

## ORIGINAL ARTICLE

# Cost-effectiveness of the polypill versus risk assessment for prevention of cardiovascular disease

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## ABSTRACT

**Objective** There is an international trend towards recommending medication to prevent cardiovascular disease (CVD) in individuals at increasingly lower cardiovascular risk. We assessed the cost-effectiveness of a population approach with a polypill including a statin (simvastatin 20 mg) and three antihypertensive agents (amlodipine 2.5 mg, losartan 25 mg and hydrochlorothiazide 12.5 mg) and periodic risk assessment with different risk thresholds.

**Methods** We developed a microsimulation model for lifetime predictions of CVD events, diabetes, and death in 259 146 asymptomatic UK Biobank participants aged 40–69 years. We assessed incremental costs and quality-adjusted life-years (QALYs) for polypill scenarios with the same combination of agents and doses but differing for starting age, and periodic risk assessment with 10-year CVD risk thresholds of 10% and 20%.

**Results** Restrictive risk assessment, in which statins and antihypertensives were prescribed when risk exceeded 20%, was the optimal strategy gaining 123 QALYs (95% credible interval (CI) –173 to 387) per 10 000 individuals at an extra cost of £1.45 million (95% CI 0.89 to 1.94) as compared with current practice. Although less restrictive risk assessment and polypill scenarios prevented more CVD events and attained larger survival gains, these benefits were offset by the additional costs and disutility of daily medication use. Lowering the risk threshold for prescription of statins to 10% was economically unattractive, costing £40 000 per QALY gained. Starting the polypill from age 60 onwards became the most cost-effective scenario when annual drug prices were reduced below £240. All polypill scenarios would save costs at prices below £50.

**Conclusions** Periodic risk assessment using lower risk thresholds is unlikely to be cost-effective. The polypill would become cost-effective if drug prices were reduced.

periodic risk assessment until the age of 85 years instead of 75.<sup>2</sup>

Instead of prescribing preventive medication based on assessment of CVD risk, a more ubiquitous approach has been proposed with a combination pill, the polypill.<sup>3</sup> The polypill is intended for people selected only on the basis of age without the need for risk assessment. It would improve the distribution of risk factors population-wide, resulting in a tremendous decrease of CVD event rates. The polypill currently marketed consists of simvastatin 20 mg and three half-standard dose antihypertensive agents (amlodipine 2.5 mg, losartan 25 mg and hydrochlorothiazide 12.5 mg),<sup>4</sup> and was associated with blood pressure and low-density lipoprotein cholesterol reductions in a randomised trial.<sup>5</sup>

A recent cost-effectiveness analysis demonstrated that treating low-risk individuals with statins would be optimal, but blood pressure management was not considered.<sup>6</sup> Yet, antihypertensive treatment for individuals with lower risk or blood pressure levels has now become relevant based on the results of a large individual-level meta-analysis and the Systolic Blood Pressure Intervention Trial (SPRINT).<sup>7–8</sup> At present, few cost-effectiveness analyses of the polypill approach have been performed,<sup>9</sup> but without comparison with recommended periodic risk assessment. The aim of our study was to compare lifetime costs and health effects of the polypill approach and periodic risk assessment with different risk thresholds.

## METHODS

### Decision model

We developed the UK PReventiOn of Myocardial Infarction and Stroke Evaluation (UK-PROMISE) model, an individual-level state-transition (microsimulation) model. The model individualises lifetime risks for CVD, diabetes and non-CVD death based on QRResearch data including 2 343 759 subjects.<sup>10–11</sup> With the model, we simulated life courses of participants of UK Biobank,<sup>12</sup> a large population-based study conducted in individuals recruited from the general population aged 40–69 years. UK Biobank's protocols were approved by the North West Research Ethics Committee (REC reference number: 06/MRE08/65).

The study population was selected from 503 120 UK Biobank participants attending baseline visits between 2006 and 2010. We excluded participants with stroke (n=7669), transient ischaemic attack (TIA) (n=1684), myocardial infarction (MI) (n=11 609) or angina (n=16 183), and those using

## INTRODUCTION

Influential guideline committees recently recommended wider use of statins for the prevention of cardiovascular disease (CVD). The American College of Cardiology and American Heart Association changed their cholesterol treatment guidelines including risk assessment every 5 years using a broader CVD endpoint and a lower risk threshold for prescription.<sup>1</sup> In the UK, the National Institute for Health and Care Excellence (NICE) updated its statin guidelines using a lower 10-year CVD risk threshold of 10% instead of the formerly recommended 20% and extended



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statin (n=86 911) or antihypertensive medication (n=104 032). In addition, participants with incomplete information on risk factors (n=69 334) precluding calculation of QRisk risk scores were excluded. This resulted in a study population of 259 146 individuals (for baseline characteristics see table 1 and eTable 1 in the online supplementary file).

The model included health states for: 'Alive and Well', 'Alive and Diabetes Mellitus (DM)', 'Post Cardiovascular Disease (CVD) event', 'Post CVD event and DM', and 'Dead' (eFigure 1 in the online supplementary file). Each simulated individual faced a yearly probability of developing CVD, defined as: MI, angina, stroke, TIA, or dying due to causes other than CVD. The probabilities for CVD and competing non-CVD deaths were individualised using age- and gender-specific survival functions adjusted for ethnicity, social deprivation, cholesterol, body mass index, smoking, systolic blood pressure (SBP), atrial fibrillation, diabetes, chronic renal disease, rheumatoid arthritis, treated hypertension, and family history of coronary heart disease (for validity of calculated probabilities see eTable 2 in the online supplementary file).<sup>6</sup> Case-fatality of MI and stroke was based on age and gender dependent UK statistics. After survival of CVD, modelled all-cause mortality was increased with a relative risk due to CVD. In addition, individuals without

diabetes had a risk of developing diabetes, based on age, gender, ethnicity, social deprivation, body mass index, smoking status, family history of diabetes, history of CVD, treated hypertension, and regular steroid use.<sup>11</sup> The model's predictions of life expectancy until age 95 were compared with forecasts based on 2010–2012 UK life tables.<sup>13</sup>

### Scenarios

We evaluated current practice, three guideline and five polypill strategies. Current practice was defined by modelled event rates assuming absence of a systematic prevention programme. We defined the guideline scenarios as: (1) 'old guidelines' recommending periodic risk assessment with prescription of statin and antihypertensive medication at 10-year CVD risk of 20%;<sup>14</sup> (2) 'current guidelines' recommending statins at a lower 10% threshold;<sup>2</sup> and (3) 'alternative guidelines' recommending both statin and antihypertensive medication at 10%. In guideline scenarios, a health check organised by the National Health Service (NHS) was offered to individuals with assessment of 10-year CVD risk every 5 years from the age of 40–75 years, unless diabetes was present or statin or antihypertensive medication was started.<sup>15</sup> In individuals not eligible for the NHS health check, primary care physicians continued risk assessment until the age of 75 for the old guidelines and until the age of 85 for the current and alternative guidelines. An annual cardiovascular risk assessment was offered to diabetes patients free of CVD.<sup>16</sup>

Statins were offered to individuals whose 10-year risk was above the threshold and to elderly subjects at the age of 75 for the old guidelines and age 85 for the other guidelines. Antihypertensive medication was prescribed according to hypertension guidelines when individuals with SBP  $\geq$ 140 mm Hg had a 10-year risk above the risk threshold or when SBP was  $\geq$ 150 mm Hg regardless of risk.<sup>17</sup> Uptake of health checks was based on NHS data. We modelled full uptake of cardiovascular risk assessment in diabetes patients, assuming this would be included in their annual medical examination. Adherence to preventive medication was based on cohort data. Individuals who became non-adherent to preventive medication could restart once after a new prescription within a later screening visit, but the discontinuation rate was modelled to be twice as high. After a second time of becoming non-adherent, attendance to risk assessment became zero. We assumed that statins were offered to elderly individuals only once, during a doctor's visit with the same attendance as risk assessment.

We defined five polypill scenarios in which primary care physicians would offer a polypill with the same combination of agents and doses from the age of 40, 45, 50, 55 or 60 and over. We based these starting ages on the age ranges used as inclusion criterion in combination pill trials.<sup>10–18</sup> For each polypill scenario, we assumed that participants who initially took up risk assessment would also participate in the polypill programme. Persistence of polypill use was assumed to be the same as for statins.

### Treatment effects

For antihypertensive drugs, we applied a relative CVD rate reduction associated with the expected decrease in SBP.<sup>7</sup> This decrease depended on the number and dose of the agents used.<sup>19</sup> In guideline scenarios, the number of prescribed agents was determined by the difference between the individual's SBP at the screening visit and the target blood pressure recommended in hypertension guidelines.<sup>17</sup> Types of prescribed antihypertensive drugs were based on the individual's age at the

**Table 1** Baseline characteristics of UK Biobank study population

	UK Biobank cohort (n=259 146)
Age (years)	55.0 $\pm$ 8.1
Male gender	111 825 (43.2%)
Smoking status	
Non-smoker	127 593 (49.2%)
Former smoker	99 255 (38.3%)
Light smoker (<10 cigarettes/day)	15 316 (5.9%)
Moderate smoker (10–19 cigarettes/day)	9320 (3.6%)
Heavy smoker ( $\geq$ 20 cigarettes/day)	7662 (3.0%)
Social deprivation (Townsend score)	-1.4 $\pm$ 3.0
Ethnic group	
White or not recorded	246 056 (94.9%)
Indian	2757 (1.1%)
Pakistani	788 (0.3%)
Bangladeshi	97 (0.0%)
Other Asian	862 (0.3%)
Caribbean	2162 (0.8%)
Black African	1575 (0.6%)
Chinese	804 (0.3%)
Other	4045 (1.6%)
Clinical conditions	
Family history of early heart disease	28 102 (10.8%)
Family history of diabetes	23 161 (8.9%)
Type 2 diabetes	2131 (0.8%)
Atrial fibrillation	912 (0.4%)
Rheumatoid arthritis	2276 (0.9%)
Chronic renal disease	112 (0.0%)
Treated with corticosteroids	1953 (0.8%)
Clinical values	
Body mass index (kg/m <sup>2</sup> )	26.8 $\pm$ 3.9
Total cholesterol to high-density lipoprotein cholesterol ratio	4.1 $\pm$ 0.4
Systolic blood pressure (mm Hg)	136.0 $\pm$ 18.2

Data are presented as mean $\pm$ SD for continuous variables and as frequencies (%) for categorical data.

screening visit and ethnicity (for the decision making algorithm see eTable 3 in the online supplementary file). For statins we used risk ratios from a recent meta-analysis.<sup>20</sup> If combined, we assumed absence of interaction between statin and antihypertensive drugs. We modelled the effect on developing diabetes by statin and antihypertensive drugs using odds ratios reported in meta-analyses.<sup>21–22</sup> We assumed that subjects with serious side effects, for example, muscle pains or significant hepatic impairment, would discontinue preventive medication. In order to avoid double counting, we did not simulate occurrence of side effects and subsequent non-adherence in addition to the non-adherence rates already included in the model. More detailed information on the model is given in the eMethods and eTable 4 in the online supplementary file.

### Quality of life and cost data

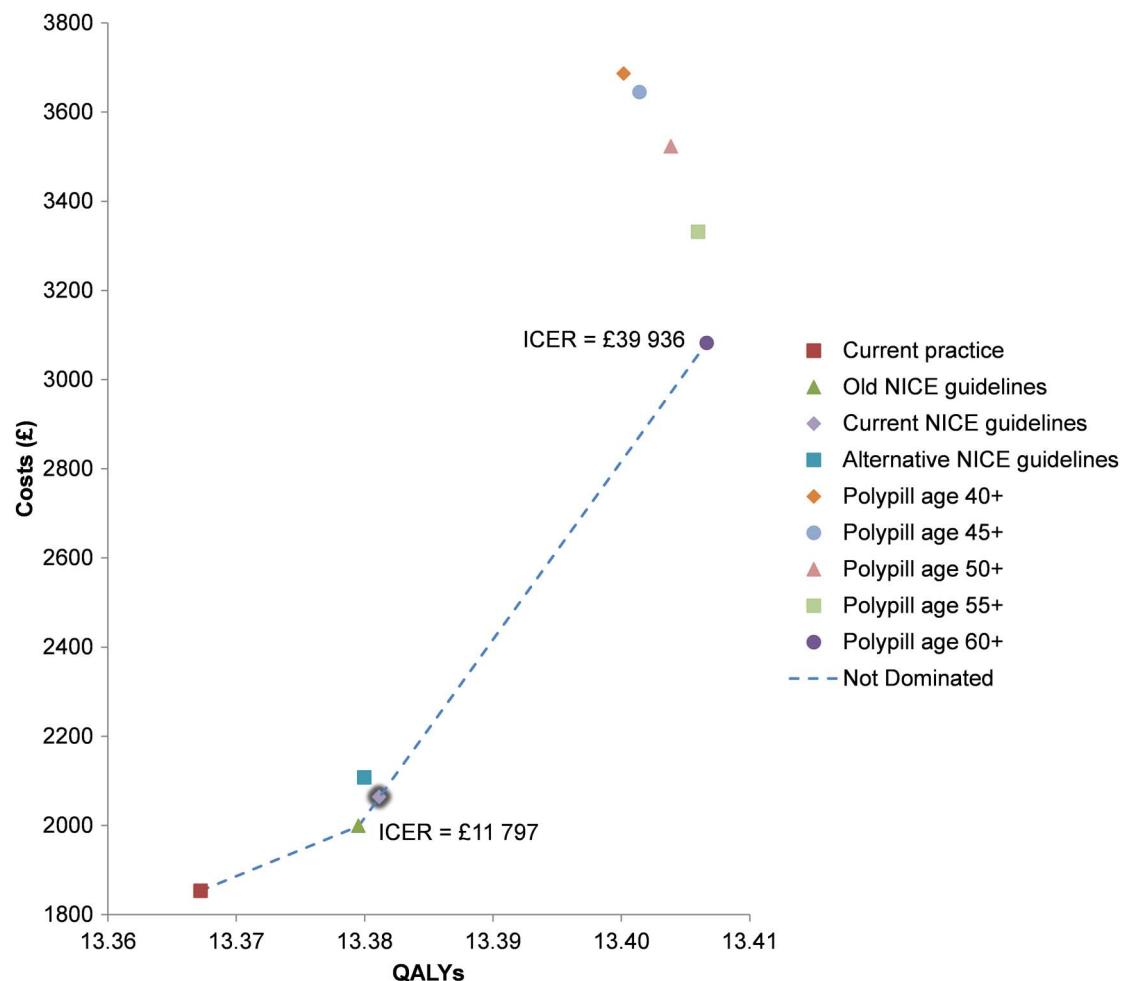
We included utility values dependent on age, gender and history of angina, MI or stroke as estimated for the general population. Utility values for TIA and diabetes were multiplied assuming independence. In case of CVD, a short-term disutility was subtracted. The disutility of daily preventive pill use was based on values obtained for the general population.<sup>23–24</sup> We estimated all costs from a UK health system perspective for the financial year 2012/2013. Polypill prices were based on Polypill.com.<sup>4</sup>

We assumed no costs and disutility when medication was discontinued. See eMethods and eTable 5 in the online supplementary file for more detailed information on utilities and costs.

### Analyses

In the base-case analysis, we modelled 10 000 randomly selected individuals by microsimulation and calculated events, costs, and quality-adjusted life-years (QALYs) until age 95. We discounted both costs and QALYs at an annual rate of 3.5%.<sup>25</sup> Incremental cost-effectiveness ratios (ICERs), defined as the difference in costs divided by the difference in QALYs, were calculated after exclusion of dominated scenarios. An ICER of less than £20 000–£30 000 per QALY gained was considered as being cost-effective.<sup>25</sup> We calculated average net health benefits by the formula: average QALY—average cost divided by £20 000 or £30 000 per QALY. To calculate 95% credible intervals (CIs) and the probability of being the most cost-effective scenario, we performed a probabilistic sensitivity analysis by randomly sampling from all parameter distributions. For 500 sets of sampled parameters, the 10 000 individuals were modelled accounting for population heterogeneity.

In threshold analyses we varied the costs of medication, the costs of CVD health care utilisation, the costs and relative risk of developing diabetes, and the disutility associated with



**Figure 1** Cost-effectiveness graph of base-case analysis results. Costs (in UK pounds) and quality-adjusted life-years (QALYs) are means in the UK Biobank study population. The grey shaded area indicates that the scenario has been eliminated by extended dominance. Extended dominance implies that the programme is less costly than the next not absolutely dominated programme, but also has a larger incremental cost-effectiveness ratio (ICER) than this next programme. NICE, National Institute for Health and Care Excellence.

**Table 2** Cost-effectiveness outcomes

Scenarios ranked according to increasing costs	Costs (95% CI)	QALYs (95% CI)	Incremental cost-effectiveness ratio	Incremental cost vs current practice (95% CI)	Incremental QALYs vs current practice (95% CI)	Net health benefit at £20 k/QALY (95% CI)	Net health benefit at £30 k/QALY (95% CI)	% cost-effective at £20 k/QALY	% cost-effective at £30 k/QALY
Current practice	1854 (1607 to 2294)	13.367 (12.415 to 14.243)	–	–	–	13.275 (12.327 to 14.136)	13.305 (12.358 to 14.171)	36.0	28.4
Cardiovascular risk assessment scenarios									
Old guidelines	1999 (1753 to 2423)	13.380 (12.426 to 14.243)	11 797	145 (89 to 194)	0.012 (–0.017 to 0.039)	13.280 (12.325 to 14.142)	13.313 (12.359 to 14.174)	29.0	24.6
Current guidelines	2064 (1823 to 2486)	13.381 (12.426 to 14.250)	(40 089 Extendedly dominated)	210 (136 to 277)	0.014 (–0.026 to 0.047)	13.278 (12.318 to 14.144)	13.312 (12.354 to 14.178)	22.6	19.0
Alternative guidelines	2107 (1868 to 2531)	13.380 (12.428 to 14.248)	Absolutely dominated	254 (174 to 326)	0.013 (–0.029 to 0.049)	13.275 (12.318 to 14.138)	13.310 (12.354 to 14.172)	9.0	10.2
Subtotal:									
Polypill scenarios									
Polypill age 60+	3082 (2851 to 3591)	13.407 (12.452 to 14.284)	39 945	1229 (1134 to 1296)	0.039 (–0.013 to 0.085)	13.253 (12.294 to 14.123)	13.304 (12.346 to 14.177)	2.8	12.4
Polypill age 55+	3331 (3104 to 3743)	13.406 (12.452 to 14.272)	Absolutely dominated	1478 (1375 to 1551)	0.039 (–0.024 to 0.091)	13.239 (12.280 to 14.096)	13.295 (12.335 to 14.155)	0.4	3.2
Polypill age 50+	3523 (3394 to 3919)	13.404 (12.447 to 14.261)	Absolutely dominated	1669 (1561 to 1748)	0.037 (–0.032 to 0.095)	13.228 (12.269 to 14.076)	13.286 (12.329 to 14.138)	0.2	1.6
Polypill age 45+	3645 (3419 to 4041)	13.401 (12.444 to 14.258)	Absolutely dominated	1791 (1682 to 1873)	0.034 (–0.038 to 0.097)	13.219 (12.260 to 14.070)	13.280 (12.321 to 14.131)	0.0	0.4
Polypill age 40+	3686 (3462 to 4083)	13.400 (12.444 to 14.256)	Absolutely dominated	1833 (1721 to 1915)	0.033 (–0.037 to 0.097)	13.216 (12.258 to 14.066)	13.277 (12.320 to 14.128)	0.0	0.2
Subtotal:									
								3.4	17.8

Costs (in 2012/2013 UK pounds), QALYs and net health benefits (in QALYs) are provided as mean from the base-case analysis with 95% CI from the probabilistic sensitivity analysis. Incremental cost-effectiveness ratios are given, calculated by comparison of undominated strategies. Absolutely dominated indicates a less effective and more costly programme than the previous programme. Extendedly dominated indicates a programme that is less costly than the next not absolutely dominated programme, but also has a larger incremental cost-effectiveness ratio than this next programme. CI, credible interval; QALYs, quality-adjusted life-years.

preventive pill use. Different scenarios for the uptake of prevention programmes and medication were evaluated. Furthermore, we evaluated modifications of prevention programmes by varying the stop age of periodic risk assessment and the age for starting the polypill beyond age 60, and restricting polypill prescriptions to those with a minimal SBP of 120 mm Hg, 130 mm Hg, and 140 mm Hg at ages of eligibility. More information on the analyses is given in the eMethods in the online supplementary file.

**RESULTS**

The average life expectancy estimated was 28.70 (95% CI 28.47 to 28.99) vs 28.01 by life tables (also see eFigure 2 in the online supplementary file). In the base-case analysis, the old guideline scenario was the optimal strategy. This would gain 123.1 QALYs (95% CI -173.0 to 386.8) and cost £1.45 million (0.89 to 1.94) extra per 10 000 individuals as compared with current practice with an ICER of £11 797/QALY (figure 1 and table 2). With these old guidelines, the population's current CVD risk of 34.0% (95% CI 33.0% to 34.9%) would decrease by 2.6% (95% CI 1.8% to 3.3%), whereas the diabetes incidence of 22.7% (95% CI 21.9% to 23.5%) would increase by 0.6% (95% CI -0.1% to 1.3%) (table 3).

Implementation of current guidelines would result in a larger reduction of CVD risk by 0.6% (95% CI 0.3% to 1.0%). However, as compared with the old guidelines, diabetes risk would increase by 0.2% (95% CI 0.0% to 0.4%) and the total number of risk assessments per 10 000 individuals would increase by 3699 (95% CI 3240 to 4222), with 1307 (95% CI 1235 to 1368) more individuals receiving a statin prescription and 502 (95% CI 443 to 565) more receiving a prescription for antihypertensive drugs (table 3). The ICER was £40 089 per QALY compared with old guidelines (table 2).

Polypill scenarios were more effective than risk assessment, with gains of 190 to 270 QALYs per 10 000 individuals, but also more costly. Offering the polypill at age 60 was a potentially cost-effective scenario, but then a cost-effectiveness threshold of more than £30 000/QALY should be considered. Other polypill strategies were absolutely dominated, that is, less effective and more costly than if started at age 60 (figure 1 and table 2). As compared with the old guideline scenario, polypill use above age 60 reduced lifetime CVD risk further by 2.5% (95% CI 1.8% to 3.1%). Also, diabetes risk was lower with polypill use: 0.2% (95% CI -1.7% to 1.7%) (table 3).

Superiority of the old guidelines was sensitive to the disutility of daily preventive pill use perceived as losing 6 months life expectancy. If these were to be 8 months or more, current practice was optimal, and if less than 5.5 months, current or alternative guideline scenarios were most cost-effective depending on the cost-effectiveness threshold. In addition, with a cost-effectiveness threshold of £30 000/QALY, current guidelines were more cost-effective than old guidelines if the odds ratio of statins for increasing diabetes risk was close to 1. These findings were furthermore sensitive to the prices of statins and antihypertensive drugs (table 4).

The polypill scenario starting at age 60 became the most cost-effective strategy at annual drug prices below £240 and would become cost-saving at prices below £60 per year. All five polypill scenarios would save costs at prices below £50. Average savings would be up to £1.85 million per 10 000 individuals if annual prices were £10. Starting the polypill if the individual's SBP was ≥140 mm Hg or at later ages up to 75 improved its cost-effectiveness with ICERs below £30 000 per QALY (table 4 and eFigure 3 in the online supplementary file).

**Table 3** Population health outcomes in 10 000 individuals

Scenarios ranked according to increasing costs	No. of NHS health checks performed (95% CI)	No. of primary care risk assessments performed (95% CI)	No. of individuals selected for antihypertensives (95% CI)	No. of individuals selected for statins (95% CI)	No. of individuals with incident CVD (95% CI)	No. of incident diabetes mellitus (95% CI)	Average life expectancy (years, undiscounted) (95% CI)
Current practice	0	0	0	0	3401 (3305 to 3490)	2249 (2168 to 2327)	28.70 (28.47 to 28.99)
Cardiovascular risk assessment scenarios							
Old guidelines	13 665 (13 306 to 13 992)	10 552 (10 014 to 11 103)	2761 (2688 to 2840)	3822 (3721 to 3912)	3144 (3040 to 3257)	2304 (2200 to 2410)	28.81 (28.57 to 29.08)
Current guidelines	11 596 (11 266 to 11 865)	16 320 (15 637 to 17 119)	3263 (3180 to 3349)	5128 (5033 to 5218)	3082 (2976 to 3203)	2320 (2209 to 2434)	28.83 (28.60 to 29.10)
Alternative guidelines	11 596 (11 266 to 11 865)	16 066 (15 347 to 16 919)	3994 (3901 to 4082)	5129 (5033 to 5218)	3069 (2959 to 3193)	2332 (2208 to 2464)	28.84 (28.61 to 29.10)
Polypill scenarios							
Polypill age 60+	0	0	4593 (4491 to 4677)	4593 (4491 to 4677)	2897 (2767 to 3037)	2283 (2123 to 2482)	28.91 (28.68 to 29.18)
Polypill age 55+	0	0	4712 (4604 to 4807)	4712 (4604 to 4807)	2877 (2742 to 3021)	2286 (2115 to 2492)	28.92 (28.69 to 29.19)
Polypill age 50+	0	0	4769 (4658 to 4860)	4769 (4658 to 4860)	2868 (2734 to 3014)	2288 (2111 to 2503)	28.93 (28.70 to 29.20)
Polypill age 45+	0	0	4787 (4687 to 4897)	4787 (4687 to 4897)	2865 (2732 to 3013)	2289 (2109 to 2506)	28.93 (28.71 to 29.20)
Polypill age 40+	0	0	4792 (4682 to 4882)	4792 (4682 to 4882)	2865 (2732 to 3013)	2289 (2108 to 2506)	28.93 (28.70 to 29.20)

Numbers are provided from the base-case analysis with 95% CI from the probabilistic sensitivity analysis. CI, credible interval; CVD, cardiovascular disease; NHS, National Health Service.

**Table 4** Results of threshold and scenario analyses

	Current practice	Old guidelines	Current guidelines	Alternative guidelines	Polypill age 60+	Polypill age 55+	Polypill age 50+	Polypill age 45+	Polypill age 40+
<b>Threshold analyses</b>									
Cost of the NHS health check: 50–150% of base-case value	None	All	None	None	None	None	None	None	None
Cost of antihypertensives: 50–500% of base-case value	200–500% (290–500%)	50–200% (50–290%)	None	None	None	None	None	None	None
Cost of ARB: £10–£300	£80–£300 (£150–£300)	£10–£80 (£10–£150)	None	None	None	None	None	None	None
Cost of CCB: £10–£500	£60–£500 (£120–£500)	£10–£60 (£10–£120)	None	None	None	None	None	None	None
Cost of diuretic: £5–£50	None	All	None	None	None	None	None	None	None
Cost of statins: £10–£300	£100–£300 (£210–£300)	£10–£100 (£10–£210)	None	None	None	None	None	None	None
Cost of annual polypill use: £10–£400	None	£240–£400 (£320–£400)	None	None	£10–£240 (£10–£320)	None	None	None	None
Cost of acute care of CVD events: 50–150% of base-case value	None	All	None	None	None	None	None	None	None
Cost of chronic care after CVD: 50–150% of base-case value	None	All	None	None	None	None	None	None	None
Cost of chronic care after DM: 50–150% of base-case value	None	All	None	None	None	None	None	None	None
Disutility pill use: 0–18 months required gain in life expectancy	8–18 (8.5–18) months	5–8 (5.5–8.5) months	0–5 (0–5.5) months	None	None	None	None	None	None
Odds ratio of statins for DM risk: odds ratio varying from 1–2	1.5–2 (1.7–2)	1–1.5 (1.02–1.7)	None (1–1.02)	None	None	None	None	None	None
<b>Scenario analyses</b>									
No additional prescription of statins in elderly regardless of 10-year CVD risk	–	ICER=£12 175	ICER=£29 307	Absolutely dominated	ICER=£39 925	Absolutely dominated	Absolutely dominated	Absolutely dominated	Absolutely dominated
Periodic cardiovascular risk assessment until age 85 in old guidelines	–	ICER=£13 719	Extensively dominated (ICER=£71 076)	Absolutely dominated	ICER=£40 336	Absolutely dominated	Absolutely dominated	Absolutely dominated	Absolutely dominated
Periodic cardiovascular risk assessment until age 75 in current and alternative guidelines	–	ICER=£11 797	Extensively dominated (ICER=£57 348)	Absolutely dominated	ICER=£39 945	Absolutely dominated	Absolutely dominated	Absolutely dominated	Absolutely dominated
Different uptake of preventive programmes for age >55 vs age <55: odds ratio equals 2	–	ICER=£10 975	Extensively dominated (ICER=£51 737)	Absolutely dominated	ICER=£43 028	Absolutely dominated	Absolutely dominated	Absolutely dominated	Absolutely dominated
Adherence to periodic risk assessment in diabetics equal to non-diabetics	–	ICER=£13 136	Extensively dominated (ICER=£39 637)	Absolutely dominated	ICER=£37 320	Absolutely dominated	Absolutely dominated	Absolutely dominated	Absolutely dominated
Full adherence to prevention programmes	–	ICER=£15 156	Extensively dominated (ICER=£162 296)	Absolutely dominated	ICER=£50 280	Absolutely dominated	Absolutely dominated	Absolutely dominated	Absolutely dominated
Full adherence to preventive medication use	–	ICER=£8 576	ICER=£31 723	Absolutely dominated	ICER=£52 164	Absolutely dominated	Absolutely dominated	Absolutely dominated	Absolutely dominated
Full adherence to prevention programmes and preventive medication use	–	ICER=£9 780	Extensively dominated (ICER=£48 799)	Absolutely dominated	ICER=£43 469	Absolutely dominated	Absolutely dominated	Absolutely dominated	Absolutely dominated

Continued

Table 4 Continued

	Current practice	Old guidelines	Current guidelines	Alternative guidelines	Polypill age 60+	Polypill age 55+	Polypill age 50+	Polypill age 45+	Polypill age 40+
Prescription of polypill if eligible age and SBP $\geq 120$ mm Hg	–	ICER=£11 797	(40 089 Extendedly dominated)	Absolutely dominated	ICER=£36 356	ICER=£2 260 942	Absolutely dominated	Absolutely dominated	Absolutely dominated
Prescription of polypill if eligible age and SBP $\geq 130$ mm Hg	–	ICER=£11 797	(40 089 Extendedly dominated)	Absolutely dominated	ICER=£34 016	ICER=£421 474	Absolutely dominated	Absolutely dominated	Absolutely dominated
Prescription of polypill if eligible age and SBP $\geq 140$ mm Hg	–	ICER=£11 797	(40 089 Extendedly dominated)	Absolutely dominated	ICER=£29 207	ICER=£168 483	Absolutely dominated	Absolutely dominated	Absolutely dominated

For each threshold analysis, it is indicated at which value(s) the strategy will be the most cost-effective programme as compared with the other strategies at £20 k (£30 k). For scenario analyses, incremental cost-effectiveness ratios (ICERs) are given, calculated by comparison of undominated strategies. Absolutely dominated indicates a less effective and more costly programme than the previous programme. Extendedly dominated indicates a programme that is less costly than the next not absolutely dominated programme, but also has a larger incremental cost-effectiveness ratio than this next programme.

ARB, angiotensin receptor blocker; CCB, calcium channel blocker; CVD, cardiovascular disease; DM, diabetes mellitus; NHS, National Health Service; SBP, systolic blood pressure.

## DISCUSSION

We found that periodic risk assessment with prescribing preventive drugs at a 10-year risk of 20% was most cost-effective. Risk assessment using a lower 10-year risk threshold of 10% and polypill scenarios were more effective, in the sense that the total number of CVD events prevented and QALYs was higher. These scenarios were, however, also more costly and the incremental costs per QALY gained were high. Starting the polypill at the age of 60 and over was the most cost-effective scenario when the annual polypill price was lower than £240; polypill scenarios would save costs at prices below £50. The disutility of daily preventive medication use had a major influence on our findings, favouring the current practice scenario when this disutility was greater than or equal to losing 8 months life expectancy. Our results were furthermore sensitive to assumptions about the adverse risk of statins for development of diabetes, albeit to a lesser extent.

We demonstrated that the polypill's benefits were partly offset by the disutility of daily pill use, and its drug price outweighed potential cost savings. In contrast to our findings, two studies demonstrated that population-wide use of combination pills is cost-effective as compared with treating high-risk individuals only.<sup>18 26</sup> However, both studies assumed that the price of the combination pill would be the sum of the prices of its components and no pill disutility was considered.

Our analysis has a number of strengths. We predicted lifetime risks of CVD and non-CVD death using validated equations derived from 2.3 million individuals.<sup>6</sup> To model heterogeneity in risk factor profiles, we simulated participants of a large population-based study, the UK Biobank.<sup>12</sup> In addition, we individualised the incidence of diabetes,<sup>11</sup> and modelled its consequences for health-related costs and quality of life. The effects of statins and antihypertensive drugs on CVD and diabetes were derived from large meta-analyses of randomised trials.<sup>7 20–22</sup>

Nevertheless, we had to make a number of assumptions that may have led to bias. First, we assumed that reductions in blood pressure by the polypill would follow calculations for use of the three antihypertensive drugs separately.<sup>19</sup> Two recent meta-analyses concluded that reductions in blood pressure with the polypill are generally lower than those previously projected.<sup>9 27</sup> However, most of the included trials used one or two antihypertensive drugs instead of three. When the equation for estimation of the decrease in SBP with three half-dose antihypertensive drugs is applied to the average baseline SBP of the trial evaluating this polypill (143 mm Hg), the expected decrease is similar to that observed: 18.4 vs 17.9 (95% CI 15.7 to 20.1) mm Hg. Second, we did not explicitly model subsequent CVD events. This could contribute to an underestimation of the cost savings that can be achieved by preventing first CVD events, favouring restrictive scenarios. Nonetheless, our findings were robust within a wide range of costs associated with the care after a CVD event. Third, the increase in the odds of developing diabetes as observed in statin trials could be an artefact, because subjects who were randomised to statins had lower fatal CVD rates than subjects in the placebo group, and as a result, may have developed higher diabetes rates due to increased subject-time of follow-up. We evaluated our assumption in a sensitivity analysis, and found that if the odds ratios associated with statins were to be closer to 1, recommendations for wider use of statins could be supported. Fourth, we did not consider differential effects of preventive medication according to the individual's characteristics and risk profile. For example, it has been reported that statins have a different effect in men and women without a history of CVD.<sup>28</sup> Meta-analyses that also

included the JUPITER trial, however, showed that relative reductions in coronary and stroke event rates are similar for men and women in a primary prevention setting.<sup>29 30</sup> Nevertheless, we acknowledge that individualisation of treatment effectiveness and its implications for the design and content of prevention programmes should be further investigated.

There is an international trend towards recommending medication use to prevent CVD in individuals at lower cardiovascular risk.<sup>1 2</sup> It has been estimated that the new US cholesterol treatment guidelines will increase the number of adults eligible for statins by 11%.<sup>31</sup> Around the world these changes to guidelines have sparked the debate on 'over-medicalization'.<sup>32 33</sup> We now provide evidence that expanding the use of statins and antihypertensive drugs for CVD prevention appears to improve survival but that the incremental costs per QALY gained are high, mainly because the general population assigns a small quality of life decrement to preventive pill use. Therefore, future research should compare the cost-effectiveness of non-pharmacological preventive strategies to interventions that give rise to long-term medication use.

## CONCLUSION

Periodic risk assessment with lower risk thresholds to initiate preventive drugs is unlikely to be cost-effective. A population approach with the polypill would become cost-effective if drug prices were reduced.

### Key messages

#### What is already known on this subject?

- ▶ Guideline committees recently changed their recommendations for periodic cardiovascular risk assessment, which will potentially result in wider use of drugs for the primary prevention of cardiovascular disease.
- ▶ As an alternative to periodic risk assessment, a population approach with a polypill including a statin and three half-standard dose antihypertensive agents has been proposed; this polypill was associated with significant cardiovascular risk factor reductions in a randomised trial.

#### What might this study add?

- ▶ Periodic cardiovascular risk assessment using a restrictive threshold for prescription of statins and antihypertensive drugs, as recommended in the guidelines before the updates, is most cost-effective.

#### How might this impact on clinical practice?

- ▶ A population approach with the polypill is currently too costly to be implemented in the UK, but would become cost-effective if drug prices were reduced.

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## IMAGE CHALLENGE

## A case of recent myocardial infarction with cardiac failure

## CLINICAL INTRODUCTION

A 50-year-old hypertensive smoker presented with a typical angina of 2 days duration. An urgent ECG revealed extensive anterior wall myocardial infarction. In view of the delayed presentation, the patient was conservatively managed with heparin. In-hospital echocardiogram showed akinesia of entire left anterior descending artery (LAD) territory with severe left ventricular (LV) dysfunction. He was discharged with a plan for early coronary intervention. However, he presented a fortnight later with acute pulmonary oedema. General

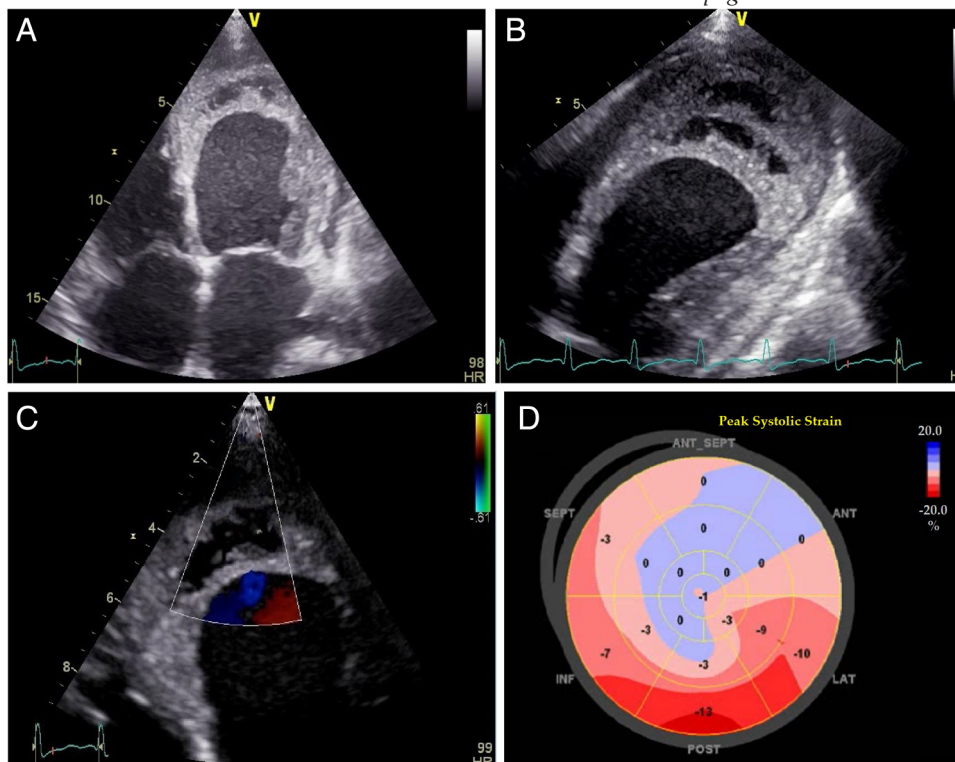
appraisal revealed a restless individual who was dyspnoeic and diaphoretic at rest. On clinical examination, the patient was in hypotension with features of biventricular failure. A 12-lead ECG showed QS pattern with persistent ST segment elevation in precordial leads. The chest radiograph demonstrated features of pulmonary oedema, cardiomegaly and bilateral pleural effusion. Creatine Phosphokinase-MB (CPK-MB) was negative. A preliminary transthoracic echocardiography was done (figure 1 and see online supplementary video 1).

## QUESTION

What is the most likely diagnosis based on the echocardiogram?

- A. LV pseudo-aneurysm with contained rupture  
 B. Dissecting intramural haematoma of LV apex  
 C. Ventricular apical aneurysm with thrombus  
 D. LV non-compaction with prominent ventricular trabeculations

For the answer see page 529



**Figure 1** (A) Trans thoracic echocardiogram-apical 4 chamber view; (B) zoomed view of apex; (C) colour Doppler at left ventricular (LV) apex and (D) bulls-eye plot of strain imaging.