proportional hazard regression models were used to compare strategies.

Findings Three large randomised trials were included in the analysis (TIPS-3, HOPE-3, and PolyIran), with a total of 18 162 participants. Mean age was 63·0 years (SD 7·1), and 9038 (49·8%) participants were female. Estimated 10-year cardiovascular disease risk for the population was 17·7% (8·7). During a median follow-up of 5 years, the primary outcome occurred in 276 (3·0%) participants in the fixed-dose combination strategy group compared with 445 (4·9%) in the control group (HR 0·62, 95% CI 0·53–0·73, p<0·0001). Proportional reductions were also observed for the separate components of the primary outcome: myocardial infarction (0·52, 0·38–0·70), revascularisation (0·54, 0·36–0·80), stroke (0·59, 0·45–0·78), and cardiovascular death (0·65, 0·52–0·81). Significant reductions in the primary outcome and its components were observed in the analyses of fixed-dose combination strategies with and without aspirin, with greater reductions for strategies including aspirin. Treatment effects were similar at different lipid and blood pressure levels, and in the presence or absence of diabetes, smoking, or obesity. Gastrointestinal bleeding was uncommon but slightly more frequent in the fixed-dose combination strategy with aspirin group versus control (19 [0·4%] *vs* 11 [0·2%], p=0·15). The frequencies of haemorrhagic stroke (10 [0·2%] *vs* 15 [0·3%]), fatal bleeding (two [<0·1%] *vs* four [0·1%]), and peptic ulcer disease (32 [0·7%] *vs* 34 [0·8%]) were low and did not differ significantly between groups. Dizziness was more common with fixed-dose combination treatment (1060 [11·7%] *vs* 834 [9·2%], p<0·0001).

Interpretation Fixed-dose combination treatment strategies substantially reduce cardiovascular disease, myocardial infarction, stroke, revascularisation, and cardiovascular death in primary cardiovascular disease prevention. These benefits are consistent irrespective of cardiometabolic risk factors.

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Introduction

Approximately 19 million people die of cardiovascular disease every year, and twice as many experience myocardial infarction or stroke.[1–3] Most cardiovascular disease events occur in individuals without a previous history of vascular disease. Therefore, effective primary prevention strategies are crucial for reducing the cardiovascular disease burden at the population level.[3] Although tobacco avoidance, healthy diet, and increased physical activity are recommended, additional strategies to prevent cardiovascular disease are needed. Pharmacological reductions in LDL cholesterol and blood

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See Online for appendix

Research in context

Evidence before this study

The combination of two or more blood pressure lowering drugs and a statin (with or without aspirin) at fixed doses (usually termed a polypill when in a single formulation) has been proposed to reduce cardiovascular disease to a substantial extent. However, the magnitude of benefit on specific cardiovascular disease outcomes, whether aspirin should be included as part of a fixed-dose combination treatment strategy, and whether specific groups derive greater benefits is unclear. To address these questions, we aimed to do a meta-analysis of large (≥1000 participants), long-term (≥2 years of follow-up) randomised controlled trials testing fixed-dose combination treatment strategies in primary prevention. A review of the literature based on a previous systematic review, and an updated literature search of MEDLINE and Cochrane Central Register of Controlled Trials up to April, 2021, confirmed that only three such trials have been published.

Added value of this study

This analysis included data on 18 162 participants with no known vascular disease from three large randomised controlled trials with a median follow-up of 5 years. A fixed-dose combination strategy significantly reduced a composite of cardiovascular disease events, as well as individual cardiovascular events (myocardial infarction, stroke, revascularisation, and cardiovascular death), compared with control groups. Proportional reductions in risk were largest for fixed-dose combinations containing aspirin. The benefits of a fixed-dose combination strategy were similar irrespective of cardiometabolic risk factors. Dizziness was more common with fixed-dose combination strategies and there was small, non-significant excess in gastrointestinal bleeds compared with control. This study shows that fixed-dose combination strategies are effective in reducing myocardial infarction, strokes, revascularisations, and deaths due to cardiovascular causes in those without previous cardiovascular disease.

Implications of all the available evidence

A fixed-dose combination treatment strategy leads to important reductions in both fatal and non-fatal cardiovascular disease events in primary prevention. Given its low cost and wide applicability, a fixed-dose combination approach should be an integral part of the strategy to achieve the UN Sustainable Development Goal to reduce premature cardiovascular disease deaths globally.

pressure have each been shown to reduce cardiovascular disease in those with vascular disease and in high-risk populations without established vascular disease.[4–6] However, the use of statins, blood pressure lowering drugs, and aspirin in primary prevention is low, particularly in middle-income or low-income countries where about 80% of cardiovascular disease cases occur.[3,7,8]

Fixed-dose combination treatment strategies, with two or more blood pressure lowering medications and a statin (with or without aspirin), have been hypothesised to substantially reduce cardiovascular disease risk in both primary and secondary prevention. When used as a single formulation, they are commonly termed polypills. The concept of a combination pill was first proposed in the early 2000s as a strategy to substantially reduce cardiovascular disease in secondary prevention, as well as at the population level.[9–11] Early trials showed improved adherence and greater risk factor control with a polypill strategy compared with the use of single drugs, usual care, or placebo.[12] Larger clinical outcome trials have shown that fixed-dose combination treatments are effective at reducing a composite of cardiovascular disease outcomes in primary prevention,[13–15] but several important questions remain unanswered. These questions include whether aspirin should be part of a fixed-dose combination strategy in primary prevention, the magnitude of benefits on specific cardiovascular disease events, safety and tolerability, and whether effects differ in different subgroups. To address these questions, we did an individual participant data meta-analysis of three large randomised controlled trials that have evaluated a fixed-dose combination strategy in cardiovascular disease primary prevention.

Methods

Study design and selection criteria

We did an individual participant data meta-analysis of large randomised trials that compared the efficacy and safety of a fixed-dose combination treatment strategy versus control in a primary cardiovascular disease prevention population. A literature search of MEDLINE and Cochrane Central Register of Controlled Trials was done to identify relevant trials (appendix p 1) We included trials that tested a fixed-dose combination strategy consisting of at least two blood pressure lowering agents plus a statin (with or without aspirin), either given together or separately, versus placebo or usual care; that included individuals without a history of cardiovascular disease (ie, primary prevention); that enrolled at least 1000 participants; and had a mean (or median) follow-up of at least 2 years. These criteria were selected to include trials of sufficient size and duration to detect benefits on clinical events after risk factor modification. Selection of larger and longer-term studies also minimises selection biases due to lack of publication, and includes the majority of cases of cardiovascular disease that occurred in randomised trials of fixed-dose combination treatments in primary prevention.

Data analysis

The primary outcome of this meta-analysis was time to first occurrence of a composite of cardiovascular death,

myocardial infarction, stroke, or arterial revascularisation. Additional outcomes were an expanded composite cardiovascular disease outcome including angina and heart failure; individual cardiovascular outcomes; and death from any cause.

A statistical analysis plan was developed to identify variables of interest to be included from all studies, prespecified outcomes, and methods of analyses (appendix pp 15–25). Collaborating study teams were provided with a list of variables to be included in the individual participant data meta-analysis, including baseline demographics, cardiovascular risk factors, and physical measures; study treatment allocation; and clinical outcomes. Lipid and blood pressure measures were collected from each trial (appendix p 2). For each participant, dates of randomisation, outcome events, and follow-up periods were recorded. The Framingham Risk Score was used to estimate 10-year cardiovascular risk.[16] A summary of outcome definitions used for the primary outcome within each trial is provided in the appendix (pp 3–4). A summary of side-effects and adverse events of interest that were available for comparison across studies is also provided (appendix p 5). Datasets were checked for completeness and consistency, and then incorporated into a master database for the analysis.

Baseline characteristics of the overall study population, and in each study, are presented as proportions for categorical variables, and as means with SDs for continuous variables. LDL cholesterol is reported at baseline and at a mean follow-up period of 2·1 years. Systolic blood pressure is reported at baseline, at 2 years, and at 5 years. For the main comparison estimating the effect of fixed-dose combination strategies versus control, participants were analysed according to their originally allocated treatment group, which for the purposes of these analyses was designated as allocation to a fixed-dose combination strategy or to control. Kaplan-Meier survival curves were generated for each outcome for the comparison of a fixed-dose combination strategy versus control. Cox proportional hazard regression models were used to estimate the hazard ratio (HR) for a fixed-dose combination strategy versus control for each clinical outcome of interest. To account for the cluster randomisation design of the PolyIran study, shared frailty models were used with either community cluster (for the PolyIran study) or study centre (for TIPS-3 and HOPE-3) effects modelled as random effects. Because a key difference in the compositions of fixed-dose combination therapies is the inclusion of aspirin, we estimated the effects on clinical outcomes separately in strata with participants randomised to a fixed-dose combination strategy either with or without aspirin versus their respective control groups. The former stratum included all participants in the PolyIran study (n=6101), and participants in TIPS-3 allocated to either both polypill and aspirin or to double placebo (n=2850). The analysis of fixed-dose combination without aspirin included all participants allocated to double active or double placebo included in HOPE-3 (n=6348), and all participants allocated to the polypill or to matching placebo in TIPS-3 (n=5713). Although some participants from TIPS-3 were also allocated to receive study aspirin as part of the

	TIPS-3	HOPE-3	PolyIran
Locations	Bangladesh, Canada, Colombia, India, Indonesia, Malaysia, Philippines, Tanzania, Tunisia	Argentina, Australia, Brazil, Canada, China, Colombia, Czech Republic, Ecuador, Hungary, India, Israel, South Korea, Malaysia, Netherlands, Philippines, Russia, Slovakia, South Africa, Sweden, UK, Ukraine	Iran
Overall trial population	5713 participants without known vascular disease but at intermediate cardiovascular disease risk*	12 705 participants without known vascular disease but at intermediate cardiovascular disease risk*	6838 participants with or without vascular disease
Population included in meta-analysis	All participants (n=5713)	Participants randomly assigned to double active group or double placebo group (polypill concept; n=6348)	Participants without a history of vascular disease (n=6101)
Study design	Double-blind, placebo-controlled	Double-blind, placebo-controlled	Pragmatic, cluster-randomised
Intervention†	2 × 2 × 2 factorial design: daily oral polypill consisting of simvastatin 40 mg, ramipril 10 mg, atenolol 100 mg, hydrochlorothiazide 25 mg; daily aspirin 75 mg; monthly oral vitamin D 60 000 IU	2 × 2 factorial design: daily oral rosuvastatin 10 mg; daily oral candesartan 16 mg and hydrochlorothiazide 12·5 mg	Daily oral polypill consisting of atorvastatin 20 mg, hydrochlorothiazide 12·5 mg, enalapril 5 mg (or valsartan 40 mg), and aspirin 81 mg
Comparator (or control)†	Matching placebos	Matching placebos	Minimal care (blood pressure measurement and risk factor counselling)
Median (IQR) follow-up, years	4·4 (3·2–5·9)	5·5 (5·1–6·2)	5·0 (4·9–5·0)

*Based on estimated cardiovascular risk by the Framingham Risk Score. †Counselling to enhance healthy behaviours (eg, diet, activity, and avoidance of tobacco) was recommended for all participants in TIPS-3 and HOPE-3, and was included in both the intervention and control group in the PolyIran study.

Table 1: **Characteristics of included trials**

	Overall (n=18 162)	TIPS-3 (n=5713)	HOPE-3 (n=6348)	PolyIran (n=6101)
Age, years	63·0 (7·1)	63·9 (6·6)	65·7 (6·3)	59·3 (6·7)
Sex				
Female	9038 (49·8%)	3025 (52·9%)	2943 (46·4%)	3070 (50·3%)
Male	9124 (50·2%)	2688 (47·1%)	3405 (53·6%)	3031 (49·7%)
Diabetes	3523 (19·4%)	2095 (36·7%)	574 (9·0%)	854 (14·0%)
Hypertension	11 519 (63·4%)	4790 (83·8%)	3831 (60·3%)	2898 (47·5%)
Smoking history	4243 (23·4%)	1426 (25·0%)	1780 (28·0%)	1037 (17·0%)
Body-mass index, kg/m²	26·5 (5·0)	25·8 (4·7)	27·1 (4·7)	26·5 (5·3)
Blood pressure, mm Hg				
Systolic	137·7 (19·1)	144·5 (16·8)	138·1 (14·7)	130·8 (22·4)
Diastolic	81·5 (10·7)	83·9 (9·7)	81·9 (9·3)	78·7 (12·2)
Cholesterol, mg/dL				
Total	200·0 (43·3)	196·2 (45·6)	201·2 (42·6)	202·5 (41·4)
LDL	121·7 (37·4)	120·7 (40·7)	127·4 (36·5)	117·1 (34·1)
HDL	50·6 (14·9)	47·7 (13·0)	44·7 (14·0)	58·9 (13·7)
Cholesterol, mmol/L				
Total	5·2 (1·1)	5·1 (1·2)	5·2 (1·1)	5·2 (1·1)
LDL	3·1 (1·0)	3·1 (1·1)	3·3 (0·9)	3·0 (0·9)
HDL	1·3 (0·4)	1·2 (0·3)	1·2 (0·4)	1·5 (0·4)
Fasting plasma glucose, mg/dL	105·7 (37·7)	114·3 (45·0)	99·1 (21·9)	104·6 (41·3)
Fasting plasma glucose, mmol/L	5·9 (2·1)	6·3 (2·5)	5·5 (1·2)	5·8 (2·3)
Creatinine, mg/dL	1·0 (0·2)	0·9 (0·3)	0·9 (0·2)	1·1 (0·2)
Creatinine, mmol/L	84·5 (22·0)	81·5 (23·3)	79·3 (19·0)	92·8 (21·2)
10-year estimated cardiovascular disease risk, %	17·7% (8·7)	19·9% (8·1)	19·9% (7·9)	13·5% (8·6)

Data are mean (SD) or n (%). Hypertension was defined as self-reported history of hypertension or baseline systolic blood pressure of >140 mm Hg. Diabetes was defined as self-reported history of diabetes or fasting plasma glucose of >126 mg/dL.

Table 2: **Baseline participant characteristics**

2×2 factorial design of the study, no treatment interaction in results was observed between fixed-dose combination treatments and aspirin for this analysis (p-value for interaction=0·44), and therefore including all participants from the main TIPS-3 polypill or matching placebo comparison is valid.[13] Separate Cox regression models were used to estimate treatment effects with the cohort separated into periods between randomisation and the first year of follow-up, from 1 to 3 years, and after 3 years. Effect sizes were also estimated in prespecified subgroups (by age, sex, hypertension status, diabetes status, smoking status, body-mass index [BMI], LDL cholesterol, systolic blood pressure, and overall cardiovascular disease risk), with differences between dichotomous groups assessed using the Wald test for interactions, and continuous risk factors divided into tertiles and assessed using tests for trend. An exploratory sensitivity analysis for the primary outcome was done excluding participants who did not undergo allocation concealment. For the primary analysis, all unknown deaths were classified as non-cardiovascular, reflecting that in primary prevention most deaths are due to non-cardiovascular disease causes (appendix p 6).[17] However, additional sensitivity analyses were done in which unknown deaths were allocated according to original trial definitions. Effect sizes are reported as HRs with 95% confidence intervals. Due to differences in how data on adverse events were collected between studies, data are presented as the proportion of participants who had a side-effect or adverse event in treatment and control groups at any time during the period of follow-up, with differences between groups compared using Fisher's exact test. When two-sided p-values were reported, a value of 0·05 or less was considered statistically significant. The 5-year number needed to treat (NNT) was calculated for the primary outcome, and the number needed to harm (NNH) to prevent a gastrointestinal bleed was calculated for the comparison of fixed-dose combination treatment with aspirin versus control. Analyses were done using SAS, version 9.4.

Role of the funding source

The funders of the original trials had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The meta-analysis was completed through the Population Health Research Institute without study-specific funding.

Results

A review of the literature confirmed three randomised trials meeting the eligibility criteria: TIPS-3, HOPE-3,

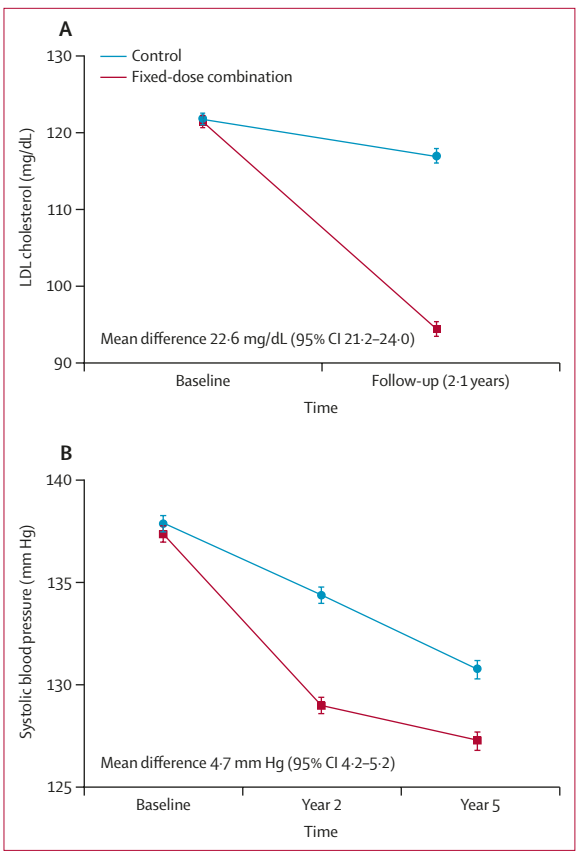


Figure 1: **Changes in low density lipoprotein cholesterol (A) and systolic blood pressure (B) with a fixed dose combination treatment strategy compared to control**

Data are presented for participants with complete data on LDL cholesterol (n=10 867) and systolic blood pressure (n=16 366) at the reported timepoints. The follow-up for LDL cholesterol was reported at a mean of 2·1 years across trials. Systolic blood pressure was 5·4 mm Hg lower in the fixed-dose combination strategy group at 2 years and 3·5 mm Hg lower at 5 years.

and the PolyIran study (appendix p 1).[13–15] Details of each trial are summarised in table 1. All participants in the TIPS-3 study were eligible for our analysis. HOPE-3 tested two blood pressure lowering agents and a statin using a factorial design; therefore, the comparisons included in this analysis were groups allocated to both study interventions (testing the polypill concept), versus those allocated to double placebo. The PolyIran study included participants with and without a previous history of vascular disease; therefore, only participants in the primary cardiovascular disease prevention strata were included in this analysis. Risk factor counselling was recommended in all participants in TIPS-3 and HOPE-3, and was part of both the intervention and minimal care groups in the PolyIran study.

A total of 18 162 participants were included. The mean age of the study population was 63·0 years (SD 7·1), 9038 (49·8%) participants were female, 11 519 (63·4%) had hypertension, 3523 (19·4%) had diabetes, and 4243 (23·4%) had a history of smoking (table 2). Mean

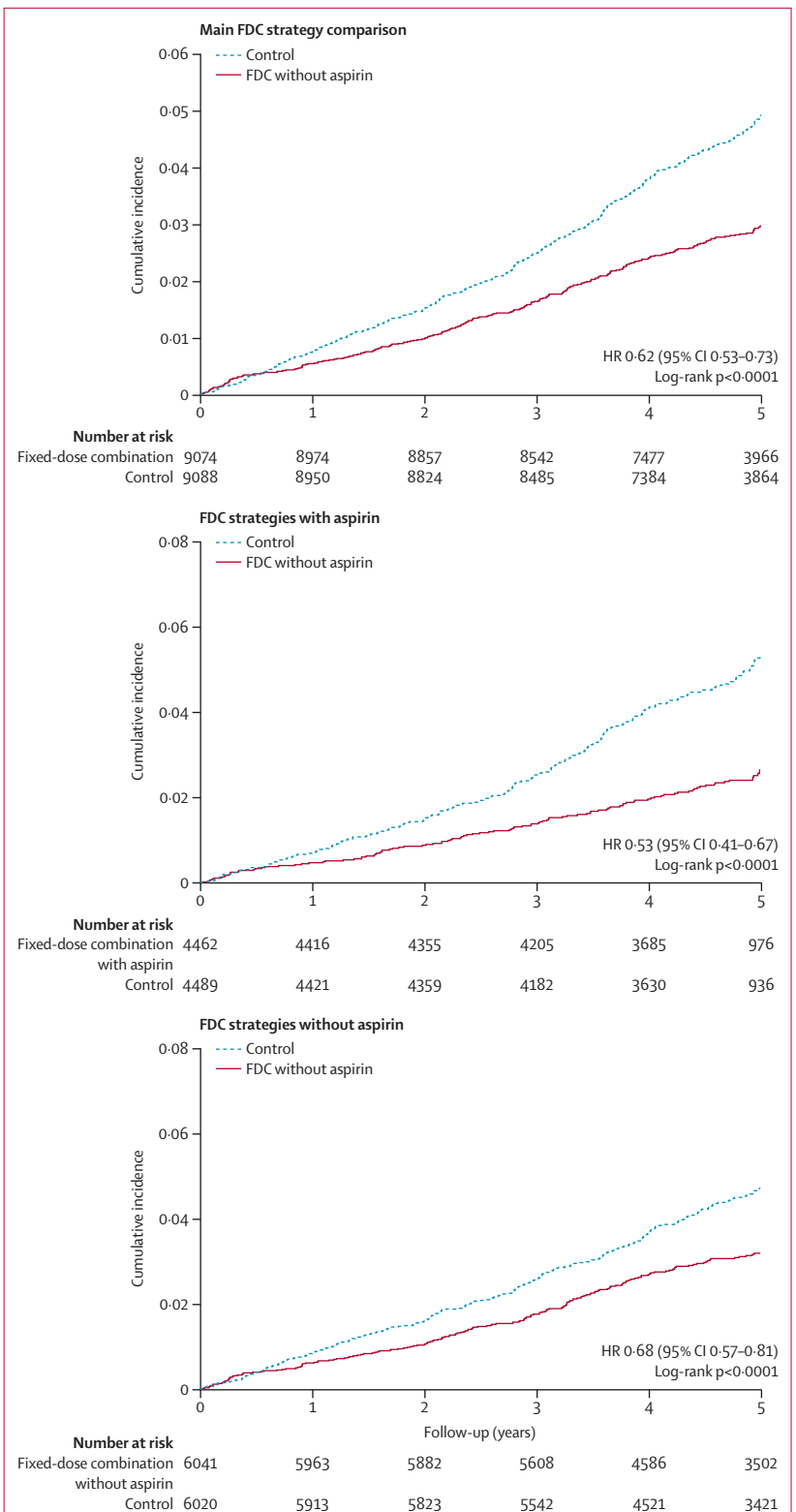


Figure 2: **Kaplan-Meier curves for the composite primary outcome of cardiovascular death, myocardial infarction, stroke, or revascularisation**

Kaplan-Meier curves are presented up to 5 years. FDC=fixed-dose combination. HR=hazard ratio.

systolic blood pressure in the overall population was 137·7 mm Hg (19·1) and mean LDL cholesterol was 121·7 mg/dL (37·4). The mean estimated 10-year risk of a cardiovascular event using the Framingham Risk Score was 17·7% (8·7), corresponding to an intermediate primary cardiovascular disease prevention population. The mean age of the study populations was highest in HOPE-3 and lowest in the PolyIran study. LDL cholesterol was highest in HOPE-3. The prevalence of hypertension and mean systolic blood pressure was highest in TIPS-3. The estimated 10-year cardiovascular disease risk was highest in TIPS-3 (19·9% [8·1]) and HOPE-3 (19·9% [7·9]), and lowest in the PolyIran study (13·5% [8·6]). Baseline characteristics were similar between treatment and control groups for each comparison (appendix p 7).

At a mean of 2·1 years after randomisation, mean LDL cholesterol was 22·6 mg/dL (0·58 mmol/L) lower in the fixed-dose combination strategy group compared with the control group (p<0·0001; figure 1A). Over a follow-up period of 5 years, mean systolic blood pressure decreased from 137·4 mm Hg to 127·3 mm Hg in the fixed-dose combination strategy group, but also decreased from 137·9 mm Hg to 130·8 mm Hg in the control group. Consequently, the average difference was 4·7 mm Hg lower in the fixed-dose combination strategy group compared with the control group (p<0·0001; figure 1B).

The median follow-up for the pooled study population was 5·0 years (IQR 4·8–5·6). During follow-up, the primary outcome occurred in 276 (3·0%) participants in the fixed-dose combination strategy group compared with 445 (4·9%) in the control group (HR 0·62, 95% CI

	Control	Fixed-dose combination	HR (95% CI)	p value
Fixed-dose combination strategy versus control				
Randomised participants	9088	9074	..	..
Primary outcome	445 (4·9%)	276 (3·0%)	0·62 (0·53–0·73)	<0·0001
Cardiovascular death, myocardial infarction, stroke, revascularisation, or angina	545 (6·0%)	362 (4·0%)	0·67 (0·58–0·77)	<0·0001
Cardiovascular death, myocardial infarction, stroke, revascularisation, angina, or heart failure	563 (6·2%)	377 (4·2%)	0·68 (0·59–0·78)	<0·0001
Individual cardiovascular outcomes				
Cardiovascular death*	227 (2·5%)	144 (1·6%)	0·65 (0·52–0·81)	<0·0001
Myocardial infarction	139 (1·5%)	70 (0·8%)	0·52 (0·38–0·70)	<0·0001
Stroke†	141 (1·6%)	83 (0·9%)	0·59 (0·45–0·78)	0·0002
Haemorrhagic stroke	27 (0·3%)	19 (0·2%)	0·69 (0·38–1·24)	..
Other stroke	115 (1·3%)	65 (0·7%)	0·57 (0·42–0·78)	..
Revascularisation	70 (0·8%)	39 (0·4%)	0·54 (0·36–0·80)	0·0023
Heart failure	39 (0·4%)	29 (0·3%)	0·75 (0·46–1·23)	0·25
Angina	141 (1·6%)	109 (1·2%)	0·80 (0·61–1·05)	0·10
Non-cardiovascular death*	299 (3·3%)	327 (3·6%)	1·08 (0·91–1·28)	0·36
All deaths*	526 (5·8%)	471 (5·2%)	0·90 (0·79–1·03)	0·13
Fixed-dose combination strategy with aspirin versus control				
Randomised participants	4489	4462	..	..
Primary outcome	217 (4·8%)	115 (2·6%)	0·53 (0·41–0·67)	<0·0001
Cardiovascular death, myocardial infarction, stroke, revascularisation, or angina	294 (6·5%)	184 (4·1%)	0·63 (0·51–0·76)	<0·0001
Cardiovascular death, myocardial infarction, stroke, revascularisation, angina, or heart failure	301 (6·7%)	192 (4·3%)	0·64 (0·53–0·78)	<0·0001
Individual cardiovascular outcomes				
Cardiovascular death*	114 (2·5%)	58 (1·3%)	0·51 (0·37–0·72)	<0·0001
Myocardial infarction	89 (2·0%)	42 (0·9%)	0·47 (0·32–0·69)	0·0001
Stroke†	73 (1·6%)	36 (0·8%)	0·49 (0·32–0·73)	0·0005
Haemorrhagic stroke	15 (0·3%)	10 (0·2%)	0·63 (0·28–1·43)	..
Other stroke	58 (1·3%)	26 (0·6%)	0·45 (0·28–0·71)	..
Revascularisation	12 (0·3%)	5 (0·1%)	0·39 (0·13–1·12)	0·080
Heart failure	14 (0·3%)	14 (0·3%)	1·07 (0·49–2·30)	0·87
Angina	91 (2·0%)	73 (1·6%)	0·83 (0·59–1·17)	0·29
Non-cardiovascular death*	164 (3·7%)	176 (3·9%)	1·06 (0·84–1·35)	0·62
All deaths*	278 (6·2%)	234 (5·2%)	0·85 (0·70–1·03)	0·10

(Table 3 continues on next page)

	Control	Fixed-dose combination	HR (95% CI)	p value
(Continued from previous page)				
Fixed-dose combination strategy without aspirin versus control				
Randomised participants	6020	6041	..	..
Primary outcome	292 (4·9%)	202 (3·3%)	0·68 (0·57–0·81)	<0·0001
Cardiovascular death, myocardial infarction, stroke, revascularisation, or angina	318 (5·3%)	222 (3·7%)	0·69 (0·58–0·81)	<0·0001
Cardiovascular death, myocardial infarction, stroke, revascularisation, angina, or heart failure	330 (5·5%)	233 (3·9%)	0·69 (0·59–0·82)	<0·0001
Individual cardiovascular outcomes				
Cardiovascular death*	149 (2·5%)	110 (1·8%)	0·73 (0·57–0·93)	0·012
Myocardial infarction	64 (1·1%)	38 (0·6%)	0·59 (0·39–0·88)	0·0093
Stroke†	91 (1·5%)	57 (0·9%)	0·62 (0·44–0·86)	0·0046
Haemorrhagic stroke	19 (0·3)	9 (0·1%)	0·47 (0·21–1·04)	..
Other stroke	73 (1·2%)	49 (0·8%)	0·66 (0·46–0·95)	..
Revascularisation	70 (1·2%)	39 (0·6%)	0·55 (0·37–0·81)	0·0026
Heart failure	28 (0·5%)	22 (0·4%)	0·78 (0·44–1·36)	0·37
Angina	60 (1·0%)	42 (0·7%)	0·69 (0·47–1·03)	0·066
Non-cardiovascular death*	192 (3·2%)	202 (3·3%)	1·04 (0·85–1·27)	0·20
All deaths*	341 (5·7%)	312 (5·2%)	0·90 (0·78–1·05)	0·69

Data are n (%) unless otherwise indicated. The comparison of fixed-dose combination versus control included all participants randomly assigned to polypill or matching placebo in TIPS-3, all participants randomly assigned to polypill or control groups in PolyIran, and all participants randomly assigned to double active or double placebo in HOPE-3. The comparison of fixed-dose combination with aspirin versus control consisted of all participants randomly assigned to polypill plus aspirin or double placebo groups in TIPS-3, and all participants randomly assigned to polypill or control groups in PolyIran. The comparison of fixed-dose combination without aspirin versus control consisted of all participants randomly assigned to polypill or matching placebo in TIPS-3 (because aspirin did not interact with this treatment comparison), and all participants randomly assigned to double active or double placebo in HOPE-3. HR=hazard ratio. *Between 60% and 66% of deaths were due to non-cardiovascular causes (which is not expected to be affected by fixed-dose combination treatments), and the effect of fixed-dose combination treatment on total mortality in all comparisons was less than the proportional risk reduction observed on cardiovascular deaths, as expected. †Some participants reported both haemorrhagic and ischaemic strokes during the follow-up period.

Table 3: **Clinical outcomes with a fixed-dose combination strategy compared with control**

0·53–0·73, p<0·0001; figure 2, table 3). Treatment effects were consistent between trials (p value for interaction 0·16; appendix pp 12–14). The 5-year NNT to prevent the primary outcome was 52. The largest proportional reductions in individual cardiovascular events with a polypill strategy were observed for myocardial infarction (0·52, 0·38–0·70), revascularisation (0·54, 95% 0·36–0·80), and stroke (0·59, 0·45–0·78; figure 3, table 3). Cardiovascular death occurred in 144 (1·6%) participants in the fixed-dose combination strategy group compared with 227 (2·5%) participants in the control group (0·65, 0·52–0·81). Effects on expanded cardiovascular outcomes including angina and heart failure were consistent with the primary outcome (table 3). Effects on non-cardiovascular death were neutral, so the difference in total mortality was not statistically significant (0·90, 0·79–1·03).

In a sensitivity analysis in which participants in the PolyIran study were included only if they had undergone concealed allocation to the intervention or control groups, estimates were similar to our main analysis for the primary outcome (HR 0·63, 95% CI 0·53–0·73) and for secondary outcomes (appendix p 8). Deaths due to an unknown cause were similar between the active and control groups (52 *vs* 51) and therefore sensitivity analyses using the original trial definitions for cardiovascular deaths led to similar, but slightly smaller, effect sizes for the primary outcome (0·67, 0·58–0·78) and for cardiovascular death (0·74, 0·61–0·89; appendix p 9).

8951 participants were included in the analysis of a fixed-dose combination strategy with aspirin versus control. The primary outcome occurred in 115 (2·6%) participants in the treatment group and 217 (4·8%) participants in the control group (HR 0·53, 95% CI 0·41–0·67, p<0·0001; figure 2, table 3). The treatment effects were consistent between trials (p value for interaction 0·30; appendix p 12). 5-year NNT to prevent the primary outcome was 37. Large proportional risk reductions were also observed for myocardial infarction, stroke, and cardiovascular death (figure 3, table 3). Effects on extended cardiovascular outcomes were consistent with the primary outcome (table 3). There was no difference in non-cardiovascular deaths, so the difference in total mortality was not statistically significant.

12 061 participants were included in the analysis of a fixed-dose combination strategy without aspirin versus control. The primary outcome occurred in 202 (3·3%) in the fixed-dose combination group compared with 292 (4·9%) in the control group (HR 0·68, 95% CI 0·57–0·81, p<0·0001; figure 2, table 3). Treatment

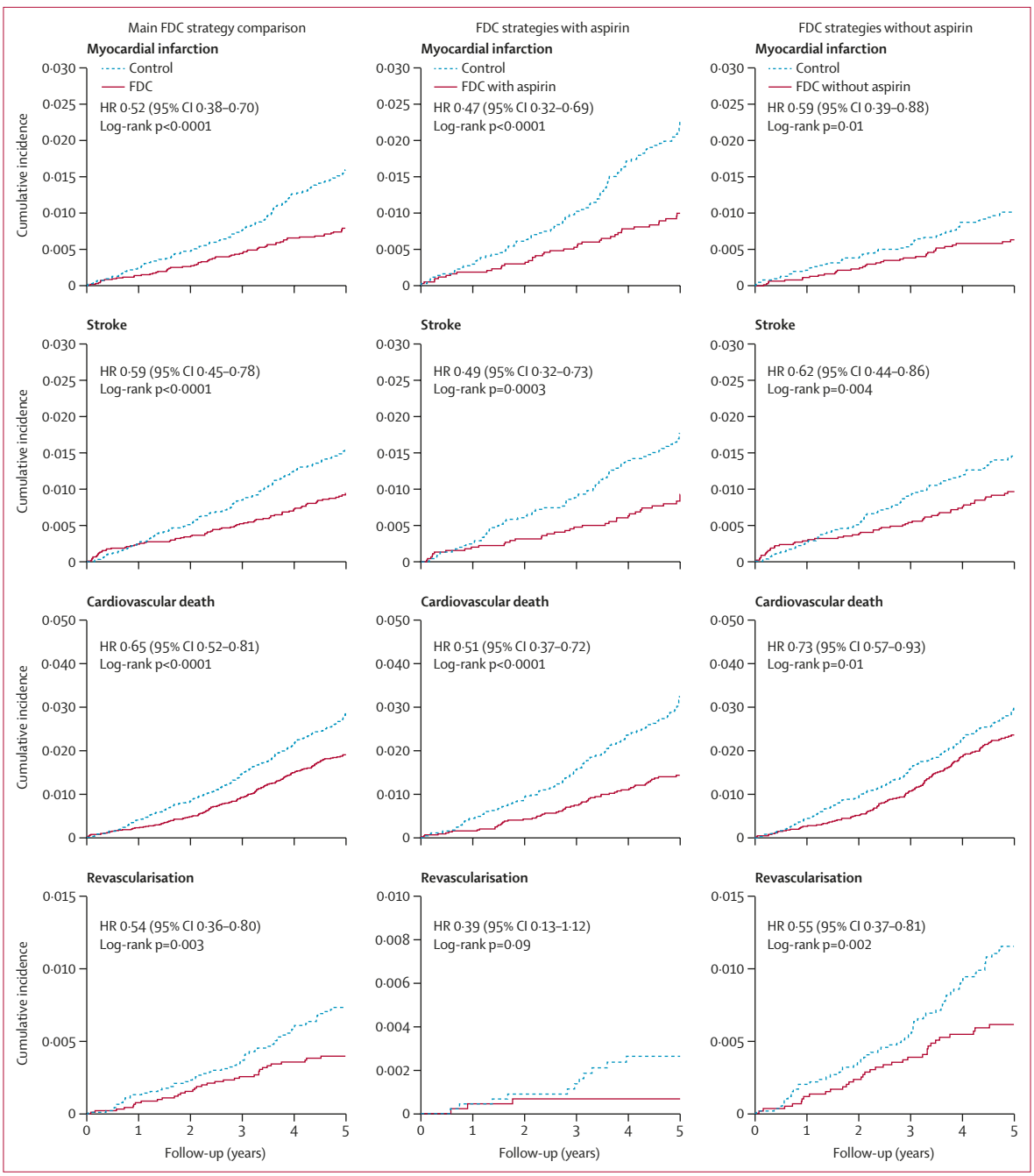


Figure 3: **Kaplan-Meier curves for components of the primary outcome**
Kaplan-Meier curves are presented up to 5 years. FDC=fixed-dose combination. HR=hazard ratio.

effects were consistent between trials (p value for interaction 0·80; appendix p 12). 5-year NNT to prevent the primary outcome was 66. Large proportional risk reductions were observed for myocardial infarction, stroke, and revascularisation (figure 3, table 3). Effects on extended cardiovascular outcomes were consistent with the primary outcome (table 3). Cardiovascular death was also reduced. There was no difference in non-cardiovascular deaths, so the difference in total mortality was not statistically significant.

For the main comparison of a fixed-dose combination strategy versus placebo, proportional risk reductions increased from 1 year after randomisation (HR 0·73, 95% CI 0·50–1·06) to more than 3 years after randomisation (0·58, 0·46–0·72; table 4). For the comparisons of fixed-dose combination strategies with

and without aspirin, proportional risk reductions also increased over time.

Treatment effects were similar in subgroups based on baseline systolic blood pressure, baseline LDL cholesterol, diabetes, BMI, smoking status, sex, and estimated 10-year cardiovascular risk (figure 4). Numerically larger reductions in the primary outcome were observed in older age groups compared with younger age groups, which reached a statistically significant trend in the comparison of fixed-dose combination strategies including aspirin (p value for trend 0·03), but not statistically significant trends observed in the other treatment comparisons.

Side-effects were reported more commonly in the PolyIran study than in HOPE-3 or TIPS-3, which was likely to be related to differences in study design (eg, run-in procedures) and approaches to data ascertainment (table 5; appendix pp 5, 10–11). Commonly reported side-effects in the cohort were muscle pain (7·8%), dizziness (10·4%), and dyspepsia (34·4%), of which only dizziness was reported more frequently in the fixed-dose combination strategy group compared with the control group (11·7% *vs* 9·2%, p<0·0001). Renal dysfunction (0·5%), haemorrhagic stroke (0·3%), fatal bleeding (0·1%), and peptic ulcer disease (0·7%) were infrequent, and were not significantly more common in the fixed-dose combination strategy group. The number of gastrointestinal bleeds was numerically higher with treatment compared with control (19 [0·4%] *vs* 11 [0·2%]) but this excess was not statistically significant (NNH of 554).

In the intervention group, 7354 (82·7%) of 8892 participants were on study medication at 2 years, and 6250 (72·1%) of 8670 were on study medication at the final visit. In the control group, 1737 (19·1%) of 9088 participants were on at least one blood pressure lowering medication at baseline, 2279 (25·7%) of 8878 at 2 years, and 2734 (31·6%) of 8644 at final study visit; 163 (1·8%) were on a lipid lowering agent at baseline, 403 (4·5%) at 2 years, and 750 (8·7%) at final study visit; and 478 (5·3%) were on an antiplatelet agent at baseline, 599 (6·8%) at 2 years, and 921 (10·7%) at final study visit. The modest contrasts between treatment and control groups in the use of blood pressure and lipid lowering drugs could explain the lower than expected differences in related risk factor levels between the treatment and control groups.

	Fixed-dose combination *vs* control	Fixed-dose combination with aspirin *vs* control	Fixed-dose combination without aspirin *vs* control
Randomisation to 1 year	0·73 (0·50–1·06)	0·68 (0·39–1·19)	0·74 (0·48–1·13)
1 year to 3 years	0·63 (0·48–0·81)	0·49 (0·33–0·72)	0·66 (0·48–0·89)
>3 years	0·58 (0·46–0·72)	0·51 (0·36–0·72)	0·68 (0·52–0·88)
Overall	0·62 (0·53–0·73)	0·53 (0·41–0·67)	0·68 (0·57–0·81)

Data are hazard ratios (95% CIs).

Table 4: **Effect of fixed-dose combination strategies on the primary outcome over time**

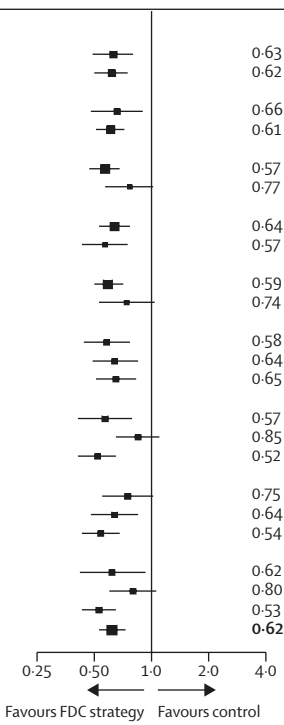
Discussion

To our knowledge, this meta-analysis using individual participant data provides the largest body of evidence from randomised trials to quantify the effects of a fixed-dose combination treatment strategy on major cardiovascular events in primary cardiovascular disease prevention to date. In our primary analysis, fixed-dose combination strategies resulted in a 38% proportional risk reduction for cardiovascular disease (5-year NNT of 52). Clear and large reductions in risk were observed for myocardial infarction (48% reduction), stroke (41%), and the need for revascularisation procedures (46%). Cardiovascular death was reduced by approximately one-third. The largest reductions in cardiovascular outcomes were observed for the comparison of fixed-dose combination treatment strategies that contained aspirin versus control, with approximately a halving in the risks of all cardiovascular disease events. The benefit of fixed-dose combination treatment started to become apparent within 1 year and was enhanced in subsequent periods. These reductions were observed in addition to lifestyle counselling and were observed despite modest differences in LDL cholesterol and blood pressure between treatment and control groups. This indicates that fixed-dose combination strategies can produce important and rapid reductions in both fatal and non-fatal cardiovascular events in those without previous cardiovascular disease.

The fixed-dose combination strategies tested varied in the types of blood pressure lowering agents used, type of statin used, and the inclusion of aspirin. Nevertheless, the observed treatment effects for the primary outcome were consistent across the included trials. The therapies used in our analysis resulted in relatively modest reductions in systolic blood pressure of 4·7 mm Hg and in LDL cholesterol of 22 mg/dL between treatment and control groups. These differences in systolic blood pressure and in LDL cholesterol were about half of what each trial had expected, and substantially less than the magnitude of difference expected based on previous trials with similar doses of blood pressure lowering drugs and statins.[4–6] Reasons for the lower than expected effects on risk factors could be related to the specific compositions tested, non-adherence to study medications, or open-label use of blood pressure lowering drugs. Despite these modest differences in risk factors, important reductions in cardiovascular disease were still observed. Previous statin and blood pressure lowering trials have shown that reductions in cardiovascular outcomes are directly proportional to the magnitude of LDL cholesterol and blood pressure reduction achieved.[4–6] Therefore, future fixed-dose combination formulations and better long-term adherence to these treatments would be likely to achieve larger and sustained reductions in blood pressure and LDL cholesterol, and

A

	Events/participants (%)		HR (95% CI)	p value for interaction or trend*
	FDC strategy	Control		
Sex				
Female	109/4553 (2·4%)	171/4485 (3·8%)	0·63 (0·49–0·80)	
Male	167/4521 (3·7%)	274/4603 (6·0%)	0·62 (0·50–0·75)	0·82
Hypertension				
No	69/3326 (2·1%)	105/3317 (3·2%)	0·66 (0·48–0·90)	
Yes	207/5748 (3·6%)	340/5771 (5·9%)	0·61 (0·51–0·72)	0·58
Diabetes				
No	189/7306 (2·6%)	333/7333 (4·5%)	0·57 (0·47–0·68)	
Yes	87/1768 (4·9%)	112/1755 (6·4%)	0·77 (0·57–1·02)	0·09
Smoking status				
Never smoked	197/6948 (2·8%)	308/6971 (4·4%)	0·64 (0·53–0·77)	
Ever smoked	79/2126 (3·7%)	137/2117 (6·5%)	0·57 (0·43–0·75)	0·46
BMI, kg/m²				
<30	211/7128 (3·0%)	359/7223 (5·0%)	0·59 (0·50–0·71)	
≥30	63/1933 (3·3%)	84/1858 (4·5%)	0·74 (0·53–1·04)	0·32
LDL cholesterol, mg/dL				
≤105	80/2994 (2·7%)	139/2942 (4·7%)	0·58 (0·44–0·77)	
>105 to 135	85/2838 (3·0%)	129/2805 (4·6%)	0·64 (0·49–0·85)	
>135	105/2869 (3·7%)	165/2963 (5·6%)	0·65 (0·51–0·83)	0·51
Systolic blood pressure, mm Hg				
≤130	65/3318 (2·0%)	113/3237 (3·5%)	0·57 (0·41–0·79)	
>130 to 144	100/2830 (3·5%)	121/2904 (4·2%)	0·85 (0·65–1·10)	
>144	111/2926 (3·8%)	211/2945 (7·2%)	0·52 (0·41–0·65)	0·35
Age, years				
≤60	78/3409 (2·3%)	106/3444 (3·1%)	0·75 (0·55–1·02)	
>60 to 66	82/2916 (2·8%)	125/2830 (4·4%)	0·64 (0·48–0·85)	
>66	116/2749 (4·2%)	214/2814 (7·6%)	0·54 (0·43–0·68)	0·06
Estimated 10-year CVD risk				
≤12%	43/2984 (1·4%)	67/2829 (2·4%)	0·62 (0·42–0·93)	
>12% to 22%	84/2914 (2·9%)	109/3032 (3·6%)	0·80 (0·60–1·06)	
>22%	135/3056 (4·4%)	258/3126 (8·3%)	0·53 (0·43–0·65)	0·11
Overall	**276/9074 (3·0%)**	**445/9088 (4·9%)**	**0·62 (0·53–0·73)**	



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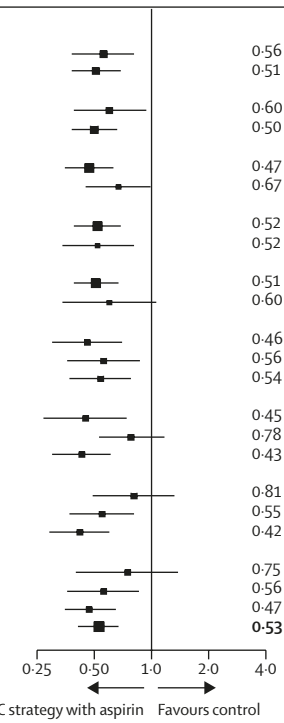
	Events/participants (%)		HR (95% CI)	p value for interaction or trend*
	FDC strategy with aspirin	Control		
Sex				
Female	45/2311 (1·9%)	79/2261 (3·5%)	0·56 (0·38–0·81)	
Male	70/2151 (3·3%)	138/2228 (6·2%)	0·51 (0·38–0·69)	0·71
Hypertension				
No	34/1841 (1·8%)	56/1841 (3·0%)	0·60 (0·39–0·94)	
Yes	81/2621 (3·1%)	161/2648 (6·1%)	0·50 (0·38–0·66)	0·43
Diabetes				
No	71/3545 (2·0%)	148/3503 (4·2%)	0·47 (0·35–0·63)	
Yes	44/917 (4·8%)	69/986 (7·0%)	0·67 (0·45–0·99)	0·16
Smoking status				
Never smoked	83/3576 (2·3%)	159/3629 (4·4%)	0·52 (0·39–0·69)	
Ever smoked	32/886 (3·6%)	58/860 (6·7%)	0·52 (0·34–0·81)	0·99
BMI, kg/m²				
<30	93/3522 (2·6%)	182/3583 (5·1%)	0·51 (0·39–0·67)	
≥30	21/938 (2·2%)	35/906 (3·9%)	0·60 (0·34–1·06)	0·75
LDL cholesterol, mg/dL				
≤101	34/1476 (2·3%)	73/1471 (5·0%)	0·46 (0·30–0·70)	
>101 to 135	32/1515 (2·1%)	54/1476 (3·7%)	0·56 (0·36–0·87)	
>135	45/1423 (3·2%)	87/1489 (5·8%)	0·54 (0·37–0·78)	0·60
Systolic blood pressure, mm Hg				
≤124	25/1573 (1·6%)	52/1458 (3·6%)	0·45 (0·27–0·74)	
>124 to 142	45/1501 (3·0%)	60/1580 (3·8%)	0·78 (0·53–1·17)	
>142	45/1388 (3·2%)	105/1451 (7·2%)	0·43 (0·30–0·61)	0·62
Age, years				
≤57	32/1714 (1·9%)	38/1654 (2·3%)	0·81 (0·49–1·32)	
>57 to 63	40/1372 (2·9%)	71/1375 (5·2%)	0·55 (0·37–0·81)	
>63	43/1376 (3·1%)	108/1460 (7·4%)	0·42 (0·29–0·60)	0·03
Estimated 10-year CVD risk				
≤9·6%	20/1546 (1·3%)	26/1426 (1·8%)	0·75 (0·40–1·38)	
>9·6% to 19·0%	32/1459 (2·2%)	58/1505 (3·9%)	0·56 (0·36–0·86)	
>19·0%	61/1445 (4·2%)	133/1551 (8·6%)	0·47 (0·35–0·65)	0·19
Overall	**115/4462 (2·6%)**	**217/4489 (4·8%)**	**0·53 (0·41–0·67)**	



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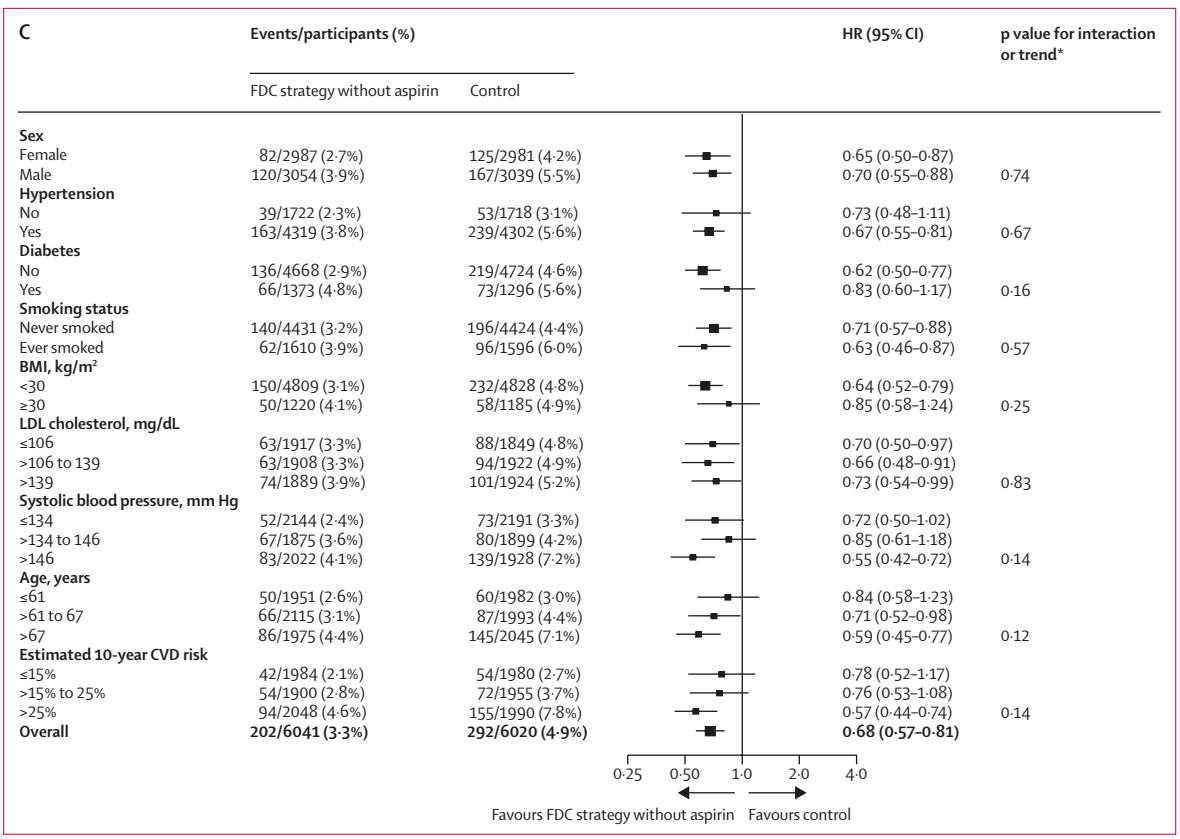

Figure 4: **Effect of FDC strategies versus control on the primary outcome in prespecified subgroups**
(A) Overall fixed-dose combination strategy versus control. (B) Fixed-dose combination strategy including aspirin versus control. (C) Fixed-dose combination strategy not including aspirin versus control. BMI=body-mass index. CVD=cardiovascular disease. FDC=fixed dose combination. *Differences in effect sizes between dichotomous subgroups were evaluated using tests for interaction, whereas continuous variables were grouped by tertile and evaluated using tests for trend.

so could be expected to reduce cardiovascular disease risk to an even larger extent than that observed in the current analysis.[4,6] Although some trials have called into question the use of aspirin in primary cardiovascular disease prevention, meta-analyses of primary prevention trials suggest that aspirin reduces the risk of vascular events by about 11%, myocardial infarction by 15%, and ischaemic stroke by 19%.[18] Even with the present modest reductions in LDL cholesterol and in blood pressure, trials that tested a fixed-dose combination strategy that included aspirin observed about a halving of cardiovascular disease events, with a 5-year NNT of 37 to prevent a cardiovascular death, myocardial infarction, stroke or revascularisation procedure. These benefits are substantial and suggest that the widespread use of such a treatment strategy (either delivered as a polypill or as separate drugs), can lead to important benefits for primary cardiovascular disease prevention.

Our meta-analysis also provides some guidance as to who would benefit most from a fixed-dose combination strategy. Based on the observed cardiovascular disease event rate in our control group, our findings would be most applicable to populations at intermediate or greater cardiovascular disease risk. Furthermore, effects

	Control	Fixed-dose combination strategy	p value
Effects potentially related to statin or blood pressure lowering medication			
Participants included in analysis	9088	9074	..
Muscle pain	787 (8·7%)	634 (7·0%)	<0·0001
Dizziness	834 (9·2%)	1060 (11·7%)	<0·0001
Death due to renal cause	7 (0·1%)	5 (0·1%)	0·77
Reported non-fatal renal failure or death due to renal cause	41 (0·5%)	44 (0·5%)	0·75
Effects potentially related to aspirin			
Participants included in analysis	4489	4462	..
Gastrointestinal bleed	11 (0·2%)	19 (0·4%)	0·15
Haemorrhagic stroke	15 (0·3%)	10 (0·2%)	0·42
Death due to bleeding	4 (0·1%)	2 (<0·1%)	0·69
Peptic ulcer disease	34 (0·8%)	32 (0·7%)	0·90
Dyspepsia	1589 (35·4%)	1489 (33·4%)	0·05

Data are n (%) unless otherwise indicated.

Table 5: **Side-effects and adverse events**

of fixed-dose combination treatment were similar in groups with or without elevated systolic blood pressure, hypertension, diabetes, or by LDL cholesterol level. This finding suggests broad applicability of a fixed-dose combination treatment strategy across a range of cardiometabolic risk factor profiles, rather than in a specific at-risk group. Of note, we observed that reductions in cardiovascular disease with a fixed-dose combination strategy tended to be larger with older age. This difference was statistically significant in the comparison of fixed-dose combination strategies that included aspirin, and directionally consistent (but not statistically significant) in the other comparisons. Therefore, fixed-dose combination treatment strategies could be of particular benefit in older populations, which has also been suggested previously.[10,19] However, given the nominal statistical significance on a test of trend between subgroups related to this finding, additional confirmation is needed.

Subjective symptoms such as dyspepsia, muscle pain, and dizziness differed in their frequency between trials, which was likely to be related to differences in study design and how symptoms were ascertained. Nevertheless, dizziness was consistently more common in the fixed-dose combination treatment group. We also observed that fatal bleeding and haemorrhagic stroke were uncommon in this population, and were not significantly higher with fixed-dose combination strategies. In the analysis of trials with aspirin as part of the fixed-dose combination, more gastrointestinal bleeds occurred with aspirin compared with control (19 [0·4%] *vs* 11 [0·2%]). Although this difference is not statistically significant, it is directionally consistent with the results of previous trials indicating an excess of gastrointestinal bleeds with aspirin. The aforementioned meta-analysis of aspirin studies in primary cardiovascular disease prevention[18] reported an NNT of 241 to prevent a cardiovascular event; compared with an NNH of 210 for a major bleeding event to occur, 334 for a major gastrointestinal bleeding event to occur, and 927 for an intracranial haemorrhage to occur. In this context, some excess in gastrointestinal bleeds might occur with the inclusion of aspirin in a fixed-dose combination, but the magnitude of this excess is likely to be small and unlikely to detract significantly from the potential benefits of the fixed-dose combination treatment.[18] The higher risk of haemorrhagic stroke reported with aspirin alone in previous studies would also be small in comparison with the potential reduction in both fatal and non-fatal cardiovascular disease events with a fixed-dose combination treatment strategy comprised of blood pressure lowering drugs, a statin, and aspirin. In our meta-analysis, a fixed-dose combination of statin, blood pressure lowering medications, and aspirin required an NNT of 37 to avoid a vascular event, compared with an NNH of 554 to cause one gastrointestinal bleed. Therefore, the balance of benefit compared with potential harm is in favour of the use of a fixed-dose combination strategy that includes aspirin.

Given that several generic blood pressure lowering drugs, statins, and aspirin are widely available, a fixed-dose combination strategy (used either as separate agents or as a single polypill) is feasible in most parts of the world. Several different polypill formulations are currently marketed in different countries and therefore polypills will become increasingly accessible.[20,21] Components of fixed-dose combination strategies are usually generic and available at low costs, so they are also likely to be cost effective.[22,23] Availability and affordability could be further increased through the inclusion of cardiovascular disease medications included in a fixed-dose combination strategy through programmes such as WHO prequalification programs (two-drug combinations of blood pressure lowering medications at fixed doses have already been added to the WHO Model List of Essential Medicines), as well as bulk pre-purchasing investments by governments.[24] Although fixed-dose combination treatment could be implemented using medications given separately, their combined use in a polypill would probably result in better adherence to this strategy.[12] A fixed-dose combination strategy should be used in conjunction with other individual-level and population-level so-called best buy strategies for cardiovascular disease prevention. These include policies to control tobacco, promote activity, and increase the consumption of healthy diets. An additional and complementary strategy is to improve access to cardiovascular disease prevention by using non-physician health-care workers to integrate community-based screening and treatment of cardiovascular disease risk factors into primary care. The value of such an approach was shown in the HOPE-4 trial, which was a community-based, cluster-randomised trial done in Colombia and Malaysia, where a health-care worker-led intervention (along with support from family and friends) that included use of cardiovascular disease medications lowered blood pressure, lipids, and estimated cardiovascular disease risk by about half.[25] Integrating a fixed-dose combination strategy as part of comprehensive community-level initiatives could be an effective method to rapidly reduce cardiovascular disease risk at the population level, and warrants further study. Given the large reductions in cardiovascular disease risk we have observed with fixed-dose combination treatments, their integration into primary prevention could be an effective method in many populations to help achieve the UN Sustainable Development Goals of reducing premature mortality from non-communicable disease by one-third by 2030, and to avoid several tens of millions of cardiovascular disease events and related cardiovascular deaths over the next decade.[26]

Some limitations of our analysis warrant consideration. The included trials differed with respect to the methods used to measure baseline clinical variables (eg, LDL cholesterol, blood pressure, and self-reported factors) and

to define clinical outcomes, although the same methods were used in the active and control groups within each study. These variations do not materially affect our conclusions, because fixed-dose combination treatment had similar effects on cardiovascular disease risk irrespective of the levels of these risk factors. Furthermore, in all trials, the component events included in our primary outcome, as well as deaths, underwent adjudication, and the results remained consistent after sensitivity analyses accounting for methodological differences between studies. Compared with cardiovascular events, adverse events were collected using different definitions in the various studies, and dates of events were not routinely available, thereby limiting our ability to conduct time-to-event analyses for adverse events. In two of the trials, patients also underwent a run-in period before randomisation, which might have diminished any potential excess rates of adverse events. Furthermore, in some countries, participants might have interacted with health practitioners less frequently, and therefore some events, such as gastrointestinal bleeding, might have been identified only in more severe cases. In this context, gastrointestinal bleeding not requiring hospitalisation or intervention might have been underreported. However, unreported gastrointestinal bleeding would be likely to have been less severe, and fatal bleeding and haemorrhagic stroke were clearly and consistently defined across all three trials as part of adjudication processes. Finally, the larger benefits observed with fixed-dose combination strategies that included aspirin are based in part on indirect comparisons with groups that did not include aspirin. However, this is consistent with direct observations from TIPS-3 alone, which, in a 2×2 factorial design, observed incremental benefits of a polypill with aspirin regimen compared with a polypill regimen alone. and trials of aspirin in primary prevention that report an 11% relative risk reduction in cardiovascular disease.[13] These collective data support our findings that aspirin adds moderately to the benefits of lipid and blood pressure lowering.

In conclusion, fixed-dose combination treatment strategies reduce cardiovascular disease substantially in populations without vascular disease. The largest reductions in cardiovascular disease risk are observed for formulations that combine blood pressure lowering medications, a statin, and aspirin. Implementation of such treatment strategies should be considered in primary cardiovascular disease prevention.

Contributors

PJ did the literature search. SY, PJ, RM, GR, and SIB were responsible for conceptualisation. PJ, SY, RM, GR, LL, AA, JB, KS, HG, PP, DX, AD, PL-J, LL, JZ, RD, GRD, and EL were responsible for data curation. PG did the formal statistical analysis. SY acquired the funding. SY, PJ, RM, GR, and SIB were responsible for developing the study methodology. PJ and SY wrote the original draft. SY, PJ, RM, GR, EL, JB, KS, HG, PP, DX, AD, PL-J, KT, PG, SIB, JMC, VF, MDH, AR, DP, LL, JZ, AA, GRD, and RD edited and reviewed the manuscript. PJ, SY, and PG verified the underlying data. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Declaration of interests

SY reports grants from the Canadian Institutes of Health Research, Wellcome Trust, AstraZeneca, and Cadila Pharmaceuticals related to conducting the HOPE-3 or TIPS-3 studies. PJ, PG, EL, SIB, KT and JB report institutional grants from the Wellcome Trust, Canadian Institutes of Health Research, Heart and Stroke Foundation of Ontario, Cadila Pharmaceuticals, and AstraZeneca related to the TIPS-3 or HOPE-3 studies (or both). RM and GR report institutional grant funding from Tehran University of Medical Sciences, Barakat Foundation, and Alborz Darou related to the PolyIran study. SY reports receiving honoraria and reimbursement for travel expenses from AstraZeneca, Bayer, Boehringer Ingelheim, and Ferrer. EL reports consulting fees from Amgen Canada, consulting fees and speaker honoraria from HLS Canada, institutional research grant from Boehringer Ingelheim, and consulting fees from Novo-nordisk. MDH reports grants from the World Heart Federation via unrestricted educational grants from Boehringer Ingelheim and Novartis, grants from the American Heart Association, Verily, AstraZeneca, and personal fees from the American Medical Association outside the submitted work. In addition, MDH has a patent pending for heart failure polypills. PP reports funding from St John's Research Institute, Bangalore, India, during the conduct of the study. AR reports that George Health Enterprises, the social enterprise arm of The George Institute for Global Health, has received investment to develop fixed-dose combination products containing aspirin, statin and blood pressure lowering drugs. George Health Enterprises has submitted patents for low-dose blood pressure combinations, on which AR is listed as one of the inventors. AR is seconded part-time to George Medicines. All staff employed by The George Institute have an institutional interest to declare with respect to George Health Enterprises, although none of the staff have a direct financial interest in these investments. DX reports grants from AstraZeneca, Boehringer Ingelheim, Bristol Myers Squibb, Coca-Cola India, Eli Lilly, the Indian Council of Medical Research, Pfizer, Sanofi, UK Medical Research Council, and Wellcome Trust, outside the submitted work. JB reports personal fees from Bayer, outside the submitted work. RD reports grants from Amarin, DalCor, and the Population Health Research Institute, outside the submitted work. VF and JMC report grants from H2020 related to the ongoing SECURE trial. JMC reports receiving honoraria and reimbursement for travel expenses from Ferrer, Pfizer, and Bayer. AA reports grants from Bayer, EMS Pharma, and the Population Health Research Institute; and consulting fees from Bayer, Eli Lilly, NovoNordisk, and EMS Pharma outside the submitted work. All other authors declare no competing interests.

Data sharing

Individual participant data will not be made available.

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