Table S6. Study treatment used in the polypill arm (N=1237)

	No. patients (%)
Polypill	
Ramipril 10mg - Atorvastatin 40mg - ASA 100mg	229 (18.5)
Ramipril 5mg - Atorvastatin 40mg - ASA 100mg	400 (32.3)
Ramipril 2.5mg - Atorvastatin 40mg - ASA 100mg	506 (40.9)
Ramipril 10mg - Atorvastatin 20mg - ASA 100mg	22 (1.8)
Ramipril 5mg - Atorvastatin 20mg - ASA 100mg	31 (2.5)
Ramipril 2.5mg - Atorvastatin 20mg - ASA 100mg	49 (4.0)

Table S7. Lipid lowering treatment in the usual care arm (N=1229)

	No. patients (%)
High-intensity statin therapy	1020 (83.0)
Atorvastatin 40mg	520 (42.3)
Atorvastatin 80mg	446 (36.3)
Rosuvastatin 20-40mg	51 (4.1)
Moderate-intensity statin therapy	167 (13.6)
Atorvastatin 10-20mg	99 (8.1)
Rosuvastatin 5-10mg	15 (1.2)
Simvastatin 20-40mg	47 (3.8)
Pravastatin 40-80mg	3 (0.2)
Lovastatin 40mg	2 (0.2)
Pitavastatin 2-4mg	1 (0.1)
Low-intensity statin therapy	4 (0.3)
Pravastatin 10-20mg	1 (0.1)
Lovastatin 20mg	1 (0.1)
Fluvastatin 20-40mg	2 (0.2)
No statin	38 (3.0)

Table S8. ACE inhibitor treatment in the usual care arm (N=1229)

ACE inhibitor	No. patients
Ramipiril	**819**
2.5mg	4457
5mg	282
10mg	79
Enalapril	**121**
2.5mg	32
5mg	42
10mg	25
20/30mg	22
Perindopril	**80**
≤2mg	5
>2 and ≤4mg	18
>4 and ≤8mg	45
10mg	12
Lisinopril	**28**
2.5mg	7
5mg	10
10mg	3
20mg	8
Other	**52**
Unknown	**129**

ACE- angiotensin converting enzyme

Table S9. Concomitant medication in both groups.

	Polypill (n=1237)	Usual care (n=1229)
Non-aspirin antiplatelet agent	1163 (94.0)	1172 (95.4)
Beta-blocker	1014 (82.0)	1037 (84.4)
Calcium channel blocker	229 (18.5)	252 (20.5)
Diuretic	385 (31.1)	419 (34.1)
Nitrate	119 (9.6)	148 (12.0)
Ezetimibe	97 (7.8)	98 (8.0)

Table S10. Distribution of the number of cardiovascular therapies per patient at baseline by treatment arm

No. cardiovascular therapies	Polypill (n=1237)	Usual care (n=1229)
Mean (standard deviation)	3.4 (0.9)	5.4 (0.9)
Median (interquartile range)	3 (3-4)	5 (5-6)

Table S11. Treatment satisfaction at 6 and 24 months

	Polypill (n=1237)		Usual care (n=1229)			
	N	Mean (SD)	N	Mean (SD)	Mean difference (95% CI)[1]	
Patient satisfaction at 6 months						
Effectiveness score	845	72.26 (17.85)	819	69.17 (17.57)	3.09 (1.38, 4.79)	
Side effects score	64	61.52 (23.18)	89	66.71 (23.38)	-5.19 (-12.73, 2.35)	
Convenience score	845	76.56 (14.78)	817	69.47 (16.87)	7.09 (5.57, 8.62)	
Global satisfaction score	847	71.50 (18.06)	818	67.71 (18.53)	3.79 (2.04, 5.55)	
Patient satisfaction at 24 months						
Effectiveness score	879	74.06 (17.86)	847	68.79 (17.65)	5.26 (3.59, 6.94)	
Side effects score	47	68.75 (24.83)	70	64.20 (23.14)	4.55 (-4.35, 13.46)	
Convenience score	879	77.30 (15.95)	849	70.19 (17.06)	7.11 (5.55, 8.67)	
Global satisfaction score	877	74.36 (17.52)	850	67.76 (17.87)	6.60 (4.93, 8.27)	

TSQM – Treatment satisfaction questionnaire for medication
https://www.iqvia.com/landing/treatment-satisfaction-questionnaire-for-medication-tsqm
Scores range from 0 to 100; higher scores indicate greater satisfaction.
There was no prespecified plan to adjust for multiple testing. Secondary outcomes are reported with 95% confidence intervals, without p values. The 95% CI and 95% CI are not adjusted for multiple testing and should not be used to infer definitive treatment effects.

Table S12. Causes of Death.

Cause of death	Polypill	Usual care
Cardiovascular death		
Cardiovascular death	48	71
Non-cardiovascular death		
Cancer	23	14
COVID	8	9
Respiratory insufficiency	4	4
Septic shock	3	2
Accident	2	2
Bleeding	3	0
Multiorgan failure	3	0
Pneumonia	0	2
General deterioration	0	2
Cachexia and severe anemia	0	1
Acidosis	0	1
Autoimmune disease	1	0
Cholecystitis	1	0
Hyponatremia	1	0
Neurologic death	0	1
Renal insufficiency	0	1
Syncope	1	0
Undetermined	17	7
Total	67	46

Table S13. Primary and key secondary outcomes in the per-protocol population

	Polypill (n=1228)		Usual Care (n=1222)		HR (95% CI)	P
	N	%	N	%		
Primary outcome (at 24 months	117	9.5	155	12.7	0.76 (0.60, 0.96)	Non-inferiority p<0.001
						Superiority p=0.02
Components of primary outcome (at 24 months)						
CV death	47	3.8	71	5.8	0.66 (0.46, 0.95)	
Type 1 MI	44	3.6	61	5.0	0.73 (0.49, 1.07)	
Ischemic stroke	19	1.5	27	2.2	0.70 (0.39, 1.27)	
Urgent revascularization	27	2.2	28	2.3	0.96 (0.57, 1.63)	
Key secondary outcome (at 24 months)						
Composite of CV death, type 1 MI or ischemic stroke	100	8.1	143	11.7	0.70 (0.54, 0.90)	
Safety (at 24 months)						
All-cause mortality	114	9.3	117	9.6	0.96 (0.74, 1.24)	
Non-CV mortality	67	5.5	46	3.8	1.42 (0.97, 2.07)	

CV- Cardiovascular; MI- myocardial infarction

There was no prespecified plan to adjust for multiple testing. Secondary outcomes are reported with 95% confidence intervals, without p values. The 95% CI and 95% CI are not adjusted for multiple testing and should not be used to infer definitive treatment effects.

Table S14. Sensitivity analysis of the primary and key secondary outcomes adjusting for age ≥ 75 years, sex, diabetes, chronic kidney disease and prior vascular event

	Polypill (n=1237)		Usual Care (n=1229)		Adjusted HR (95% CI)	P
	N	%	N	%		
Primary outcome (at 24 months)	118	9.5	156	12.7	0.78 (0.61, 0.99)	Non-inferiority p<0.001
						Superiority p=0.04
Key secondary outcome (at 24 months)						
Composite of CV death, Type 1 MI or ischemic stroke	101	8.2	144	11.7	0.71 (0.55, 0.92)	
Components of primary outcome (at 24 months)						
CV death	48	3.9	71	5.8	0.68 (0.47, 0.98)	
Type 1 MI	44	3.6	62	5.0	0.74 (0.50, 1.09)	
Ischemic stroke	19	1.5	27	2.2	0.70 (0.39, 1.26)	
Urgent revascularization	27	2.2	28	2.3	0.99 (0.58, 1.69)	
Safety (at 24 months)						
All-cause mortality	115	9.3	117	9.5	0.97 (0.75, 1.26)	
Non-CV mortality	67	5.4	46	3.7	1.44 (0.98, 2.10)	

CV- Cardiovascular; MI- myocardial infarction

There was no prespecified plan to adjust for multiple testing. Secondary outcomes are reported with 95% confidence intervals, without p values. The 95% CI and 95% CI are not adjusted for multiple testing

and should not be used to infer definitive treatment effects.

Table S15. Randomization stratification by center for the primary and key secondary analyses.

	Polypill (n=1258)		Usual Care (n=1241)		HR (95% CI)	P
	N	%	N	%		
Primary outcome	118	9.5	156	12.7	0.76 (0.60, 0.97)	Non-inferiority p<0.001
						Superiority p=0.03
Key secondary outcome						
Composite of CV death, type 1 MI or ischemic stroke	101	8.2	144	11.7	0.70 (0.54, 0.90)	
Components of primary outcome						
CV death	48	3.9	71	5.8	0.66 (0.46, 0.96)	
Type 1 MI	44	3.6	62	5.0	0.73 (0.50, 1.08)	
Ischemic stroke	19	1.5	27	2.2	0.70 (0.39, 1.27)	
Urgent revascularization	27	2.2	28	2.3	0.97 (0.57, 1.66)	
Safety						
All-cause death	115	9.3	117	9.5	0.95 (0.73, 1.23)	
Non-CV death	67	5.4	46	3.7	1.40 (0.96, 2.05)	

CV- Cardiovascular; MI- myocardial infarction

There was no prespecified plan to adjust for multiple testing. Secondary outcomes are reported with 95% confidence intervals, without p values. The 95% CI and 95% CI are not adjusted for multiple testing and should not be used to infer definitive treatment effects.

Table S16. Sensitivity analysis considering non-cardiovascular death as a competing risk for the primary outcome, key secondary outcome and CV death and considering all-cause death as a competing risk for Type 1 MI, ischemic stroke and urgent revascularization using Fine-Gray subdistribution hazard models.

	sHR (95% CI)	P
Primary outcome	0.75 (0.59, 0.95)	Non-inferiority p<0.001
		Superiority p=0.02
Components of primary outcome		
CV death	0.67 (0.47, 0.97)	
Type 1 MI	0.71 (0.48, 1.05)	
Ischemic stroke	0.70 (0.39, 1.26)	
Urgent revascularization	0.97 (0.57, 1.65)	
Key secondary outcome		
Composite of CV death, type 1 MI or ischemic stroke	0.69 (0.54, 0.89)	

CV- Cardiovascular; MI- myocardial infarction, sHR-subdistribution Hazard ratio

There was no prespecified plan to adjust for multiple testing. Secondary outcomes are reported with 95% confidence intervals, without p values. The 95% CI and 95% CI are not adjusted for multiple testing and should not be used to infer definitive treatment effects.

Table S17. Adverse events and non-fatal serious adverse events.

	Polypill (n=1237)	Usual Care (n=1229)
Total AEs, n	704	688
Patients experiencing an AE, n (%)	404 (32.7)	388 (31.6)
Total non-fatal SAEs, n	339	346
Patients experiencing a non-fatal SAE, n (%)	237 (19.2)	224 (18.2)
Specific AEs of interest		
BARC bleeding	57 (4.6)	49 (4.0)
Refractory cough*	40 (3.2)	35 (2.8)
Renal†	24 (1.9)	22 (1.8)
Drug allergy	14 (1.1)	7 (0.6)

AE – Adverse Event; SAE – Serious Adverse Events; BARC - Bleeding Academic Research Consortium[31]

*Leading to drug discontinuation

†Leading to drug discontinuation