SUPPLEMENTARY MATERIAL

SUPPLEMENTARY FILE 1: ADDITIONAL TABLES

Supplementary Table S1.1. Epidemiology/Population Inputs Data Selected to Nourish the Model

	Weighted Cohort Population Data ± SE	**Source**
Starting age, y	69.37 ± 0.04506	Timóteo and Mimoso,[1] Santos et al[2]
Male, %	61.8 ± 0.08252	Timóteo and Mimoso,[1] Santos et al[2]
Smokers, %	17.4% ± 0.02962	Timóteo and Mimoso,[1] Santos et al[2]
Diabetes, %	27.8% ± 0.03321	Timóteo and Mimoso,[1] Santos et al[2]
AF, %[(a)]	13.2% ± 0.01260	Timóteo and Mimoso,[1] Santos et al[2]
LVH, %[(a)]	6.2% ± 0.00762	Assumed as HF from Castellano et al,[3] Santos et al[2]
SBP, mm Hg	145.1 ± 0.66679	Ferreira et al,[4] Heuschmann et al[5(c)]
Total cholesterol, mg/dL	190.8 ± 1.06355	Ferreira et al,[4] Heuschmann et al[5(c)]
HDL-cholesterol, mg/dL	45.2 ± 0.25492	Ferreira et al,[4] Heuschmann et al[5(c)]
hs-CRP, mg/dL[(b)]	2.2 ± 0.94388	Dorresteijn et al[6 (d)]
e-GFR, ml/min/1.73m^2[(b)]	74.3 ± 2.65473	Timóteo et al,[7] Dorresteijn et al[6 (d)]
History of AAA, % [b)]	2.1% ± 0.00561	Castro-Ferreira et al[8 (e)]
History of PAD, %[(b)]	3.2% ± 0.01519	Timóteo et al,[9] Santos et al[2]
History of both CHD and stroke, %	8.0% ± 0.01594	Timmis et al[10]
Fatality rate recurrent stroke—women[(f)(g)]	17%	Burn et al[11]
Fatality rate recurrent stroke—men [(f)(g)]	17%	Burn et al[11]
Fatality rate subsequent CHD—women[(f)]	16.7%	D'Agostino et al[12]
Fatality rate subsequent CHD—men[(f)]	24.9%	D'Agostino et al[12]

Abbreviations: AAA, acute aortic aneurysm; AF, atrial fibrillation; CHD, coronary heart disease; e-GFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; HF, heart failure; LVH, left ventricular hypertrophy; PAD, peripheral arterial disease; SBP, systolic blood pressure.

All data weighted from individual cohorts (57.9% post-CHD and 42.1% post-stroke).[10]

All inputs are necessary for both risk equations, except (a) which are only used in Framingham equations and (b) which are only used in SMART equations. All data come from post-CHD or post-stroke patients in Portugal with the exception of (c) data from post-stroke European population, (d) data from the original SMART cohort, (e) data from general population in Portugal ≥65 years, (f) where assumed the same for both post-CHD and post-stroke populations, and (g) where assumed the same for men and women.

Supplementary Table S1.2. SMART Risk Score Model Coefficients (Dorresteijn et al[6])

Parameter	Coefficient	SE
Intercept, γ_0	2.0987	0.4197
Age, γ_1	-0.0850	0.0170
Age squared, γ_2	0.0010	0.0002
Male sex, γ_3	0.1561	0.1209
Diabetes, γ_4	0.2232	0.1122
Current smoking, γ_5	0.2617	0.1011
SBP, γ_6	0.0043	0.0022
TC, γ_7	0.0959	0.0415
HDL, γ_8	-0.4256	0.1512
ln(hs-CRP), γ_9	0.1394	0.0279
eGFR, γ_{10}	-0.0532	0.0106
eGFR squared, γ_{11}	0.0003	0.0001
Years since first vascular event, γ_{12}	0.0229	0.0050
History of CeVD, γ_{13}	0.4058	0.1179
History of CAD, γ_{14}	0.1401	0.1231
History of AAD, γ_{15}	0.5578	0.1348
History of PAD, γ_{16}	0.2832	0.1179
$S_0(t = 10)$	0.8107	

Abbreviations: AAD, abdominal aortic disease; CAD, coronary artery disease; CeVD, cerebrovascular disease; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; hs-CRP, high-sensitivity C-reactive protein; PAD, peripheral arterial disease; SE, standard error; SBP, systolic blood pressure; TC, total cholesterol.

Age in years; SBP in mm Hg; TC and HDL-c in mmol/L; hs-CRP in mg/dL; eGFR in mL/min/1.73m^2.

Supplementary Table S1.3. Model Assumptions

A1	In the baseline population inputs, % of patients with LVH equals the % of patients with HF (Castellano et al[3])
A2	In the baseline population inputs, the % of patients with a history of AAA is assumed from the general population of Portugal (≥65 y) (Castro-Ferreira et al[8])
A3	Fatality rate for recurrent stroke assumed the same for both sexes
A4	Utility of death is 0
A7	In the Framingham equation for the risk of primary stroke, S_0 estimate corresponds to $t = 10$ years (D'Agostino et al[13])
A8	In the RR calculation of secondary vs primary stroke RR of year 5 assumed for all subsequent years
A9	SE is ±20% of the mean

Abbreviations: AAA, abdominal aortic aneurysm; HF, heart failure; LVH, left ventricular hypertrophy; RR, relative risk; SE, standard error.

Supplementary Table S1.4. Medications Used in the NEPTUNO Study Cohorts[14]

	Cohort 1 (CNIC-Polypill) (n = 1614)	Cohort 2 (Same Monocomponents) (n = 1614)	Cohort 3 (Equivalent Potency Monocomponents) (n = 1614)	Cohort 4 (Other Monocomponents) (n = 1614)
Antiplatelets	**100%**	**100%**	**100%**	**86.1%**
ASA 100 mg	100%	100%	100%	47.5%
ASA 325 mg	—	—	—	21%
Clopidogrel	—	—	—	16.4%
Other	—	—	—	1.2%
Statins	**100%**	**100%**	**100%**	**70.7%**
Atorvastatin 20 mg	57.1%	56.1%	—	12.8%
Atorvastatin 40 mg	42.9%	43.9%	—	7.20%
Simvastatin 40 mg	—	—	15.1%	3.2%
Simvastatin 80 mg	—	—	11.4%	2.9%
Rosuvastatin 5 mg	—	—	43.5%	7.2%
Rosuvastatin 10 mg	—	—	30%	2.2%
Atorvastatin 10 mg	—	—	—	9.5%
Simvastatin 20 mg	—	—	—	8.8%
Lovastatin various strengths	—	—	—	8.2%
Pravastatin various strengths	—	—	—	6.9%
Others	—	—	—	1.8%
Antihypertensives	**100%**	**100%**	**100%**	**87.7%**
Ramipril 2.5 mg	34%	33.5%	—	5%
Ramipril 5 mg	34.8%	33.6%	—	7.6%
Ramipril 10 mg	31.2%	32.9%	—	4.5%
Enalapril 5 mg	—	—	23.3%	3.2%
Enalapril 10 mg	—	—	10.8%	5.5%
Enalapril 20 mg	—	—	29.2%	8.5%
Valsartan 40 mg	—	—	10.3%	4.2%
Valsartan 80 mg	—	—	20.3%	8.8%
Valsartan 160 mg	—	—	6.1%	3%
Captopril various strengths	—	—	—	4.9%
Losartan various strengths	—	—	—	3.2%
Others	—	—	—	29.3%

Abbreviations: ASA, acetylsalicylic acid; CNIC, Centro Nacional de Investigaciones Cardiovasculares.

Supplementary Table S1.5. Clinical Effectiveness of the CNIC-Polypill Compared With the Monocomponents in Each of the NEPTUNO Study Cohorts[14]

	CNIC Polypill vs Cohort 2 (Same Monocomponents)	CNIC Polypill vs Cohort 3 (Monocomponents of Equivalent Potency)	CNIC Polypill vs Cohort 4 (Other Monocomponents)
SBP reduction (%)	1.80	2.70	2.62
DBP reduction (%)	2.33	3.0	4.0
TC reduction (%)	5.28	10.09	10.09
LDL-c reduction (%)	5.37	5.7	8.1
HDL-c increment (%)	4.01	5.57	7.36
Triglycerides reduction (%)	3.33	4.9	5.6

Abbreviations: CNIC, Centro Nacional de Investigaciones Cardiovasculares; DBP, diastolic blood pressure; HDL-c, high-density lipoprotein cholesterol; LDL-c, low-density lipoprotein cholesterol; SBP, systolic blood pressure; TC, total cholesterol.

Supplementary Table S1.6. Direct Costs

MEDICATION REIMBURSEMENT COSTS							
	Dose (mg)	**Pack Size (No. of Tablets)**	**Market Share/ Distribution***	**Cost per Pack (€)**	**Daily Cost (€)**	**Reimbursement**	**Reimbursed Annual Cost (€) ± SE**
Polypill strategy							
ASA/ atorvastatin/ ramipril	100/20/2.5 mg	28	19.41%	12.23	0.44	37%	**84.62 ± 16.90**
	100/20/5 mg	28	19.87%	13.95	0.50	37%	
	100/20/10 mg	28	17.82%	18.94	0.68	37%	
	100/40/2.5 mg	28	14.59%	18.89	0.67	37%	
	100/40/5 mg	28	14.93%	20.79	0.74	37%	
	100/40/10 mg	28	13.38%	23.60	0.84	37%	
NEPTUNO cohort 2 (same monocomponents)							
ASA	100 mg	30	100%	2.44	0.081	69%	**63.44 ± 12.7**
Atorvastatin#	20/40 mg	28	100%	3.76	0.134	37%	
Ramipril#	2.5/5/10 mg	56	100%	5.52	0.098	69%	
NEPTUNO cohort 3 (monocomponents with the same potency)							
ASA	100 mg	30	100%	2.44	0.081	69%	**60.64 ± 12.1**
Statins#	Various drugs/doses	28	100%	3.38	0.121	37%	
Antihypertensives#	Various drugs/doses	56	100%	5.30	0.095	69%	
NEPTUNO cohort 4 (other monocomponents)							
Antiplatelets#	Various drugs/doses	30	86.1%	2.95	0.098	69%	**62.24 ± 12.4**
Statins#	Various drugs/doses	28	70.7%	2.82	0.101	37%	
Antihypertensives#	Various drugs/doses	56	87.7%	5.31	0.095	69%	

EVENT MANAGEMENT COSTS		
	Cost CV event management (€) ± SE	**Source**
Acute events (cost per event):		
CHD (nonfatal) [1, 2]	4560.1 ± 912.0	Costa et al[15]
CHD (fatal) [1]	3153.5 ± 630.7	Silva Miguel and Ferreira[16]
Stroke (nonfatal) [2]	8653.3 ± 1730.7	Costa et al[15]
Stroke (fatal)	6381.2 ± 1276.2	Costa et al[15]
Follow-up (annual cost) [3,4]:		
Post-CHD	643.3 ± 128.7	Costa et al[15]
Post-stroke	534.8 ± 107.0	Costa et al[15]

Abbreviations: ACE, angiotensin-converting enzyme; ASA, acetylsalicylic acid; SE, standard error.

*For the polypill strategy, the table shows the distribution of each preparation in NEPTUNO cohort 1. For the other cohorts, the table shows the distribution for each monocomponent class in the NEPTUNO study of patients receiving antiplatelets, statins and antihypertensives

For cohorts 2, 3, and 4, the weighted cost of all the presentations of each class of drugs used by patients in the different cohorts has been calculated using the reference price plus value added tax of each presentation.

(1) Assumed as myocardial infarction (MI).

(2) Includes the first two weeks of hospitalization and rehabilitation during the first three months.

(3) Applied in each year of the simulation after the first episode.

(4) Includes costs of consultations, emergencies and transport, diagnostic exams, medication, and technical assistance.

Supplementary Table S1.7. Health Utility Values Selected to Nourish the Model

	Health Utilities ± SE (Ara et al[17])
Chronic CHD(1)	0.84 ± 0.167
Chronic stroke	0.69 ± 0.138
Acute CHD	0.76 ± 0.152
Acute stroke	0.63 ± 0.126
Death(2)	0.00 ± 0.000

Abbreviations: CHD, coronary heart disease; SE, standard error.

(1) Assumed as myocardial infarction, no unstable angina.

(2) Utility value of death was assumed to be 0.00.

Supplementary Table S1.8. CHEERS Checklist[18]

Topic	No.	Item	Location Where Item Is Reported
Title	1	Identify the study as an economic evaluation and specify the interventions being compared.	Lines 2-4
Abstract	2	Provide a structured summary that highlights context, key methods, results, and alternative analyses.	Lines 6-39
Introduction			
Background and objectives	3	Give the context for the study, the study question, and its practical relevance for decision making in policy or practice.	Lines 43-97
Methods			
Health economic analysis plan	4	Indicate whether a health economic analysis plan was developed and where available.	Line 109-110
Study population	5	Describe characteristics of the study population (such as age range, demographics, socioeconomic, or clinical characteristics).	Lines 111-114
Setting and location	6	Provide relevant contextual information that may influence findings.	Lines 107-109
Comparators	7	Describe the interventions or strategies being compared and why chosen.	Lines 107-108
Perspective	8	State the perspective(s) adopted by the study and why chosen.	Lines 131-133
Time horizon	9	State the time horizon for the study and why appropriate.	Line 108-109
Discount rate	10	Report the discount rate(s) and reason chosen.	Lines 132-133
Selection of outcomes	11	Describe what outcomes were used as the measure(s) of benefit(s) and harm(s).	Lines 134-137; 165-181
Measurement of outcomes	12	Describe how outcomes used to capture benefit(s) and harm(s) were measured.	Lines 115-130; 183-209;
Valuation of outcomes	13	Describe the population and methods used to measure and value outcomes.	Lines 134-138; 228-234
Measurement and valuation of resources and costs	14	Describe how costs were valued.	Lines 212-225
Currency, price date, and conversion	15	Report the dates of the estimated resource quantities and unit costs, plus the currency and year of conversion.	Lines 213-214
Rationale and description of model	16	If modelling is used, describe in detail and why used. Report if the model is publicly available and where it can be accessed.	Lines 101-257
Analytics and assumptions	17	Describe any methods for analysing or statistically transforming data, any extrapolation methods, and approaches for validating any model used.	Lines 111-162; 180-181
Characterizing heterogeneity	18	Describe any methods used for estimating how the results of the study vary for subgroups.	Lines 143-162
Characterizing distributional effects	19	Describe how impacts are distributed across different individuals or adjustments made to reflect priority populations.	Lines 253-257

Topic	No.	Item	Location Where Item Is Reported
Characterising uncertainty	20	Describe methods to characterize any sources of uncertainty in the analysis.	Lines 242-252
Approach to engagement with patients and others affected by the study	21	Describe any approaches to engage patients or service recipients, the general public, communities, or stakeholders (such as clinicians or payers) in the design of the study.	Not applicable
Results			
Study parameters	22	Report all analytic inputs (such as values, ranges, references) including uncertainty or distributional assumptions.	Tables 1-2-3 and Supplementary materials
Summary of main results	23	Report the mean values for the main categories of costs and outcomes of interest and summarize them in the most appropriate overall measure.	Lines 269-277
Effect of uncertainty	24	Describe how uncertainty about analytic judgments, inputs, or projections affect findings. Report the effect of choice of discount rate and time horizon, if applicable.	Lines 282-294; 299-319
Effect of engagement with patients and others affected by the study	25	Report on any difference patient/service recipient, general public, community, or stakeholder involvement made to the approach or findings of the study	Not applicable
Discussion			
Study findings, limitations, generalisability, and current knowledge	26	Report key findings, limitations, ethical or equity considerations not captured, and how these could affect patients, policy, or practice.	Lines 324-437
Other relevant information			
Source of funding	27	Describe how the study was funded and any role of the funder in the identification, design, conduct, and reporting of the analysis	Cover letter (per journal requirements)
Conflicts of interest	28	Report authors conflicts of interest according to journal or International Committee of Medical Journal Editors requirements.	Cover letter (per journal requirements)

SUPPLEMENTARY FILE 2. ADDITIONAL RISK EQUATIONS

Risk of Recurrent CHD

- The CV risk equations used in the sensitivity analysis of this economic model are the Framingham risk equations.
- The risk of subsequent CHD is calculated using the Weibull model from D'Agostino et al,[12] where *t* takes the cycle-length in years to obtain cycle-adjusted risk estimates:

$$\text{Risk}_{recurrent\ CHD}(t = \text{cycle-length}) = \\ = 1 - \exp\left(-\exp\left(\frac{ln(t) - (\beta_0 + \beta_1 \times age + \beta_2 \times \ln(TC/HDL) + \beta_3 \times \ln(SBP) + \beta_4 \times diabetes + \beta_5 \times smoker)}{\sigma}\right)\right)$$

- Age is updated each cycle
- Values of the patients' clinical characteristics along the lifetime horizon are those at baseline.
- For the CNIC-Polypill arm, effectiveness results from the NEPTUNO study are applied to the baseline values of SBP, TC, and HDL-c.
- The sex-specific model parameters for the subsequent CHD risk equation are shown in **Table S2.1**.

Table S2.1. Sex-specific Model Parameters for Subsequent CHD Risk Equation (D'Agostino et al[12])

	Women		Men	
Parameter	**Coefficient**	**SE**	**Coefficient**	**SE**
Intercept, β_0	13.5370	3.4794	4.9950	1.2839
Age, β_1	-0.0225	0.0191	-0.0145	0.0091
ln(TC/HDL), β_2	-0.8340	0.3843	-0.6738	0.2180
ln(SBP), β_3	-1.3713	0.8337		
Diabetes, β_4	-0.7829	0.2849	-0.3042	0.1738
Smoker, β_5	-0.3669	0.2749		
Extreme value scale parameter, σ	1.0313		0.9994	

Abbreviations: HDL, high-density lipoprotein; ln, natural algorithm; SE, standard error; SBP, systolic blood pressure; TC, total cholesterol.
Age in years; TC and HDL in mg/dL; SBP in mmHg.

Risk of Recurrent Stroke

- Since there is no Framingham model to predict the risk of recurrent stroke, the risk of primary stroke was calculated and then multiplied by the increased relative risk (RR) of recurrence over first stroke.
- The following Cox proportional hazards regression model from D'Agostino et al[19] was used to calculate the risk of primary stroke:

$$\text{Risk}_{primary\ stroke} = 1 - S_0(t)^{\exp\left(\begin{matrix}\eta_1\times(age-age_0)+\eta_2\times(SBP-SBP_0)+\eta_3\times(NEWHRXSBP-NEWHRXSBP_0)+\eta_4\times(CVD-CVD_0)+\\ +\eta_5\times(LVH-LVH_0)+\eta_6\times(smoker-smoker_0)+\eta_7\times(AF-AF_0)+\eta_8\times(diabetes-diabetes_0)\end{matrix}\right)}$$

- Reference values in the equation—those with subscript 0—correspond to reference risk factor profile from the population of the model derivation by Wolf et al.[20]
- The use of antihypertension medication and its interaction with SBP is entered into the model as the variable NEWHRXSBP. NEWHRXSBP=HRX×(SBP-110)×(200-SBP), where HRX is a dummy variable defined as 1 if the individual is on antihypertensive medication and 0 if not, and SBP is the individual's SBP. In cases with SBP below 110 mm Hg or greater than 200 mm Hg, the variable NEWHRXSBP equals 0.[19]
- Age is updated each cycle.
- Clinical characteristics along the lifetime horizon are the same as those at baseline.
- For the CNIC-Polypill cohort, a reduction in SBP is applied from the effectiveness results of the NEPTUNO study.
- The sex-specific model parameters for primary stroke are shown in **Table S.2.2**.

Table S2.2. Sex-specific Model Parameters for Primary Stroke (D'Agostino et al[19])

	Women		Men	
Parameter	**Coefficient**	**SE**	**Coefficient**	**SE**
Age, η_1	0.0699	0.0089	0.0488	0.0103
SBP, η_2	0.0161	0.0024	0.0152	0.0031
NEWHRXSBP, η_3	0.00026	0.00007	0.00019	0.00010
CVD, η_4	0.4404	0.1462	0.5460	0.0151
LVH, η_5	0.8055	0.2429	0.7864	0.2846
Smoker, η_6	0.5419	0.1453	0.5224	0.1429
AF, η_7	1.1173	0.2302	0.5998	0.3011
Diabetes, η_8	0.5604	0.1706	0.3429	0.1894
$S_0(t=10)$	0.9898		0.9883	

Abbreviations: AF, atrial fibrillation; HDL, high-density lipoprotein; LVH, left ventricular hypertrophy; SE, standard error. SBP, systolic blood pressure; TC, total cholesterol.

Age in years; TC and HDL in mg/dL; SBP in mm Hg.

- Since the S_0 estimate corresponds to a period of 10 years,[13] risk estimates obtained for primary stroke are adjusted to the cycle-length assuming a constant rate over the period as follows:

$$\text{Rate}_{primary\ stroke} = -\ln\left(1 - \text{Risk}_{primary\ stroke}(t = 10)\right)/10$$

$$\text{Risk}_{primary\ stroke}(t = \text{cycle-length}) = 1 - \exp\left(-\text{Rate}_{primary\ stroke} \times \text{cycle-length}\right)$$

- To obtain risk estimate of recurrent stroke, the risk of primary stroke is multiplied by RR of recurrent vs primary stroke from Burn et al,[11] shown in **Table S2.3**, and assuming no incremental risk beyond the fifth year after the first stroke.

$$\text{Risk}_{recurrent\ stroke} = \text{Risk}_{primary\ stroke} \times RR_{recurrent\ vs\ primary}$$

Table S2.3. Relative Risk for Recurrent Stroke vs Primary Stroke by Year After the First Ever Stroke (Burn et al[11]).

Year After First Stroke	Relative Risk (95% Confidence Interval)
1	15.4 (12.1; 19.0)
2	8.5 (5.6; 11.8)
3	6.7 (3.9; 10.7)
4	4.5 (2.1; 8.6)
5	2.0 (0.3; 7.4)
6+	1.0

SUPPLEMENTARY FILE 3: LITERATURE SEARCH STRATEGIES AND PRISMA DIAGRAMS

Table S3.1. Search Strategy

#	Search Terms, Strategy	PubMed, Hits (n)	Scopus, Hits (n)
	Limit all searches to English or Portuguese language. Limit PubMed searches #6, #7, #13, #14, #15 and #16 to Clinical study, Clinical trial, Randomized controlled trial. Limit searches #45, #49, #51 and #53 to dates from 2014 to 2020. Limit all other PubMed searches to 10 years.		
1	Coronary heart disease		
2	Stroke		
3	Polypill		
4	Effectiveness		
5	Secondary prevention		
6	**#1 OR #2 AND #3 AND #4**	**8**	**26**
7	**#1 OR #2 AND #3 AND #5**	**4**	**24**
8	Cardiovascular disease		
9	Cerebrovascular disease		
10	Blood pressure		
11	Lipids		
12	Cholesterol		
13	**#8 OR #9 AND #3 AND (#10 OR #11 OR #12) AND #5**	**10**	**67**
14	**#8 OR #9 AND #3 AND (#10 OR #11 OR #12)**	**24**	**182**
15	**#8 OR #9 AND #3 AND #4**	**24**	**103**
16	**#8 OR #9 AND #3 AND #5**	**15**	**157**
17	Epidemiology		
18	Portugal		
19	**#1/#17[Majr] OR #2/#17[Majr] AND #18**	**82**	
20	**#8/#17[Majr] OR #9/#17[Majr] AND #18**	**530**	
21	Ischemic heart disease		
22	Myocardial infarction		
23	Incidence		
24	Prevalence		
25	Mortality		
26	**#2 OR #8 AND #23 AND #18**		**92**
27	**#2 OR #8 AND #24 AND #18**		**172**
28	**#2 OR #8 AND #25 AND #18**		**237**
29	**#2 OR #21 AND #23 AND #18**		**70**
30	**#2 OR #21 AND #24 AND #18**		**71**
31	**#2 OR #21 AND #25 AND #18**		**156**
32	**#2 OR #22 AND #23 AND #18**		**85**
33	**#2 OR #22 AND #24 AND #18**		**80**
34	**#2 OR #22 AND #25 AND #18**		**206**
35	Secondary		
36	Recurrent		
37	Subsequent		
38	**(#1/#17[Majr] OR #2/#17[Majr]) AND (#35 OR #36 OR #37) AND #18**	**19**	

#	Search Terms, Strategy	PubMed, Hits (n)	Scopus, Hits (n)
39	**(#8/#17[Majr] OR #9/#17[Majr]) AND (#35 OR #36 OR #37) AND #18**	**70**	
40	Europe		
41	**(#1/#17[Majr] OR #2/#17[Majr]) AND (#35 OR #36 OR #37) AND #40**	**28**	
42	**(#8/#17[Majr] OR #9/#17[Majr]) AND (#35 OR #36 OR #37) AND #40**	**178**	
43	Cost-effectiveness		
44	Cost of illness		
45	**(#8[Mesh] OR #9[Mesh]) AND (#43 OR #44) AND #18**	**43**	**7**
46	Use of health care resources		
47	Direct costs		
48	Indirect costs		
49	**(#8[Mesh] OR #9[Mesh]) AND (#46 OR #47 OR #48) AND #18**	**6**	**0**
50	Costs		
51	**(#2[Mesh] OR #8[Mesh]) AND #50 AND #18**	**67**	**30**
52	Heart disease		
53	**(#2[Mesh] OR #52[Mesh]) AND #50 AND #18**	**41**	**31**
54	Quality of life		
55	Prevention		
56	Cost-utility		
57	Cost-effectiveness		
58	QALY (quality-adjusted life years)		
59	Utility		
60	**(#8[Majr] OR # 9[Majr]) AND #54 AND #55 AND #18**	**28**	
61	**(#2 [Majr] OR # 52[Majr]) AND #54 AND #55 AND #18**	**16**	
62	**(#8[Majr] OR # 9[Majr]) AND (#56 OR #57) AND #55 AND #18**	**14**	
63	**(#2[Majr] OR # 52[Majr]) AND (#56 OR #57) AND #55 AND #18**	**12**	
64	**(#8[Majr] OR # 9[Majr]) AND (#56 OR #57) AND #58 AND #18**	**9**	
65	**(#2[Majr] OR # 52[Majr]) AND (#56 OR #57) AND #58 AND #18**	**3**	
66	**(#2 OR # 8) AND #58 AND #18**		**6**
67	**(#2 OR # 21) AND #58 AND #18**		**4**
68	**(#2 OR # 22) AND #58 AND #18**		**4**
69	**(#2 OR # 8) AND #59 AND #18**		**11**
70	**(#2 OR # 21) AND #59 AND #18**		**6**
71	**(#2 OR # 22) AND #59 AND #18**		**5**
	Total hits per database (all search strategies)	**1231**	**1832**
	Total hits	**3063**	

Table S3.2 Inclusion/Exclusion Criteria

Inclusion Criteria	Exclusion Criteria
• Secondary prevention of ischaemic cardiovascular or cerebrovascular disease studies (clinical trials (experimental) or observational studies (real-world evidence) • Studies involving a polypill with the components: aspirin, ACE inhibitor, statin only • Polypill effectiveness with the following end points: systolic blood pressure, total cholesterol, HDL cholesterol • Publications on ischaemic cardiovascular or cerebrovascular disease epidemiology, prevalence, incidence, mortality or risk factors • Cost-effectiveness studies containing direct and indirect costs of fatal and non-fatal cardiovascular or cerebrovascular events • Cost-effectiveness studies containing utility values for acute cardiovascular (MI) or cerebrovascular events (stroke) • Cost-effectiveness studies containing utility values for subsequent years after cardiovascular o cerebrovascular events (chronic condition) • Population: representative of general adult population with history of ischaemic cardiovascular or cerebrovascular disease • Available in English or Portuguese • Worldwide	• Study design, rationale and methods only articles • Studies of only adherence improvement • Studies of polypill components only administered separately • Studies of only subgroups of population with specific ethnicity/comorbidity characteristics: diabetic patients, indigenous people, etc. • Publications on epidemiology of external cardiovascular and cerebrovascular risk factors: diet, smoking, weight/BMI, weather/temperature, socioeconomic, education, etc. • Publications on cardiovascular or cerebrovascular epidemiology in only subgroups of population with specific ethnicity/comorbidity characteristics: diabetic patients, cancer patients, HIV patients, renal patients, etc. • Non-ischaemic cardiovascular and cerebrovascular disease epidemiology publications: DVT, PE, heart failure, endocarditis, haemorrhagic stroke, pericarditis, cardiac valve, pacemaker, etc • Cost-effectiveness studies of diagnostic or interventional techniques • Studies evaluating the economic burden of cardiovascular or cerebrovascular diseases • Cost-effectiveness studies containing weights for quality of life by level of dependence • Quality of life studies in patient population other that the population of interest (patients with cardiovascular or cerebrovascular diseases) • Quality of life studies in very specific patient population (eg, patients with neurological impairment after stroke) • Meta-analysis • Editorial comments • Guidelines and consensus documents

Abbreviations: ACE inhibitor, angiotensin converting enzyme inhibitor; BMI, body mass index; DVT, deep vein thrombosis; HDL, high-density lipoprotein; PE, pulmonary embolism.

Table S3.3 PRISMA Diagram

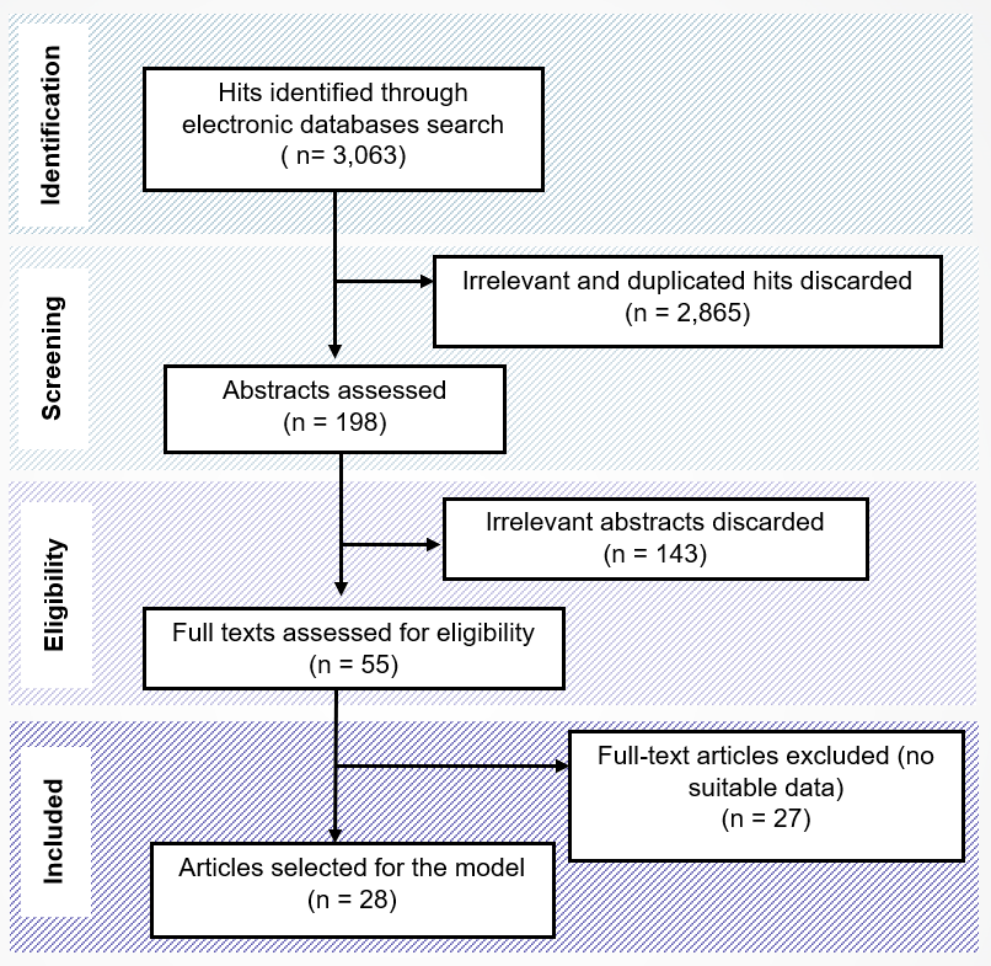

Table S3.4 Summary of Shortlisted Articles

Author, Year	Reasons for Appropriateness	Results of Interest
CLINICAL EFFECTIVENESS		
Castellano et al[3]	Largest published study on polypill containing aspirin, ramipril and atorvastatin so far (n=1193) Evidence of lowered blood pressure and significantly improved lipid profile (total cholesterol and HDL included)	At one year with the polypill: Mean SBP reduced from 145.7 to 129 mmHg (11.46% reduction) (*P*<.001) Mean HDL-c increased from 48.5 to 49.5 mg/dL (2.1% increase) (*P*<.001) Mean TC decreased from 236.7 to 193.4 mg/dL (18.3% reduction) (*P*<.001)
Gómez-Álvarez et al[21]	Post-hoc analysis of lipid profile results of SORS study (Castellano et al[3])	Total cholesterol (from 241 mg/dL [SD = 62] to 187 mg/dL [SD = 36]) LDL cholesterol (from 130 mg/dL [SD = 36] to 112 mg/dL [SD = 30]) HDL cholesterol (from 49 mg/dL [SD = 24] to 50 mg/dL [SD = 14])
Méndez-García et al[22]	Polypill (aspirin, ramipril and simvastatin) effectiveness study (n=256), Mexico	30% reduction in blood pressure and total cholesterol levels (*P*<.05). Estimated by performing the Wilcoxon-matched pairs signed

	Evidence for blood pressure and cholesterol reduction	rank test and the Kruskall-Wallis test for paired samples. Absolute levels could be calculated from baseline levels.
EPIDEMIOLOGY—STROKE POPULATION		
Abreu et al[23]	Readmission/death rate within a year from first-ever stroke in Northern Portugal. (Note that population includes ischemic stroke, intracerebral haemorrhage and subarachnoid hemorrhage, all grouped together.)	Fatality rate without readmission within a year of first event: 15.8% (all causes, it does not differentiate) Readmission rates within the 1st year: 15.8% readmission rate for cerebrovascular disease 9.9% readmission due to ischemic stroke 8.9% readmission for cardiovascular disease (3.0% MI) 18.8% fatality rate during readmission (all causes, it does not specify)
Béjot et al[24]	Incidence of stroke in several European countries at the beginning of the 21st century	Stroke recurrence grouped together for all types of stroke: 1-4% at 1 month, 7-13% at 1 year, 40% at 10 years 3-month recurrences in ischemic stroke from large artery atherosclerosis (14.3%), in cardioembolic stroke (7.7%), lacunar stroke (2%), and ischemic stroke from undetermined cause (5.6%) Risk of myocardial infarction was estimated at 2.2% after a stroke
Correia et al[25]	Stroke patient (n=608) registered in 3 community health centres in Porto, Portugal	Baseline epidemiology data: median age for men 70 years, for women 78 years, 53.8% women, 24.9% diabetes, 18.5% previous diagnosis of AF, 19.3% current smoker.
Heuschmann, 2015 (5)	EUROASPIRE III survey stroke module in Croatia, Czech Republic, Germany and Poland (n=881)	Baseline epidemiological data for stroke patients: mean age 64.1 years, 37.5% female, 23.1% diabetes, 16.6% smoking, mean SBP 143mmHg, mean total cholesterol 5.09 mmol/l, mean HDL cholesterol 1.3 mmol/L
Santos, 2017 (2)	15 years of nationwide data on ischaemic stroke in Portugal (n=275173 hospitalizations). Data obtained from the Portuguese Ministry of Health's Central Administration for the Health System	Baseline epidemiological data available: overall mean age 74 years, 49.4% male patients, 22.6% had history of AF, 27% diabetes mellitus, 7.4% left ventricular hypertrophy, 6.5% smoking, 2.3% history of PAD
Tsivgoulis et al[26]	Stroke recurrence in Northern Greek population (n=703)	7.2% of patients had a recurrent stroke within 1 year
Wawrzyńczyk et al[27]	Zabrze (southern Poland) population study of acute stroke cases between 2005 and 2006. Haemorrhagic stroke, TIA and subarachnoid hemorrhages were excluded from the study	Incidence rate and fatality rate for all strokes and first ever stroke provided (recurrent stroke incidence and fatality data could be calculated from them)
EPIDEMIOLOGY—CHD POPULATION		
André et al[28]	Portuguese ACS patients (n=3009) included in the European EURHOBOP study	Baseline epidemiology data: mean age 67.6 years, 66.6% male, 21% current smoking, 23.2% diabetes
De Bacquer et al[29]	Follow up on cohort of patients from EUROASPIRE I and II surveys (n=5216) with established CHD. Patients from Belgium, Czech Republic, Finland, France,	Fatality recurrent CHD data. Will require calculation: Fatal CVD was the cause of death in 332 patients (262 men and 70 women) denoting a CVD

	Germany, Hungary, Ireland, Poland, Slovenia, and Spain.	mortality risk of 12.3 per 1000 person-years in men and 10.2 per 1000 person-years in women. Fatal CHD events accounted for 76% of all CVD deaths.
Castro-Ferreira et al[8]	Study to estimate the prevalence of AAA in Portugal (n=715)	AAA prevalence in the sample was 2.1% (note these were not CHD patients, it is general population in Portugal)
Ferreira et al[4]	ACS patients (n=1303) admitted to a coronary care unit in Portugal	Baseline characteristics of patients divided in 4 cohorts. Will require calculation. Data available: mean age, % male, % diabetes, % smoking, % previous history of PAD, SBP, % AF, total cholesterol, HDL cholesterol, SBP
Rosello et al[30]	Population hospitalized for ACS and then discharged and followed up at year 1 and year 2. Patients from 20 different countries in Europe and Latin America.	Event rate at year 1 follow up: -Non-fatal MI rate: 1.01 per 1000 person-years at risk -Non-fatal stroke: 0.14 per 1000 person-years at risk Event rate at year 2 follow-up: -Non-fatal MI rate: 1.14 per 1000 person-years at risk -Non-fatal stroke: 0.14 per 1000 person-years at risk
Timóteo et al[7]	ACS patients (n=1423) in Portugal	Baseline eGFR 73 ml/min/1.73 (for ACS patients with and without anaemia) Within 12 months follow-up: Stroke/TIA incidence in anemia group: 2% (P = .33) Stroke/TIA incidence in the no-anaemia group: 1% (P = .33)
Timóteo et al[9]	ACS patients (n=37460) in Portugal, from nationwide ACS registry	Baseline characteristics of patients divided in 3 cohorts. Will require calculation. Data available: mean age 66years, 69.9% male, % diabetes, % smoking, % previous history of PAD, SBP. Reinfarction rate: 1.5%, 1.4% and 1.2% respectively for the 3 cohorts Stroke/TIA rate: 0.8%, 0.9% and 0.8% respectively for the 3 cohorts
Timóteo and Mimoso[1]	ACS patients (n=45141) in Portugal, from 15 years of nationwide ACS registry (up to 2016)	Baseline epidemiological data available: Mean age 66 years, 70.9% male, 28.4% diabetes, 25.4% smoking, 6.3% had previous history of AF
COSTS		
Costa et al[15]	Direct costs for MI (non-fatal) and stroke (fatal and non-fatal) and follow-up costs for both events. Calculation of costs based on unitary cost of individual healthcare resources of 2014 and the estimation of healthcare resources consumption by a national panel of experts	Event costs of non-fatal MI (acute event): €4560.10 Event cost of fatal stroke (acute event): €8653.26 Event cost of non-fatal stroke (acute event): €6381.20 Monthly follow-up costs for MI: €53.61 Monthly follow-up costs for stroke: €44.07
Gouveia et al[31]	Indirect costs associated with AF and followed by a cerebrovascular event calculated from possible scenarios after a	Mean daily salary of €96.53 in Portugal in 2012 Working days in a year: 230 days % of patients with 12 months of absenteeism after acute event: 11.8

	stroke event identified by an expert panel and using salaries of 2012	% of patients with 6 months of absenteeism after acute event: 52.0 % of patients with 3 months of absenteeism after acute event: 36.2 % of patients with permanent absenteeism: 11.8 % of patients with rehabilitation sessions (1.57 months of absenteeism: 23.5 % of patients back to work normally after acute event: 64.8
Laires et al[32]	Annual direct costs of MI (fatal and nonfatal), angina pectoris and subsequent year CHD from 2015. Calculation of costs of CVD health states based on a national expert panel discussion conducted by the Delbecq method.	Annual event costs of non-fatal MI: €8101.10 Annual event costs of angina pectoris: €4180.94 Annual event cost of fatal MI: €6632.87 Cost subsequent year CHD: €1790.49
Morais et al[33]	Direct costs related to MI and stroke as acute events and long-term follow-up from 2011.	Cost per cycle of MI (acute event): € 7270 Cost per cycle of MI (long-term follow-up): €802 Cost per cycle of major ischemic stroke (acute): €1989 Cost per cycle of major ischemic stroke (rehabilitation): € 37/day Cost per cycle of major ischemic stroke (long-term follow-up): €392
Silva Miguel and Ferreira[16]	Direct costs of MI (fatal and non-fatal) and cerebrovascular event (ischemic or haemorrhagic). Cost taken from a previous cost-effectiveness analysis in 2013.	Event cost of fatal MI (acute event): €3153 Event costs of non-fatal MI (acute event): €3077.06 Event cost of ischemic or haemorrhagic stroke: €4094.47
Timóteo et al[34]	Indirect costs of MI in the first year after admission	Indirect annual cost per patient employed: €5244.97 Indirect annual cost per patient (all sample): €3472.17
UTILITIES		
Costa et al[15]	Cerebrovascular event (ischaemic or haemorrhagic) mild: 0.6151 Cerebrovascular event (ischaemic or haemorrhagic) moderate: 0.5646 Cerebrovascular event (ischaemic or haemorrhagic) severe: 0.5142 MI: 0.6098	Sullivan, 2011[44] (UK, 2000-2003)
Laires et al[32]	Non-fatal MI: 0.76 Angina pectoris: 0.77 Subsequent year CHD: 0.808	Goodacre et al[35] (UK, 2001-2002)
Morais et al[33]	Major ischemic stroke: 0.189 Minor ischemic stroke: 0.641 Post major ischemic stroke: 0.482 Post minor ischemic stroke: 0.719	Robinson et al[36] (UK, 2000) Hallan et al[37] (Norway, 1997)
Wilson et al[38]	Stroke (first year): 0.15 Stroke (subsequent year): 0.74 CHD (first year): 0.76 CHD (subsequent year): 0.76	Gage et al[39] (US, 1996-1998) Tengs and Lin[40] (meta-analysis for stroke) Duncan et al[41] (US, 1998-2000) Fryback et al[42] (US, 1991-1993)

	American Heart Association, American Stroke Association[43] (US)

Abbreviations: AAA, acute aortic aneurysm; ACS, acute coronary syndrome; AF, atrial fibrillation; CHD, coronary heart disease; CVD, cardiovascular disease; HDL, high-density lipoprotein; LDL, low-density lipoprotein; MI, myocardial infarction; PAD, peripheral arterial disease; SBP, systolic blood pressure; TIA, transient ischemic attack.

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