Fixed Dose Combination Therapies with and without Aspirin in Primary CVD Prevention

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On behalf of the Polypill Trialists' Collaboration

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Introduction

- About 80% of cardiovascular disease (CVD) events occur in individuals without prior vascular disease.
  - Therefore, strategies that avoid a high proportion of ***first*** CVD events (i.e. primary prevention) are ***critical*** to reducing global CVD burden

- Fixed-dose combination (FDC) treatment: 2+ blood pressure (BP) lowering medications, a statin +/- aspirin
  - Termed ‘polypills’ when in a single formulation

- FDC treatments could ***substantially*** reduce CVD risk but more data needed to quantify efficacy

Study Objectives:

Individual participant data meta-analysis of long-term randomized controlled trials ***(RCTs) (>1000 participants, > 2 years follow-up***) testing FDC strategies

Primary objective:

- Effect of FDC treatment vs. control on the composite of CV death, myocardial infarction (MI), stroke or revascularization

Secondary objectives:

- Impact of FDC treatments with or without aspirin
- Impact on individual CV outcomes
- Effects in key subgroups based on demographic and CV risk factors

RCTs of FDC in Primary Prevention

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TIPS-3	HOPE-3	PolyIran
Double-blind RCT, intermediate CVD risk (N=5,713) **Interventions:** - Polypill: Ramipril 10 mg, atenolol 100 mg, HCTZ 25 mg, simvastatin 40 mg - Aspirin 75 mg **Included in meta-analysis:** All (N=5,713)	Double-blind RCT, intermediate CVD risk (N=12,705) **Interventions:** - Candesartan/HCTZ 16/12.5 mg - Rosuvastatin 10 mg **Included in meta-analysis:** Double active vs double placebo (polypill concept) (N=6,348)	Pragmatic, **cluster** RCT (N=6,838) **Intervention:** -Polypill: HCTZ 12.5 mg, enalapril 5 mg (or valsartan 40 mg), atorvastatin 20 mg, aspirin 81 mg **Included in meta-analysis:** Participants without CVD (N=6,101)

Statistical Considerations

- Cox proportional hazard models to estimate hazard ratios (HRs) for each outcome
  - Shared frailty model used with community or center modelled as random effect

- **<u>Pre-specified comparisons:</u>**
  - Main comparison of FDC vs. matching control: All trials
  - FDC with aspirin vs. matching control: TIPS-3 subset + PolyIran
  - FDC without aspirin vs. matching control: TIPS-3 + HOPE-3

Baseline Characteristics by Study

	Overall	TIPS-3	HOPE-3	PolyIran
	N=18162	**N=5713**	**N=6348**	**N= 6101**
Age (years)	**63.0**	63.9	65.7	59.3
Female (%)	**49.8**	52.9	46.4	50.3
Diabetes (%)	**19.4**	36.7	9.0	14.0
Hypertension (%)	**63.4**	83.8	60.3	47.5
Smoking history (%)	**23.4**	25.0	28.0	17.0
Mean BMI (kg/m2)	**26.5**	25.8	27.1	26.5
BP (mmHg)				
Systolic	**137.7**	144.5	138.1	130.8
Diastolic	**81.5**	83.9	81.9	78.7
Mean LDL-C – (mg/dl)	**121.7**	120.7	127.4	117.1
Est 10 year CVD risk (%)	**17.7**	19.9	19.9	13.5

FDC vs Control: Risk Factor Changes

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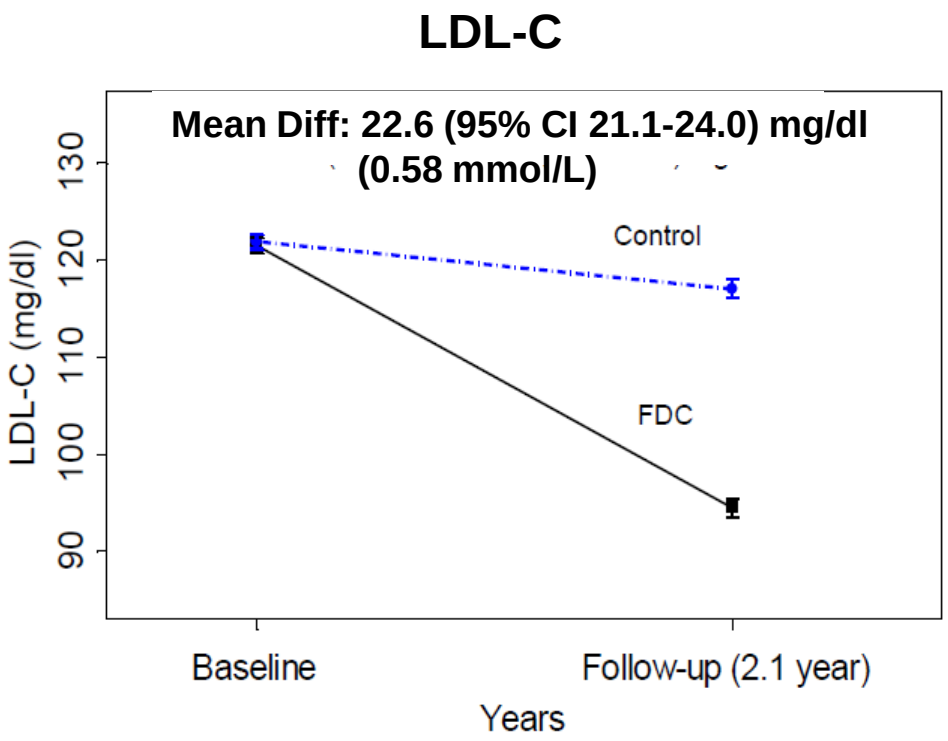
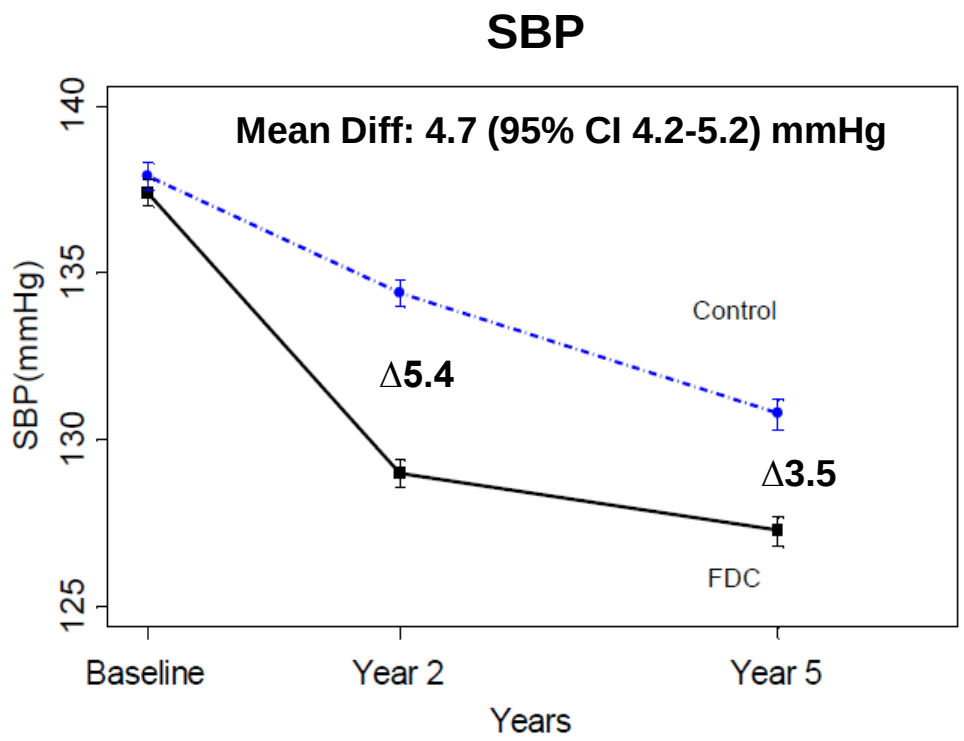
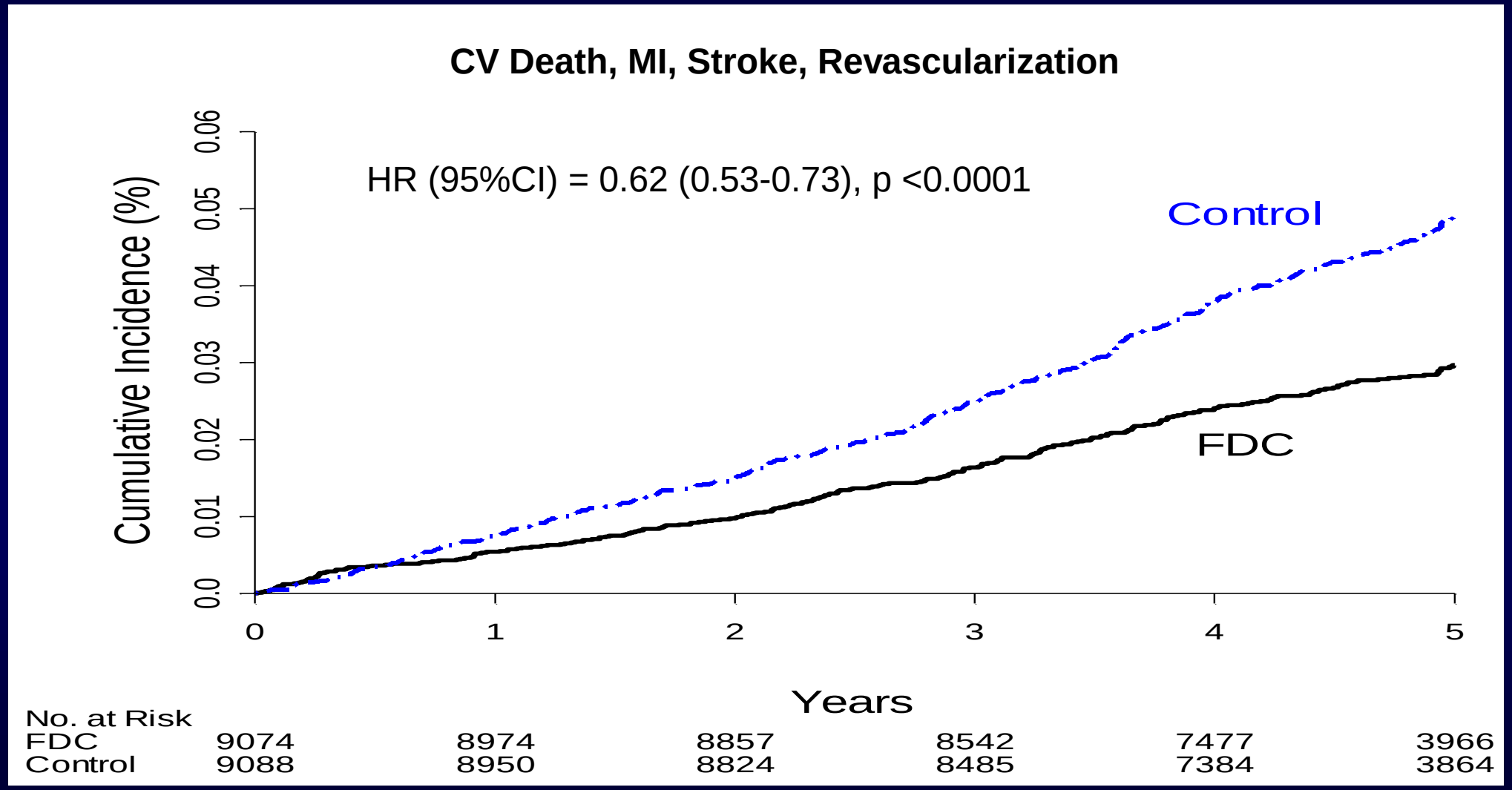




FDC versus Control: Primary Outcome



Mean FU = 5 years, 721 primary outcome events

FDC vs. Control: Clinical Outcomes

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	Control N (%)	FDC N (%)	HR (95%CI)	p-value
Primary Outcome	445 (4.9)	276 (3.0)	0.62 (0.53-0.73)	<0.0001
CV Death	227 (2.5)	144 (1.6)	0.65 (0.52-0.81)	<0.0001
MI	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
Revascularization	70 (0.8)	39 (0.4)	0.54 (0.36-0.80)	0.002
Non-CV Death	299 (3.3)	327 (3.6)	1.08 (0.91-1.28)	
All Cause Death	526 (5.8)	471 (5.2)	0.90 (0.79-1.03)	

FDC w/ Aspirin vs. Control: Clinical Outcomes

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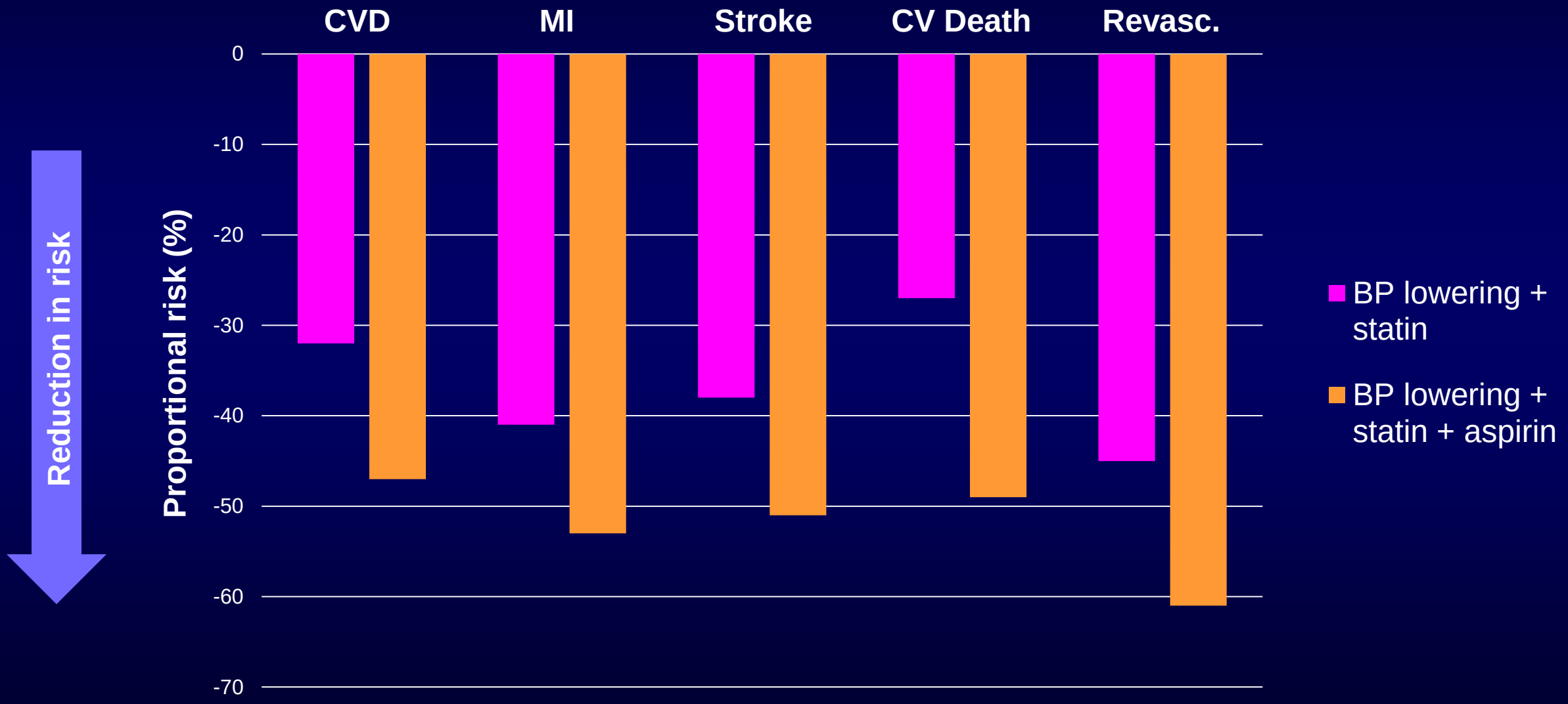
	Control N (%)	FDC N (%)	HR (95%CI)	p-value
Primary Outcome	217 (4.8)	115 (2.6)	0.53 (0·41-0·67)	<0.0001
CV Death	114 (2.5)	58 (1.3)	0.51 (0.37-0.72)	<0.0001
MI	89 (2.0)	42 (0.9)	0.47 (0.32-0.69)	0.0001
Stroke	73 (1.6)	36 (0.8)	0.49 (0.32-0.73)	0.0005
Revascularization	12 (0.3)	5 (0.1)	0.39 (0.13-1.12)	0.08
Non-CV Death	164 (3.7)	176 (3.9)	1.06 (0.84-1.35)	
All Cause Death	278 (6.2)	234 (5.2)	0.85 (0.70-1.03)	

FDC w/o Aspirin vs. Control: Clinical Outcomes

	Control N (%)	FDC N (%)	HR (95%CI)	p-value
Primary Outcome	292 (4.9)	202 (3.3)	0.68 (0.57-0.81)	<0.0001
CV Death	149 (2.5)	110 (1.8)	0.73 (0.57-0.93)	0.01
MI	64 (1.1)	38 (0.6)	0.59 (0.39-0.88)	0.009
Stroke	91 (1.5)	57 (0.9)	0.62 (0.44-0.86)	0.005
Revascularization	70 (1.2)	39 (0.6)	0.55 (0.37-0.81)	0.003
Non CV Death	192 (3.2)	202 (3.3)	1.04 (0.85-1.27)	
All Cause Death	341 (5.7)	312 (5.2)	0·90 (0.78-1.05)	

Comparative Impact of FDC +/- Aspirin



FDC vs. Control: Subgroups

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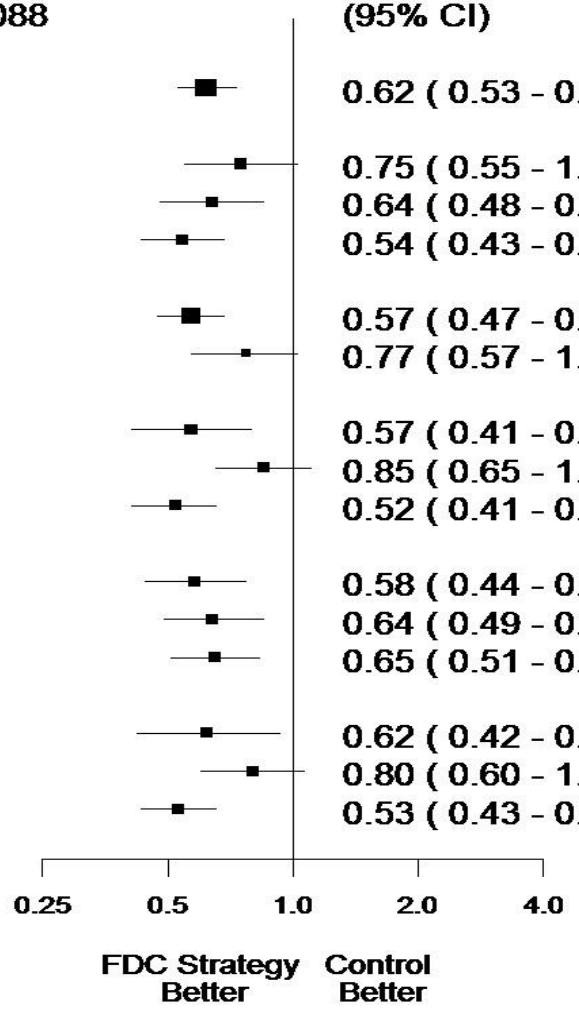
CV Death/MI/Stroke/Revascularization

	FDC Strategy N = 9074 (%)	Control N = 9088 (%)	Hazard Ratio (95% CI)	P* for interaction or trend
Overall	3.0	4.9	0.62 (0.53 - 0.73)	
Age<=60 yrs	2.3	3.1	0.75 (0.55 - 1.02)	
60<Age<=66 yrs	2.8	4.4	0.64 (0.48 - 0.85)	
Age>66 yrs	4.2	7.6	0.54 (0.43 - 0.68)	0.06
No DM	2.6	4.5	0.57 (0.47 - 0.68)	
DM	4.9	6.4	0.77 (0.57 - 1.02)	0.09
SBP<=130 mmHg	2.0	3.5	0.57 (0.41 - 0.79)	
130<SBP<=144 mmHg	3.5	4.2	0.85 (0.65 - 1.10)	
SBP>144 mmHg	3.8	7.2	0.52 (0.41 - 0.65)	0.35
LDL<=105 mg/dl	2.7	4.7	0.58 (0.44 - 0.77)	
105<LDL<=135 mg/dl	3.0	4.6	0.64 (0.49 - 0.85)	
LDL>135 mg/dl	3.7	5.6	0.65 (0.51 - 0.83)	0.51
EST. 10-yr CVD risk <=12%	1.4	2.4	0.62 (0.42 - 0.93)	
EST. 10-yr CVD risk 12-22%	2.9	3.6	0.80 (0.60 - 1.06)	
EST. 10-yr CVD risk >22%	4.4	8.3	0.53 (0.43 - 0.65)	0.11



*P-value for interaction for dichotomous groups, and for trend for continuous variables

FDC w/ Aspirin vs. Control: Subgroups

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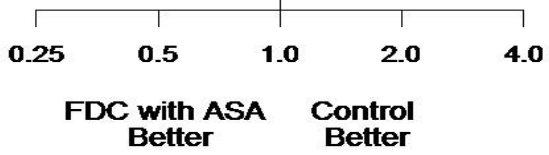
CV Death/MI/Stroke/Revascularization

	FDC with ASA N = 4462 (%)	Control N =4489 (%)	Hazard Ratio (95% CI)	P* for interaction or trend
Overall	2.6	4.8	0.53 (0.41 - 0.67)	
Age<=57 yrs	1.9	2.3	0.81 (0.49 - 1.32)	
57<Age<=63 yrs	2.9	5.2	0.55 (0.37 - 0.81)	
Age>63 yrs	3.1	7.4	0.42 (0.29 - 0.60)	0.03
No DM	2.0	4.2	0.47 (0.35 - 0.63)	
DM	4.8	7.0	0.67 (0.45 - 0.99)	0.16
SBP<=124 mmHg	1.6	3.6	0.45 (0.27 - 0.74)	
124<SBP<=142 mmHg	3.0	3.8	0.78 (0.53 - 1.17)	
SBP>142 mmHg	3.2	7.2	0.43 (0.30 - 0.61)	0.62
LDL<=101 mg/dl	2.3	5.0	0.46 (0.30 - 0.70)	
101<LDL<=131 mg/dl	2.1	3.7	0.56 (0.36 - 0.87)	
LDL>131 mg/dl	3.2	5.8	0.54 (0.37 - 0.78)	0.60
EST. 10-yr CVD risk <=9.6%	1.3	1.8	0.75 (0.40 - 1.38)	
EST. 10-yr CVD risk 9.6-19%	2.2	3.9	0.56 (0.36 - 0.86)	
EST. 10-yr CVD risk >19%	4.2	8.6	0.47 (0.35 - 0.65)	0.19



*P-value for interaction for dichotomous groups, and for trend for continuous variables

FDC w/o Aspirin vs. Control: Subgroups

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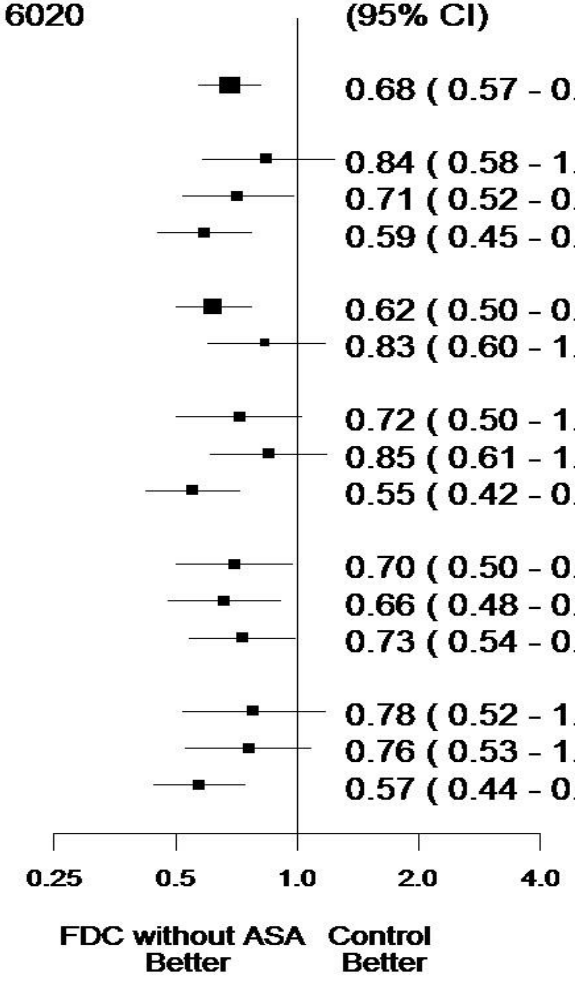
CV Death/MI/Stroke/Revascularization

	FDC without ASA N = 6041 (%)	Control N = 6020 (%)	Hazard Ratio (95% CI)	P* for interaction or trend
Overall	3.3	4.9	0.68 (0.57 - 0.81)	
Age<=61 yrs	2.6	3.0	0.84 (0.58 - 1.23)	
61<Age<=67 yrs	3.1	4.4	0.71 (0.52 - 0.98)	
Age>67 yrs	4.4	7.1	0.59 (0.45 - 0.77)	0.12
No DM	2.9	4.6	0.62 (0.50 - 0.77)	
DM	4.8	5.6	0.83 (0.60 - 1.17)	0.16
SBP<=134 mmHg	2.4	3.3	0.72 (0.50 - 1.02)	
134<SBP<=146 mmHg	3.6	4.2	0.85 (0.61 - 1.18)	
SBP>146 mmHg	4.1	7.2	0.55 (0.42 - 0.72)	0.14
LDL<=106 mg/dl	3.3	4.8	0.70 (0.50 - 0.97)	
106<LDL<=139 mg/dl	3.3	4.9	0.66 (0.48 - 0.91)	
LDL>139 mg/dl	3.9	5.2	0.73 (0.54 - 0.99)	0.83
EST. 10-yr CVD risk <=15%	2.1	2.7	0.78 (0.52 - 1.17)	
EST. 10-yr CVD risk 15-25%	2.8	3.7	0.76 (0.53 - 1.08)	
EST. 10-yr CVD risk >25%	4.6	7.8	0.57 (0.44 - 0.74)	0.14



*P-value for interaction for dichotomous groups, and for trend for continuous variables

Side Effects and Adverse Events

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	Control N (%)	FDC N (%)	P-value
Potentially related to statin/BP lowering			
Muscle Pain	787 (8.7)	634 (7.0)	<0.0001
Dizziness	834 (9.2)	1060 (11.7)	<0.0001
Renal failure	41 (0.5)	44 (0.5)	0.75
Potentially related to aspirin			
Hemorrhagic stroke	15 (0.3)	10 (0.2)	0.42
Fatal bleeding	4 (0.1)	2 (0.0)	0.69
GI bleed	11 (0.2)	19 (0.4)	0.15
Peptic ulcer	34 (0.8)	32 (0.7)	0.90

Conclusions: FDC in primary prevention

- Despite modest differences in BP and LDL-C between randomized groups, FDC treatments ***substantially*** reduced fatal and non-fatal CVD events:
  - **CVD ↓38% (NNT=52),** MI ↓48%, Stroke ↓42%, CV death ↓35%
- Larger effects with FDCs that include aspirin
  - **CVD ↓47% (NNT = 37),** MI ↓53%, Stroke ↓51%, CV death ↓49%
- Benefits consistent at different metabolic risk factor levels
- Benefits appear larger in older populations
- Safe and well tolerated, NNH = 554 to prevent one GI bleed.

Clinical and Public Health Implications

- FDC treatments are a widely applicable, low cost approach that will ***substantially*** reduce CVD in the population
  - Trials included participants from HICs, MICs, and LICs: results globally applicable
  - Avoids 5 - 10 million CVD events each year
  - Can assist achieving U.N. SDG goal to reduce premature deaths from NCDs by 1/3 by 2030

FDC treatment should be a key strategy in primary CVD prevention