Work programme 1

Evidence from a Screening Study.

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This section discusses the data collected as part of a screening study that followed the collection of data from practice information systems (full description of electronic data collection is described in appendix 1).

Background

The results from this study, combined with the findings from practice information systems provide an accurate assessment of the proportion of people in primary care aged ≥50 who would benefit from treatment to lower CVD risk according to current guidelines. The data will primarily be used to populate the economic modelling study.

Methods

Practice information data was used to identify patients aged 50+ who have unknown CV risk, including those on treatment for either raised cholesterol or raised blood pressure in whom there is not sufficient information to calculate a risk score (to judge whether they should receive additional treatment). These patients were then invited to attend their practice for a screening assessment using standard letters and patient information sheets. One reminder was sent to non-responders two weeks following the initial invitation. A short covering letter in a variety of languages was also sent with the invitation. This briefly summarised the study for those in whom English is not the first language, and encouraged them to speak to someone who can help them understand the study information. For patients attending screening, the practice's usual translation/interpretation processes was used.

The screening assessment appointment was held at the patient's surgery and was carried out by research nurses. During this appointment the nurses:

1. Obtained informed consent;
2. Took systolic and diastolic BP measurements in a standardised way;
3. Measured total, HDL and LDL cholesterol, glucose and creatinine using near patient testing devices;
4. Carried out an assessment of medical history, including questions relating to CV risk factors (such as smoking status); existing CV disease; and questions related to the national screening programme (such as family history of CVD and ethnicity);
5. Performed an ECG on patients who have no record of left ventricular hypertrophy on computer reports;

6. Measured height and weight and calculated body mass index
7. Measured waist circumference
8. Calculated CV risk score (high risk patients were referred to their GP;
9. Requested that patients in the existing or high risk groups complete the Beliefs about Medicines Questionnaire (BMQ); and a questionnaire on personal costs of attending the clinic

Results

Population characteristics

From the nine screening practices there were 12416 patients aged 50 years and over, 6850 had an unknown cardiovascular risk score and were eligible for inclusion in the screening study. Of those invited to screening 2642 (38.6%) attended the appointment. Attendees were predominantly female with a mean age of 62 years and a mean blood pressure of 128/78mmHg, all characteristics are summarised in table 1. There were 1021 patients who had both a baseline and screening blood pressure measurement available for comparison, for these patients there was a significant difference between mean blood pressure readings extracted from patient records at baseline, 136/80mmHg, and the mean measurement obtained at the screening appointment, 129/78mmHg ($p < 0.001$).

Table 1: Characteristics of patients who attended the screening appointment, all values presented as mean (SD) unless otherwise stated

Characteristic	Screening
Population (n) attended for screening	2642
Age (years)	62 (8.7)
Sex (% Male)	43.6
SBP (mmHg)	128 (18.3)
DBP (mmHg)	78 (10.1)
Total cholesterol (mmol/L)	5.5 (1.1)
HDL cholesterol (mmol/L)	1.4 (0.4)
LDL cholesterol (mmol/L)	3.3 (0.98)
Total cholesterol:HDL ratio	4.3 (1.7)
Glucose (mmol/L)	6.3 (1.95)
Creatinine (umol/L)	69.1 (19.1)
Smoking status (%)	
- Current	13.8
- Ex	36.4
- Never	49.5
- Unknown	0.2
Personal history of Diabetes (%)	0.7
Personal history of CKD (%)	1.4
Family history of CVD (%)[#]	53.9
ECG evidence of LVH (%)	0.8
Waist circumference (cm)	93.5 (13.6)
Height (cm)	166.2 (9.9)
Weight (kg)	75.4 (13.4)
BMI (kg/m^2)	27.2 (4.6)

[#]Angina, MI or stroke in a parent, sibling or child of any age

Based on systolic blood pressure measures alone approximately twenty five percent of screened patients would at least require further monitoring (home or ambulatory blood pressure monitoring) and investigation (to determine 10-year cardiovascular risk and end organ damage): 5.9% had a systolic blood pressure greater than or equal to 160 mmHg and 18.5% had a systolic blood pressure between 140-159 mmHg (table 2). When systolic blood pressure was analysed in the context of 10-year cardiovascular risk groups 15.68% of patients were potentially eligible for pharmacological treatment: 5.95% had stage 2 hypertension with a systolic blood pressure greater than or equal to 160 mmHg and 9.73% had a systolic blood pressure between 140-159 mmHg and were either known to have established cardiovascular disease or were at high risk of developing cardiovascular disease over the next 10-years (table 3).

Table 2: Percentage of patients potentially eligible for pharmacological therapy or further monitoring on the basis of systolic pressure

Systolic BP (mmHg)	Percentage of screened patients
<140	75.6
140 – 159	18.5
≥160	5.9

Table 3: Percentage of patients potentially eligible for pharmacological therapy on the basis of CVD risk group and systolic blood pressure

	Cardiovascular risk group			
Systolic BP group	**Known CVD**	**High risk**	**Low risk**	**Unknown risk**
<140	1.17	14.92	58.80	0.68
140-159	0.42	9.31	8.67	0.08
≥160	0.23	4.28	1.40	0.04

10-year cardiovascular risk

At baseline 16.4% of patients were known to have cardiovascular disease: 10.6% with CHD; 3.4% with PVD and 4.7% with previous stroke or TIA (note these are not mutually exclusive). Of the individuals screened 1.3% had known cardiovascular disease, this includes any with known diagnoses not documented in the general practice records but elicited by the research nurse at the screening appointment and those who received a diagnosis of CVD between the GP records search and the screening appointment.

Searching routine GP data identified 30.7% of the population required intervention: 16.4% with known cardiovascular disease eligible for secondary prevention therapy and 14.3% at high risk for CVD eligible for primary prevention. Of the screened population 37.1% were eligible for primary (20.4%) or secondary (16.7%) prevention (table 4

). Table 5 summarises the change in prevalence for the entire eligible population following screening.

Table 4: Percentage of the screening population in each CVD risk group

Framingham 10 year risk group (%)	Screening population
Known CVD	1.3
High Risk (≥20)	28.7
Low Risk (<20)	69.2
Unknown risk	0.8

Table 5: Percentage of patients eligible for pharmacological intervention on the basis of known cardiovascular risk scores at baseline and baseline plus screening

Framingham 10 year risk group (%)	Baseline	Baseline + Screening
Known CVD	16.4	16.7
High risk (≥20)	14.3	20.4
Low risk (<20)	14.1	28.7
Unknown risk %	55.2	34.2

+ Adjusted for ethnicity and family history of premature CHD

If we assume that those with unknown cardiovascular risk scores and who did not attend screening are the same as those who did attend screening it is possible to estimate the overall population prevalence of cardiovascular disease and 10-year CVD risk. When combining known risk scores with assumed scores almost half of this population would be potentially eligible for pharmacological intervention including 17% of patients with known cardiovascular disease and 30% of patients with high 10-year cardiovascular risk (table 6).

Table 6: Percentage of patients eligible for pharmacological intervention on the basis of known cardiovascular risk scores and assumed values for those with unknown risk scores

Framingham 10 year risk group (%)	Percentage
Known CVD	17
High Risk (≥20)	30
Low Risk (<20)	53
Unknown risk	0

+ Adjusted for ethnicity and family history of premature CHD

Discussion

As previously stated, the primary use of the data collected for this screening project is to carry out a cost effectiveness analysis of primary prevention in people with unknown CV risk. Therefore, discussion around these findings can be found in the paper on this analysis**.**

Cost-effectiveness analysis of primary prevention of cardiovascular disease with a polypill for all versus screen and treatment as per guidelines in a population with unknown cardiovascular (CV) risk

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Paper in preparation.

Introduction

Although a number of clinical trials have been or are currently being conducted with regards to the clinical effectiveness of a fixed- dose polypill, there are very few published cost-effectiveness analyses concerning the use of a polypill in a primary prevention population. Franco et al (2006) used decision modelling to consider the price at which a polypill would be cost-effective for different risk profiles.[1] Again using decision modelling, van Gils et al (2011) compared three different polypill options (with prior opportunistic screening for CV risk) with usual care for a Dutch population, and found all options to be cost-effective. [2] However, in essence, the original proposal of the potential role of a polypill was of its use in an unscreened population.[3] There have been no cost effectiveness analyses to date of using a polypill without prior cardiovascular screening and comparing that strategy to usual care, which in the UK is currently to offer health checks and treating those identified to be at raised cardiovascular risk according to national guidelines.

The aim of the following study was therefore to estimate the cost-effectiveness of treating all patients aged 50 and over with unknown cardiovascular risk with a polypill compared with screening for cardiovascular risk and treating with statins and antihypertensives as per clinical guidelines. Decision modelling was undertaken and utilised patient-level data with information on 10-year cardiovascular risk from a large-scale primary care cardiovascular screening study

Methods

A Markov cohort model, built in TreeAge Pro, was developed to estimate the cost-effectiveness of primary prevention with a polypill strategy compared with screening for cardiovascular (CV) risk and treating as per guidelines. The model considered patients aged 50 and over with unknown CV risk and no history of CVD, who were not on statins or antihypertensive therapy.

The model considered patient lifetime with a monthly time cycle to take into account early (short-term) changes in compliance with treatment. All patients started the model in a well health state and on no treatment. Patients could move to other health states in the model, dependent on whether they had been screened and were receiving treatment. Once a CV event occurred, they either died from this event, or remained in this health state and incurred costs and a reduction in quality of life as assigned to that disease state until death (Figure 1). The CV events included in the model are stroke, myocardial infarction (MI), angina, heart failure and peripheral vascular disease (PVD). All base-case model inputs are shown in table 1.

The polypill strategy consisted of a pill a day containing a statin (40mg simvastatin) and three antihypertensives at half-dose (12.5mg hydrochlorothiazide, 5mg lisinopril, 2.5mg amlodopine). An initial polypill take-up rate of 50% was assumed, with a further 16% who agreed to take the drug then discontinuing by 12 weeks (TIPS, 2009).[4] The guideline strategy considered primary care-based screening to determine ten-year CV risk and baseline blood pressure for each patient and subsequent treatment dependent on NICE guidelines (NICE, 2008, 2011).[5 6] Screening occurred in the first month and every five years thereafter (for patients who were CV event-free and on no treatment) until the age of 75. For the 75 and over age group, it was assumed they would be screened only once. The screening uptake rate was set at 50%, in line with the rate of uptake found in the screening study. Screened patients were then allocated the appropriate treatment regimen.

Statin therapy (simvastatin 40mg) was assumed to be prescribed if CV risk was 20% or higher. Antihypertensives were assumed to be prescribed if BP was greater than 160/100mm/Hg but CV risk less than 20%, or if BP was greater than 140/90mm/Hg and CV risk was 20% or greater (NICE, 2011).[5] The average number of full-dose antihypertensives required to reach a target systolic BP of 140 mm/Hg was calculated using tables presented by from Law et al (2009). [7] The tables provided information on the level of BP lowering expected from a range of starting BPs for one, two and three full and half dose antihypertensives. The information required for each patient subgroup was the starting systolic BP and the degree of BP lowering required from that starting BP to reach the 140mm/Hg target. Linear interpolation was employed to firstly determine the level of lowering expected for a specific starting BP for all drug quantities, then interpolate number of drugs required to achieve a specific level of lowering. The tables also provided information on the estimated risk reduction for CHD and stroke for 10-year age groups. The class of antihypertensives prescribed were assumed to be an equal split between a diuretic (indapamide 2.5mg) and calcium channel blocker (CCB) (amlodopine 5mg) for the first drug, an ACE inhibitor (ramipril 5mg) for the second drug and an equal split between a diuretic and CCB for the third-line therapy. An assumption was made that 88% of patients complied with antihypertensive therapy (Hansson, 1989).[8] The effectiveness estimate for statins took into account 85% compliance whilst taking the drug (Heart Protection Study, 2002).[9] Cost of treatment was still incurred even if patients did not comply.

The model was run for eight separate age and gender cohorts (50-59, 60-69, 70-74, 75 and over). Patient level data on age, gender, blood pressure and ten-year CV risk was obtained from a screening study undertaken in 10 practices in the West Midlands. This allowed the stratification of patients in each age/gender cohort into four CV risk subgroups, which were required for determining the correct treatment (post-screen) as recommended by the lipid and hypertension guidelines. Ten year CV risk was calculated using the Framingham equation (Anderson, 1991).[10] The sub-groups were i) CV risk <20%, BP ≤140/90 mm/Hg (no treatment with guidelines); ii)

CV risk ≥20%, BP≤140/90 mm/Hg (statin only); iii) CV risk ≥20%, BP > 140/90 mm/Hg (statin and antihypertensives) and iv) CV risk <20%, BP > 160/100 mm/Hg (antihypertensives). The appropriate CV risk and effectiveness of interventions were applied according to the risk sub-group in each age/gender cohort. Each risk sub-group was characterised by a mean age, BP and CV risk (Table 2).

In order to take account of the increase in BP and CV risk with age, a new BP was calculated after five years and for every ten years thereafter up to the age of 75 for each patient in the screening data set. The increase in BP with age was taken from the Health Survey for England 2003 (Department of Health, 2004).[11] A new ten-year CV risk was also calculated at each time point taking into account increased BP and age. The new proportion in each CV risk group was then determined for each time point.

Ten-year CV risk was split between five possible events (stroke, MI, angina, heart failure and PVD). The weight attributed to each type of event was determined by CV risk profiles measures within the Framingham study, with intermittent claudication as a proxy for PVD (D'Agostino, 2008).[12] Coronary heart disease (CHD) was then sub-divided into MI and angina, using data on the breakdown of CHD events (Wood, 2004).[13]. The ten-year CV risk for each event type was subsequently converted into a monthly probability, calculated at an individual patient level in order that a mean probability and distribution for each sub-group (taking into account age, gender and CV risk sub-group) could be entered into the model. In the event of a stroke, MI or heart failure, there was a risk of death from that event.

Gender-specific life tables were used to determine the probability of death at all ages (ONS, 2013).[14] The risk of death was adjusted to ensure there was no double counting of CVD death, using mortality statistics data on the proportion of deaths by

CVD causes (ONS, 2012).[15] There was an increased risk of death once in a CV event health state, which was applied to the adjusted probability of death.

Effectiveness

Effectiveness estimates for statins were taken from a meta-analysis of statins trials,[16] taking into account 85% compliance with treatment (Heart Protection study, 2002)[9] with non-coronary vascularisations used as a proxy for PVD. The estimates for reduction in CHD and stroke risk with antihypertensives were taken from a meta-analysis of BP lowering trials (Law, 2009).[7] As previously described, this gave the estimated reduction in risk for stroke and CHD events for a range of pre-treatment BP values, drug number and dose and age range. The estimates for reduction in CHD risk were assumed to apply for MI, HF and angina. In the polypill strategy, for three half-dose antihypertensives, the risk reductions were interpolated for the starting systolic BP for each age/gender and CV risk subgroup. For the guidelines strategy it was assumed optimum BP control was a reduction in systolic BP to 140mm/Hg. The average number of drugs required to achieve this reduction was interpolated, again for each age/gender subgroup and appropriate CV risk subgroup. Estimates for reduction in risk for PVD were estimated from the Framingham risk calculator for PVD in Murabito (1997).[17] This provided risk reductions for moving to a lower SBP "risk" group (normal, high normal, stage one hypertension, stage two hypertension) with a reduction in risk only applied if a reduction in SBP moved someone from one SBP group to another. For both treatment options, where patients were taking statins and antihypertensives, the effectiveness of the treatments were assumed to act independently i.e. multiplicatively.

Outcome measures and costs

Outcomes were measured in quality-adjusted life years (QALYs) and costs from a UK NHS and personal social services (PSS) perspective. A baseline value was given for quality of life and, related to age and gender (NCSR, 2006).[18] Utility values were

given for all health states. When a CV event occurred within the model, the health state value for that event was applied. Values were applied multiplicatively; therefore the value for the state of the clinical event was multiplied by the value for the age. No reduction in quality of life was assumed for any of the drugs in the base-case analysis.

Table 1 shows all the costs included within the model. As there is no estimate available for a proposed cost of a polypill, we assumed a cost of approximately £1 a day, thus giving £30 a month. Additional costs associated with the polypill strategy were an initial GP visit and blood test in the first month, with an annual practice nurse visit and blood test annually thereafter. It was assumed that the cost of the polypill would only apply to those patients who agreed to take the polypill, 50% in the first three months, and 42% after three months (as it was assumed a further 16% discontinued the treatment). In the guidelines strategy, screening of patients to determine cardiovascular risk was set at £26.95, the cost calculated for vascular checks, updated to 2011/12 prices.[19] The cost was multiplied by the uptake rate of screening, therefore assuming only costs were incurred if screening was attended. The most commonly prescribed generic antihypertensive in each class (indapamide, amlodopine, ramipril) and the statin simvastatin were assumed for costing purposes for guideline directed treatment. Patients treated with antihypertensives were assumed to have an average of four consultations (mix of GP and practice nurse) per year for a blood pressure check and an annual blood test.[20] One-off acute costs of CV events were obtained from published costing studies and NHS Reference costs and long-term costs for health states were from published work.

Analysis

An incremental cost-utility analysis was undertaken to determine the cost-effectiveness of a polypill in primary prevention compared with screen and treat as per guidelines. Future costs and QALYs were discounted at the rate of 3.5%.[21] Costs

were in UK £ for 2011/12. Deterministic sensitivity analysis around key parameters was undertaken. Alternative costs of the polypill, CV screening, acute and chronic CV events and the impact of changing the assumptions concerning the proportion screened, frequency of screening and initial take up of and compliance with treatment were explored. Further analyses were undertaken to assess the impact of reducing quality of life on treatment, shortening the time horizon, reducing CV risk and reducing the effectiveness of the polypill. Where available, data were entered into the model as distributions in order to fully incorporate the uncertainty around parameter values in order that a probabilistic sensitivity analysis (PSA) could be undertaken. A log-normal distribution was used for all risk reductions and standardised mortality ratios after CV events, a beta distribution for CV event probabilities, risk of death from CV events and compliance with screening and a gamma distribution for acute and long-term costs The PSA was run with 10,000 simulations and cost-effectiveness planes and acceptability curves were produced.

Modelling results

The base-case analysis for all eight primary prevention subgroups demonstrated that a polypill is likely to be cost-effective compared with screening for cardiovascular risk and treating as per guidelines, with the incremental cost-effectiveness ratios (ICER) ranging between £8,000 and £18,000 per QALY gained (Tables 3 and 4). The polypill was the most cost-effective in the male 50-59 group (£8,115 per QALY gained), and least cost-effective for the oldest male age group (75+) (£18,438 per QALY gained). The results of the probabilistic sensitivity analysis support these findings with a 100% chance of the polypill being cost-effective for all patient sub-groups except for men aged 75+ with a 64% chance of being cost-effective.

Sensitivity analyses were undertaken to determine the impact on results of changing values of key parameters, using the males, aged 50-59 subgroup as the reference case (Table 5). The polypill was no longer cost-effective at the lower NICE threshold

of £20,000/QALY (NICE, 2012) [22] when the price was doubled, take-up was reduced to 25% or quality of life reduction on the polypill was 2% or more. In addition, the results favoured the screen and treat as per guidelines strategy if screening was annual rather than every five years, the time horizon was reduced to 10 years or antihypertensive treatment was 50% less effective than in the base case for the polypill. The model was also sensitive to a 25% reduction in the effectiveness of antihypertensive medication and statins. In order to still be cost-effective at a £20,000 per QALY threshold, the maximum price for the polypill per month was approximately £54.

Discussion

The findings of the base-case analysis of the decision model demonstrate that a polypill may be cost-effective option in all patients aged 50 and over. However this is only the case if the price of a polypill is reasonably priced and there is a reasonable level of take-up of the polypill by patients. In addition, if an annual check of CV risk factors were undertaken rather than every 5 years this may also change the result in the favour of titrating treatment to target levels of cholesterol and BP.

This is the first study to compare the use of a polypill for primary prevention in people with unknown cardiovascular risk with screening for CV risk and treating as per clinical guidelines, and the work is further strengthened by the use of patient level data on cardiovascular risk. In addition, the model uses conservative treatment costs of generic statins and antihypertensives for treatment as per guidelines. In reality some patients will be on more expensive drugs, thus making the polypill even more cost-effective.

However, the limitations of this analysis are due to assumptions included in the model. Firstly, the benefits of the polypill may be overestimated in the model, as the

effects of the two types of drug are assumed to work separately are risk reductions are applied multiplicatively. The risk reductions for the three half-dose antihypertensives are derived from the Law (2009) paper and may be over-optimistic. However, sensitivity analysis shows that even when effectiveness of statins and antihypertensives are both reduced by 25%, for the men aged 50-59 age group, the polypill still remains a cost-effective option. Moreover, the model may actually underestimate the effectiveness of the polypill as it assumes that if a patient decides not to take up the polypill then they are on no treatment. It may be the case that their GP prescribes a statin and/or antihypertensives instead, depending on the CV risk factors. The model does not take into account treatment effectiveness once a CV event occurs, and the assumption is made there is no recurrence of CV events. Again, this may underestimate the cost-effectiveness of a polypill which may have secondary prevention benefits.

The ideal comparator in economic analyses is usual care, yet this model does not include this as a possible option and this is due to the fact that it would be very difficult to predict how these currently untreated patients would be treated in the future. It is likely that if a usual care arm was possible, the polypill is likely to be cost-effective as usual care may be less effective than treatment as per guidelines. A further limitation is the screening study included a small proportion of patients who were on a statin or an antihypertensive but for whom information on CV risk was unknown, and the data used by this model includes the CV risk information for these patients. Therefore the effectiveness of treatment, either through a polypill or treatment as per guidelines, will be overestimated.

In conclusion, this cost effectiveness analysis suggests that a polypill strategy might be a more cost effective way to prevent cardiovascular disease than identifying and treating people at high risk of cardiovascular disease by screening for risk factors. Further empirical work, ideally a trial of polypill against screening, is required, to

determine what role a polypill is likely to play in the prevention of cardiovascular disease in people of undetermined risk.

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Table 1 General base case model inputs

	Values used	Sources
Risk of cardiovascular disease		
Probability of stroke (10 years)	0.2-10.9% (age and sex dependent)	Calculated with Framingham (Anderson, 1991) and risk factor profile based on patient level data
Probability of MI (10 years)	0.2-16.3% (age and sex dependent)	
Probability of angina (10 years)	0.3-23.1% (age and sex dependent)	
Probability of heart failure (10 years)	0.1-6.8% (age and sex dependent)	
Probability of PVD (10 years)	0.2-10.9% (age and sex dependent)	
Event distribution (% of 10 year CV risk)		
Stroke	16%	D'Agostino (2008), Wood (2004)
Myocardial infarction	24%	
Angina	34%	
Heart failure	10%	
PVD	16%	
Risk reduction with statins		

Stroke	0.80 (95% CI 0.73-0.86)	CTT (2005), HPS (2002)
MI, HF, angina	0.72 (95% CI 0.69-0.76)	CTT (2005), HPS (2002)
PVD	0.85 (95% CI 0.75-0.95)	HPS (2002)
Probability of death from event		
Fatal stroke	0.19	Ward (2007)[23]
Fatal MI	0.19-0.36 (Men) 0.23-0.40 (Women)	Ward (2007)
Fatal heart failure	0.17 (r=68, n=396)	Mehta (2009)[24]
SMR after stroke	2.72 (95% CI 2.59-2.85)	Bronnum-Hansen (2001)[25]
SMR after MI	2.68 (95% CI 2.48-2.91)	Bronnum-Hansen (2001)[26]
SMR after Heart Failure	2.17 (95% CI 1.96-2.41)	de Guili (2005) [27]
SMR after Angina	2.19 (95% CI 2.05-2.33)	NCGC (2010) [28]
SMR after PVD	2.44 (95% CI 1.59-3.74)	Leng (1996)[29]
Reduction in blood pressure		
Polypill	10-24mm Hg (Dependent on age, sex and risk group)	Law (2009)
Treat to target	9-28mm Hg (Dependent on age, sex and risk group)	Law (2009)
Number of AHT drugs required to achieve target BP	1.05-3	Law (2009)
Reduction in CV risk		

with reduction in BP		
Polypill		
CHD risk	20-55%	Law (2009)
Stroke risk	22-74%	Law (2009)
PVD risk	13-32% (Dependent on age, sex and risk group)	Murabito (1997)
Treat to target		
CHD risk	16-57%	Law (2009)
Stroke risk	16-69%	Law (2009)
PVD risk	13-32% (Dependent on age, sex and risk group)	Murabito (1997)
Compliance		
Polypill		
Start of treatment	0.5	Assumption
After 12 weeks (additional 16%)	0.42	TIPS (2009)
Screening	0.5	Screening study estimate
Statins	0.85	HPS (2002)
Antihypertensives	0.88	Hansson (1989)

Quality of life weights (utilities)		
No cardiovascular event	0.704 to 0.869 (age and sex dependent)	General population utilities from EQ-5D (UK Tariff) (NCSR, 2006)[18]
Death	0	By definition
Quality of life multipliers		
	Beta	
Acute MI	0.76 (0.018)	Cooper (2008) [30]
Post MI	0.88 (0.018)	As above
Acute angina	0.77 (0.038)	As above
Post-acute angina	0.88 (0.018)	As above
Heart failure	0.68 (0.020)	As above
Stroke	0.63 (0.040)	As above
PVD	0.90 (0.020)	As above
Costs		
	£ per month	
Simvastatin 40mg	1.27	BNF March 2013[31]
Amlodopine 5mg	1.01	BNF March 2013
Indapamide 2.5mg	0.99	BNF March 2013
Ramipril 5mg	1.53	BNF March 2013
Polypill	30	Assumption

	Unit cost	
CV screening	26.35	DoH (2008)
Blood test	15	Ward (2007)[72]
GP visit	33	Curtis (2012)[32]
Practice nurse visit	11.25	Curtis (2012)
	One-off cost	
Acute events:	11,020	
Stroke	5,487	Youman (2003)[33]
MI	3,292	Palmer (2002)[34]
Angina	1,971	Assumed 60% MI cost
PVD	2,699	NHS Reference costs 2011/12[35]
Heart failure		
	£ per year	
Long-term costs:	2,721	
Stroke	572	Youman (2003)
MI	572	Cooper (2008)
Angina	302	Cooper (2008)
PVD	572	Cooper (2008)
Heart failure		Cooper (2008)

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Table 2 Patient population, treatment as per guidelines subgroups

Men, age-group (mean age)	Mean (SD) 10 year CV risk	Mean (SD) Systolic BP	Mean (SD) Diastolic BP	Proportion at baseline (%)
50-59 (54.2)				
No treatment	11.7 (4.1)	121.3 (12.4)	80.1 (7.9)	71.6
Statins only	24.8 (4.3)	125.3 (8.4)	80.1 (6.2)	13.8
Statins and antihypertensives	28.9 (8.4)	155.0 (15.7)	94.8 (9.2)	13.1
Antihypertensives only	14.7 (4.1)	155.3 (18.1)	102.9 (8.4)	1.5
60-69 (63.8)				
No treatment	14.2 (3.2)	117.5 (11.6)	75.0 (7.8)	40.9
Statins only	27.2 (7.0)	126.7 (9.2)	78.4 (6.6)	35.1
Statins and antihypertensives	31.4 (8.0)	153.9 (14.5)	89.6 (9.1)	23.6
Antihypertensives only	19.0 (0.0)	149.0 (24.0)	98.5 (3.5)	0.4
70-74 (71.9)				
No treatment	16.0 (2.7)	115.0 (10.8)	70.4 (6.4)	19.2

Statins only	29.4 (7.7)	125.5 (8.7)	73.7 (6.1)	53.6
Statins and antihypertensives	35.4 (8.8)	150.0 (10.4)	83.3 (8.5)	27.2
75+ (79.8)				
No treatment	15.1 (3.8)	107.3 (7.5)	66.3 (5.2)	5.4
Statins only	31.4 (7.1)	125.1 (9.6)	721.6 (6.8)	59.7
Statins and antihypertensives	44.4 (9.9)	158.3 (13.9)	83.7 (9.9)	34.9
Women, age group (mean age)	**Mean 10 year CV risk**	**Mean systolic BP**	**Mean diastolic BP**	**Proportion at baseline (%)**
50-59 (54.5)				
No treatment	7.0 (4.0)	120.8 (14.2)	75.6 (8.5)	94.5
Statins only	22.7 (2.9)	129.2 (6.3)	78.6 (4.6)	1.4
Statins and antihypertensives	26.2 (6.3)	163.8 (22.3)	90.1 (7.6)	1.0
Antihypertensives only	12.6 (4.0)	164.6 (12.2)	93.5 (9.4)	3.1
60-69 (63.6)				

No treatment	10.7 (4.0)	126.3 (14.6)	75.2 (8.1)	83.8
Statins only	24.5 (4.2)	127.2 (10.4)	73.0 (6.7)	4.8
Statins and antihypertensives	26.9 (9.2)	159.1 (17.7)	87.5 (9.8)	8.7
Antihypertensives only	15.9 (2.4)	164.1 (8.5)	89.9 (8.6)	2.7
70-74 (71.8)				
No treatment	13.1 (3.6)	125.5 (14.0)	71.7 (9.5)	58.6
Statins only	24.8 (3.8)	131.0 (9.1)	72.5 (6.4)	12.1
Statins and antihypertensives	27.0 (6.9)	159.4 (14.5)	83.7 (10.3)	28.3
Antihypertensives only	18.5 (0.7)	169.5 (0.7)	89.0 (12.7)	1.0
75+ (79.5)				
No treatment	14.6 (3.3)	123.9 (13.2)	69.4 (8.6)	44.0
Statins only	25.1 (5.5)	130.7 (8.4)	68.3 (8.2)	21.4
Statins and antihypertensives	27.7 (5.7)	157.1 (13.4)	79.7 (9.2)	34.7

Table 3. Base-case results for polypill-for-all versus screen and treat as per guidelines: Men

Age group	Strategy	Mean cost (£)	Mean QALYs	Incremental cost (£)	Incremental QALYs	ICER (£ per QALY gained	Probability polypill cost-effective at £20,000/QALY
50-59	Screen and treat	4,091	14.176				
	Polypill	5,333	14.329	1,241	0.153	8,115	100%
60-69	Screen and treat	3,547	10.874				
	Polypill	4,479	10.968	931	0.094	9,918	100%
70-74	Screen and treat	2,904	8.134				
	Polypill	3,746	8.228	842	0.093	9,024	100%
75+	Screen and treat	2,262	5.480				
	Polypill	2,870	5.513	609	0.033	18,438	64%

Table 4. Base-case results for polypill-for-all versus screen and treat as per guidelines: Women

Age group	Strategy	Mean cost (£)	Mean QALYs	Incremental cost (£)	Incremental QALYs	ICER (£ per QALY gained	Probability polypill cost-effective at £20,000/QALY
50-59	Screen and treat	2,566	15.235				
	Polypill	4,604	15.393	2,039	0.158	12,943	100%
60-69	Screen and treat	2,649	11.814				
	Polypill	4,164	11.978	1,515	0.164	9,231	100%
70-74	Screen and treat	2,269	9.033				
	Polypill	3,506	9.166	1,237	0.133	9,279	100%
75+	Screen and treat	1,675	6.025				
	Polypill	2,583	6.090	908	0.065	13,821	100%

Table 5. Sensitivity analysis results (men aged 50-59) for polypill strategy versus screen and treat as per guidelines

	QALY difference vs. guidelines	Cost difference vs. guidelines	Most CE strategy* (ICER (£/QALY) for polypill)
Base case	0.153	1,241	Polypill (£8,115)
Sensitivity analysis			
SA1: Cost of polypill doubled (£60 a month)	0.153	3,481	Guidelines (£22,761)
SA2: Decreased take up of polypill (25% take up)	-0.018	357	Guidelines (Dominated)
SA3: Increased percentage screened (75%)	0.103	1,083	Polypill (£10,529)
SA4: Reduced adherence with polypill at 12 weeks (68%)	0.088	904	Polypill (£10,283)
SA5: Increased compliance with guideline anti-hypertensive therapy (100%)	0.146	1,253	Polypill (£8,580)
SA6: Costs of screening halved (£13.18)	0.153	1,256	Polypill (£8,215)
SA7: Lower cost of guideline monitoring (2 visits)	0.153	1,560	Polypill (£10,197)

SA8: Change cost of CV events.			Polypill CE in all cases
Acute events increase by 30%	0.153	1,209	(£7,907)
Acute events decrease by 30%	0.153	1,273	(£8,324)
Acute and chronic increase by 30%	0.153	1,138	(£7,442)
Acute and chronic decrease by 30%	0.153	1,344	(£8,789)
SA9: Quality of life reduction with treatment			
1% Polypill			Polypill (£12,535)
Guidelines	0.099	1,241	Polypill (£6,566)
Both	0.189	1,241	Polypill (£9,193)
	0.135	1,241	
2% Polypill			Guidelines (£27,578)
	0.045	1,241	Polypill (£5,491)
Guidelines	0.226	1,241	Polypill (£10,517)
Both	0.118	1,241	
5% Polypill	-0.117	1,241	Guidelines (Dominated)
	0.335	1,241	Polypill (£3,704)
Guidelines	0.065	1,241	Polypill (£19,092)
Both			
10% Polypill	-0.388	1,241	Guidelines (Dominated)
	0.517	1,241	Polypill (£2,400)
	-0.023	1,241	Guidelines

Guidelines Both			(Dominated)
SA10: Increase frequency of screening check (annual)	0.038	852	Guidelines (£22,302)
SA11: Reduced CV risk (all CV risks reduced by 20%)	0.130	1,337	Polypill (£10,307)
SA12: Reduction in polypill effectiveness:			
AHT effect (25%)	0.107	1,327	Polypill (£12,383)
AHT effect (50%)	0.062	1,412	Guidelines (£22,791)
Statin effect (25%)	0.127	1,276	Polypill (£10,047)
AHT and statin effect (25%)	0.078	1,368	Polypill (£17,538)
SA13. Reduced time horizon			
10 years	0.033	861	Guidelines (£25,916)
20 years	0.094	1,105	Polypill (£11,730)
30 years	0.140	1,198	Polypill (£8,564)

* CE at a £20,000/QALY gained threshold

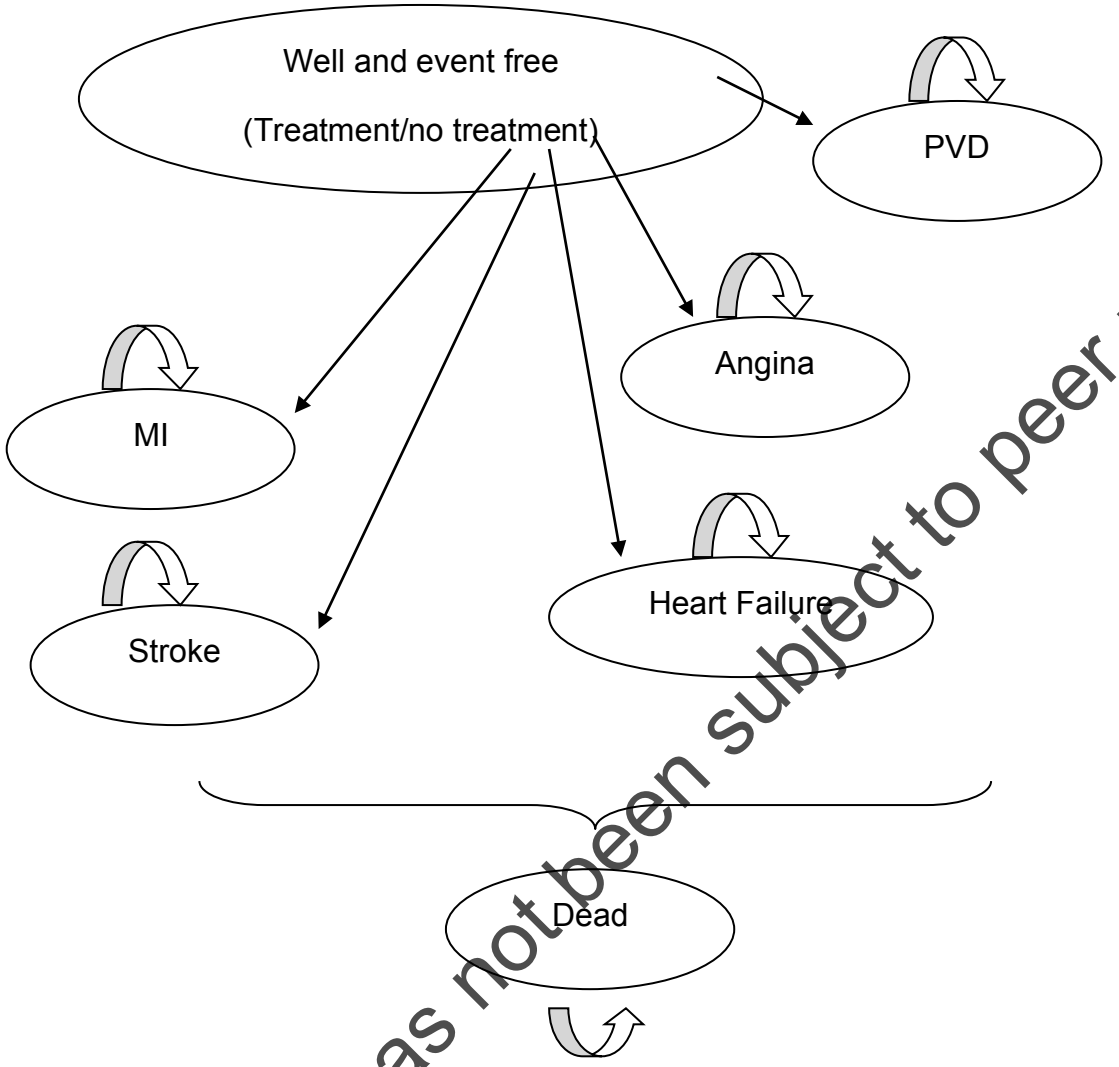

Figure 1. Model health states.

Cost-effectiveness analysis of use of a polypill versus usual care or best practice for primary prevention in people at high risk of cardiovascular disease

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Abstract

Importance: Clinical trials have demonstrated that use of fixed dose combination therapy ('polypills') can improve adherence to medication and control of risk factors of people at high risk of cardiovascular disease compared to usual care, but the cost effectiveness of such an approach has not been established.

Objective: To determine whether use of a polypill is cost effective compared to usual care and optimal guideline-recommended treatment for primary prevention in people who are already on statins and/or blood pressure lowering therapy.

Design: A Markov model with a one year time cycle and a 10 year time horizon. A threshold of £20,000 (€22,500) per quality adjusted life year (QALY) was taken to indicate cost-effectiveness. Individual patient level data were used from a retrospective cross sectional study of primary care medical records to characterise the study population. Published sources were used to estimate the impact of the different treatment strategies on risk of cardiovascular events and their associated costs and utilities.

Setting: 19 general practices in the West Midlands, UK.

Participants: People aged 40 or over on treatment for raised cardiovascular risk with no history of cardiovascular disease.

Interventions: Use of a polypill (40mg simvastatin; 12.5mg hydrochlorothiazide; 5mg lisinopril; 2.5mg amlodipine); Usual care; Optimal implementation of NICE Guidelines.

Main outcomes and measures: cost per QALY, with comparison between strategies expressed as an Incremental Cost Effectiveness Ratio (ICER).

Results: Optimal implementation of guidelines was cost effective compared to the other strategies for all sub-groups ranging from dominance to ICERs up to £2,994 (€3,368) per QALY depending on the patient sub-group. A polypill strategy was only cost effective as compared to current practice for

men aged over the age of 70. The results were sensitive to the cost of the polypill. If the annual cost of a polypill was less than £150 (€169), this approach was cost effective compared to both current practice and optimal guideline implementation.

Conclusions and Relevance: For people already on treatment to modify cardiovascular risk, it is more cost effective to optimise treatment as per guidelines rather than use a polypill, unless the cost of the polypill is sufficiently low.

Introduction

Poor uptake of pharmacotherapy for people at high risk of cardiovascular disease, and lack of adherence in people who are prescribed drugs, has generated interest in the potential for fixed dose combination pills ('polypills').[36 37] These can bring about important reductions in blood pressure and LDL cholesterol,[38] and are associated with improved adherence to therapy.[39 40 41 42]

Previous cost-effectiveness analyses of polypills have compared their use to no treatment, rather than to usual care or improved implementation of guidelines.[43 44] The aim of this study was to estimate the cost-effectiveness of a polypill strategy compared with current treatment or treatment as per guidelines for primary prevention for patients with known high cardiovascular risk who are already prescribed statins and/or blood pressure lowering therapy.

Methods

A Markov cohort model in TreeAge Pro was developed to estimate cost-effectiveness of primary prevention with a polypill strategy compared with i) current therapy and ii) optimal therapy as per guidelines. The model considered patients aged 40 and over prescribed a statin and or/blood pressure lowering therapy with no history of cardiovascular disease. The model was run over a ten year time horizon with a one year cycle.

All patients started healthy and moved to other health states if they suffered stroke, myocardial infarction (MI), angina, heart failure or peripheral vascular disease (PVD) or died. Once a cardiovascular event occurred, they either died, or remained in this health state and incurred costs and a reduction in quality of life as assigned to that disease state until death (Web Figure 1).

Study population

A cross sectional retrospective study of primary care medical records in 19 West Midland general practices in England provided data on risk factor profiles and current treatment.[45] Ten year

cardiovascular risk was calculated using the Framingham equation.[46] The dataset was subdivided into ten age/gender subgroups (40-49, 50-59, 60-69, 70-74, 75 and over). Within each of sub-group, eight treatment/cardiovascular risk strata were identified (see Web Table A) that would be treated differently according to NICE guidelines.[47 48]

Treatment strategies

Current treatment for each stratum was characterised by whether a statin was being taken, and if antihypertensives were being taken, the average number per strata.

The polypill strategy consisted of a pill a day containing a statin (40mg simvastatin) and three antihypertensives at half-dose (12.5mg hydrochlorothiazide, 5mg lisinopril, 2.5mg amlodipine).[49] As the patients were already taking medication, it was assumed the majority would take the polypill, with 16% discontinuing it and returning to their original treatment.[50] The polypill strategy was applied regardless of baseline cardiovascular risk or systolic blood pressure.

The guideline strategy assumed optimal treatment as per NICE guidelines.[48] Statin therapy (simvastatin 40mg) was prescribed if cardiovascular risk was 20% or higher, and antihypertensives if blood pressure was greater than 140/90mm/Hg and cardiovascular risk was 20% or greater. In those patients already on antihypertensives, it was assumed that additional drugs would be added in order to reach a target systolic blood pressure of 140mm/Hg, up to a maximum of three drugs. We estimated the additional number of antihypertensive drugs that would be required using the results of a meta-analysis.[51] For each subgroup we used the starting systolic blood pressure and the degree of blood pressure lowering required to determine through linear interpolation how many additional drugs would be needed.

Impact of treatment

The baseline calculated 10 year cardiovascular risk was assumed to reflect benefit of current treatment (Web table A). For optimal guideline care, the impact of additional treatments was based

on results of meta-analysis of randomised controlled trials (table 1).[51 52] We assumed 85% of people prescribed statins would take them.[53] For the polypill strategy, treatment already being received was taken into account. If already on statins, then no additional effect from statins was applied. If antihypertensives were already being taken, the baseline systolic blood pressure and average number of drugs taken was used to determine the amount of BP lowering already being achieved, and what effect switching to three half dose drugs would have.[51]

Outcomes

Outcomes were measured in quality-adjusted life years (QALYs). A baseline value was applied depending upon age and gender.[54] When a cardiovascular event occurred, the health state value for that event was applied (table 1). No reduction in quality of life was assumed for any drugs.

Gender-specific life tables were used to determine the probability of death at different ages.[55] The risk of death was adjusted to ensure there was no double counting of cardiovascular death.[56] There was an increased risk of death once in a cardiovascular event health state.

Costs

Costs assumed a UK NHS and personal social services perspective (table 1). Polypill costs comprised: £1 (€1.13) a day for the pill, an initial GP visit and blood test in the first month, and an annual practice nurse visit and blood test thereafter. In the current treatment and guideline strategies, the most commonly prescribed generic antihypertensive in each class (indapamide, amlodopine, ramipril) and the statin simvastatin were assumed.[57] Patients on antihypertensives were allocated four consultations (mix of GP and practice nurse) per year.[58] Two additional visits (one GP, one practice nurse) were included for guideline treatment in patients above target blood pressure.

Analysis

An incremental cost-utility analysis was undertaken with a threshold of £20,000 per QALY taken to indicate cost-effectiveness. Future costs and QALYs were discounted at 3.5% per annum.[59] Costs were in UK pounds for 2011/12. Conversion into Euros was via the Purchasing Power Parity (PPP) Index for 2012, using a conversion rate of £1 to €1.125.[60]A half-cycle correction was applied to costs and effectiveness. Deterministic sensitivity analysis around key parameters was performed (tables 3 and 4). Analysis of impact of price involved halving and doubling the price of a 'polypill' and reducing the cost to £57 (€64) a year, to reflect cost of individual generic agents.[57] The threshold price at which a polypill would become cost effective for each sub-group was determined. Where available, data were entered into the model as distributions so that a probabilistic sensitivity analysis could be undertaken. The Probabilistic Sensitivity Analysis (PSA) was run with 10,000 simulations and cost-effectiveness acceptability curves were produced (not shown) to provide information on the probability of interventions being cost-effective at different cost per QALY thresholds.

Results

In the base-case analysis, optimal guideline care was dominant over current practice (i.e less costly and more effective) for men aged over the age of 60, and was highly cost effective for all other sub-groups, with Incremental Cost Effectiveness Ratios (ICERs) varying from £182 (€205) to £2,994 (€3,368) per QALY (tables 2a and 2b). Optimal guideline care was dominant over polypill for men aged over the age of 75. A polypill strategy was more effective than optimal guideline care in the other sub-groups, but it was not cost-effective, with ICERs of £73,000 (€82,125) per QALY and above. Using a polypill was more effective than current practice, but only cost effective for men aged 70 and over.

The probabilistic sensitivity analysis for polypill versus treat as per guidelines showed that a polypill was not cost-effective at a £20,000 (€22,500)/QALY threshold, with all probabilities at 0%. The probabilistic sensitivity analysis for polypill versus current practice showed that it was likely to be

cost effective in men over the age of 70, but not in younger age groups or in women (tables 2a and 2b).

Sensitivity analyses for men aged 60-69 demonstrated that the superior cost effectiveness of optimal guideline care over a polypill was robust to key underlying assumptions made in the model, with the exception of cost of polypill (Table 3). If the price was reduced to 50p (€0.56) per pill, then a polypill became cost effective. If the price was further reduced to cost of the individual components, then a polypill dominated optimal guideline care. The superiority of current practice over polypill in men aged 60-69 was also sensitive to cost of polypill, and to other assumptions that were made (Table 4).

If polypill cost was halved then it would be cost-effective compared with treatment as per guidelines for most sub-groups (Web tables B & C). At this cost, polypill was also cost effective compared to current treatment for all sub-groups except women aged 40-49. Threshold analysis showed that the annual price of the polypill would need to be £152 (€171) or less to ensure cost-effectiveness at the £20,000 (€22,500)/QALY threshold for all sub-groups when compared with guidelines (Table 5).

Discussion

Better implementation of guidelines was found to be a more cost effective way of improving cardiovascular prevention in people on treatment for raised cardiovascular risk than switching to a polypill strategy. However, this result was highly sensitive to cost of a polypill. At current individual drug prices, if a polypill cost £150 (€169) per year (i.e. a cost of 41p (€0.46) per pill), a polypill would be more cost effective than achieving optimal guideline care for all people over the age of 40 who are on treatment. Given that the costs of prescribing the individual components of the polypill are only around £57 (€64) per annum, this seems a feasible price.

Previous cost effectiveness analyses have focussed on cost effectiveness of a polypill against no treatment, and found that this it is likely to be cost effective for primary prevention of high risk individuals in the developing world. [44] [61]

Trials of using a polypill compared to usual care in people at high risk of cardiovascular disease have found better self-reported use of medication in the polypill arm,[40] [41] [42] and in one trial, this was also associated with better control of risk factors.[40] None of these trials included any intervention to enhance usual care.

The results need to be interpreted in the light of certain limitations. In a number of respects, the cost effectiveness of a polypill may have been under-estimated. The analysis was restricted to higher risk people already on treatment – inclusion of people not on medication would have increased the cost-effectiveness of polypill relative to current practice. Potential benefits of improved adherence to a polypill were not included.[40] It was assumed that 100% achievement of guideline targets is possible and indeed desirable.[62] However, this has probably not had significant impact on overall results, since blood pressure target trials tend to show that mean blood pressure for the study population is below target, even if a substantial proportion of individuals have final blood pressure above target. [63] [64] Thus, the impact of blood pressure lowering will have been over-estimated in some and under-estimated in others. The base-case analysis considered a 10-year time horizon as opposed to a life time horizon (which our sensitivity analysis showed tends to favour the polypill). This limited time horizon was chosen because of the complexities of estimating changes in risk factors (and therefore cardiovascular risk) over time. Finally, the risk of further events once someone had a cardiovascular event was not modelled, so potential benefits of treatments of secondary prevention were ignored.

Conversely, other assumptions favoured polypill. The separate drugs in the polypill were assumed to have additive effects. While one trial did find additive effects,[65] others have reported smaller combined effects.[38] The polypill was assumed to have no adverse effects on quality of life –

sensitivity analysis showed that a small shift in this assumption would favour current practice. However, there is no empirical evidence of differences in quality of life between people on the polypill or usual care.[40] Optimal guideline care was based on guidelines in force in the UK up until 2014. Recent NICE guidelines have lowered the 10 year risk threshold for statin treatment from 20% to 10%.[66] This would result in a higher proportion of the study population being treated with statins in the optimal guideline implementation. This would have little effect on older age groups (see table 1), but would result in increased effectiveness (and cost) of optimal guideline care in younger age groups. European guidelines for prevention are similar to NICE for blood pressure lowering, but recommend treatment to target (with lower targets for people at higher risk) for cholesterol lowering therapy.[67] Using this guideline would have reduced the cost effectiveness of optimal guideline care, as previous economic analysis suggests this approach is not cost effective relative to the NICE recommendations.[68]

Finally, there are several other potential formulations of a polypill, which might have different effects on cardiovascular risk factors.[38]

In conclusion, this analysis suggests the most cost effective means to improve primary prevention in people with high cardiovascular risk on treatment is to optimise adherence to existing guidelines, unless the cost of a polypill is sufficiently low. If the cost of a polypill is lower than £150 (€169) per year, then this approach becomes cost effective. However, despite the growing evidence base of the effectiveness of polypills,[38 40] such combinations are not yet generally available. This perhaps in part reflects reluctance of pharmaceutical companies to invest in multi-component pills and the hurdles posed by regulatory approval.[69] At the right price, a polypill strategy could be the most cost effective way of ensuring optimal cardiovascular risk reduction in people who are on treatment with antihypertensives or lipid lowering agents to lower their cardiovascular risk.

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Table 1 Summary of Model inputs

	Data	Sources
Baseline mortality and risk of cardiovascular disease		
Probability of stroke (10 years)	0.7-6.2% (age and sex dependent)	Calculated with Framingham and risk factor profile based on patient level data
Probability of MI (10 years)	1.1-9.4% (age and sex dependent)	
Probability of angina (10 years)	1.5-13.3% (age and sex dependent)	
Probability of heart failure (10 years)	0.4-3.9% (age and sex dependent)	
Probability of PVD (10 years)	0.7-6.2% % (age and sex dependent)	
Event distribution (% of 10 year CV risk)		
Stroke	16%	D'Agostino (2008), [70] Wood (2004) [71]
Myocardial infarction	24%	
Angina	34%	
Heart failure	10%	
PVD	16%	
Risk reduction with statins		
Stroke	0.80 (95% CI 0.73-0.86)	CTT (2005),[52] HPS (2002)[53]
MI, HF, angina	0.72 (95% CI 0.69-0.76)	CTT (2005), HPS (2002)

PVD	0.85 (95% CI 0.75-0.95)	HPS (2002)
Probability of death from event		
Fatal stroke	0.19	Ward (2007)[72]
Fatal MI	0.19-0.36 (Men) 0.23-0.40 (Women)	Ward (2007)
Fatal heart failure	0.17 (r=68, n=396)	Mehta (2009)[73]
SMR after stroke	2.72 (95% CI 2.59-2.85)	Bronnum-Hansen (2001)[74]
SMR after MI	2.68 (95% CI 2.48-2.91)	Bronnum-Hansen (2001)[75]
SMR after Heart Failure	2.17 (95% CI 1.96-2.41)	de Guili (2005)[76]
SMR after Angina	2.19 (95% CI 2.05-2.33)	NCGC [77]
SMR after PVD	2.44 (95% CI 1.59-3.74)	Leng (1996)[78]
Reduction in blood pressure		
Number of AHT drugs required to achieve target BP	0.60-1.52	Law (2009)[51]
Reduction in CV risk with reduction in BP		
Polypill CHD risk Stroke risk PVD risk	 10-52% 14-65% 13-23% (Dependent on age, sex and risk group)	 Law (2009) Law (2009) Murabito (1997)[79]
Treat to target		

CHD risk	15-37%	Law (2009)
Stroke risk	20-47%	Law (2009)
PVD risk	13-32% (Dependent on age, sex and risk group)	Murabito (1997)
Polypill adherence	84%	TIPS (2009)[50]
Utility weights (utilities)		
No cardiovascular event	(age and sex dependent)	General population utilities from EQ-5D (UK Tariff) (NCSR, 2006)[54]
Death	0	By definition
Quality of life multipliers		
Acute MI	0.76 (0.018)	Cooper (2008)[48]
Post MI	0.88 (0.018)	As above
Acute angina	0.77 (0.038)	As above
Post-acute angina	0.88 (0.018)	As above
Heart failure	0.68 (0.020)	As above
Stroke	0.63 (0.040)	As above
PVD	0.90 (0.020)	As above

Costs		
	£ per year	
Simvastatin 40mg	15.26	BNF March 2013[57]
Amlodopine 5mg	12.13	BNF March 2013
Indapamide 2.5mg	11.87	BNF March 2013
Ramipril 5mg	18.13	BNF March 2013
Polypill	365.25	Assumption
	Unit cost	
Blood test	15	Ward (2007)[80]
GP visit	33	Curtis (2012) [81]
Practice nurse visit	11.25	Curtis (2012)
Acute events:	One-off cost	
Stroke	11,020	Youman (2003)[82]
MI	5,487	Palmer (2002)[83]
Angina	3,292	Assumed 60% of MI cost
PVD	1,971	NHS Reference costs 2011/12[84]
Heart failure	2,699	
	£ per year	
Long-term costs:		
Stroke	2721	Youman (2003)

MI	572	Cooper (2008)[48]
Angina	572	Cooper (2008)
PVD	302	Cooper (2008)
Heart failure	572	Cooper (2008)

SMR: Standardised Mortality Ratio; MI: Myocardial infarction; PVD: Peripheral Vascular Disease; CV: Cardiovascular

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Table 2a Results of the base-case analysis and probabilistic sensitivity analysis: Men

Age group	Strategy	Mean cost over ten years (£)	Mean QALYs over ten years	Incremental cost	Incremental QALYs	ICER (£ per QALY gained)	Polypill vs current practice	
							ICER (£ per QALY gained)	Probability polypill cost-effective at £20,000/QALY
40-49	Current practice	1,625	7.202	0	0	-		
	Optimal guideline care	1,634	7.216	8	0.014	604		
	Polypill	3,201	7.229	1,568	0.014	115,973	57,212	0%
50-59	Current practice	2,008	6.740	0	0	-		
	Optimal guideline care	2,013	6.765	5	0.025	182		
	Polypill	3,414	6.784	1,401	0.019	73,688	31,943	0%
60-69	Optimal guideline care	2,315	6.524	0	0	-		
	Current practice	2,343	6.477	28	-0.047	Dominated		
	Polypill	3,598	6.539	1,283	0.015	86,647	20,403	38%
70-74	Optimal guideline care	2,429	5.916	0	0	-		
	Current practice	2,457	5.853	28	-0.063	Dominated		
	Polypill	3,585	5.922	1,157	0.006	190,907	16,392	94%

Table 2b Results of the base-case analysis and probabilistic sensitivity analysis: Women

Age group	Strategy	Mean cost (£)	Mean QALYs	Incremental cost	Incremental QALYs	ICER (£ per QALY gained)	Polypill vs current practice	
							ICER (£ per QALY gained)	Probability polypill cost-effective at £20,000/QALY
40-49	Current practice	1,325	7.077	0	0	-		
	Optimal guideline care	1,343	7.083	18	0.006	2,994		
	Polypill	3,019	7.093	1,675	0.010	171,619	106,663	0%
50-59	Current practice	1,586	6.675	0	0	-		
	Optimal guideline care	1,599	6.688	13	0.013	950		
	Polypill	3,158	6.701	1,559	0.013	120,844	59,670	0%
60-69	Current practice	1,805	6.513	0	0	-		
	Optimal guideline care	1,829	6.530	23	0.018	1,304		
	Polypill	3,268	6.546	1,439	0.015	93,389	43,914	0%
70-74	Current practice	1,985	5.982	0	0	-		
	Optimal guideline care	2,042	6.009	57	0.027	2,105		
	Polypill	3,307	6.022	1,266	0.013	97,509	32,972	0%
75+	Current practice	1,880	4.733	0	0	-		
	Optimal guideline care	1,947	4.774	66	0.041	1,606		
	Polypill	3,030	4.779	1,083	0.005	225,002	24,948	10%

Table 3. Sensitivity analysis results (men aged 60-69) for polypill strategy vs optimal guideline care

	Cost difference vs. guidelines (£)	QALY difference vs. guidelines	Most CE strategy* and ICER (£/QALY) for polypill
Base case	1,283	0.015	Guidelines (£86,647)
Sensitivity analysis			
Cost of polypill doubled	3,561	0.015	Guidelines (£240,561)
Cost of polypill halved	143	0.015	Polypill (£9,690)
Cost of polypill reduced to £57/year	-640	0.015	Polypill (dominates)
Change cost of CV events.			
increase by 30%	1,257	0.015	Guidelines (£84,885)
decrease by 30%	1,309	0.015	Guidelines (£88,408)
Study population restricted to people with uncontrolled risk factors at baseline†	1,140	- 0.013	Guidelines (dominated)
Increase costs of achieving optimal guideline care‡	956	0.015	Guidelines (£64,605)
Reduced effectiveness of optimal guideline care††:			
-by 33%	1,200	0.030	Guidelines (£39,763)
-by 50%	1,160	0.038	Guidelines (£30,853)
Alternative time horizon			
20 years	1,848	0.048	Guidelines (£38,482)
30 years	2,043	0.078	Guidelines (£26,306)
Lifetime	2,068	0.084	Guidelines (£24,489)

* CE at a £20,000/QALY gained threshold

† i.e. ≥20% ten year cardiovascular risk and not on a statin, and/or with systolic blood pressure > 140 mmHg

‡ 4 additional (2 GP and 2 practice nurse) consultations per year over usual care, rather than 2 (1 of each).

†† Adjustment of CV risk reduction estimates with use of statins and/or antihypertensives

Table 4. Sensitivity analysis results (men aged 60-69) for polypill strategy vs current practice

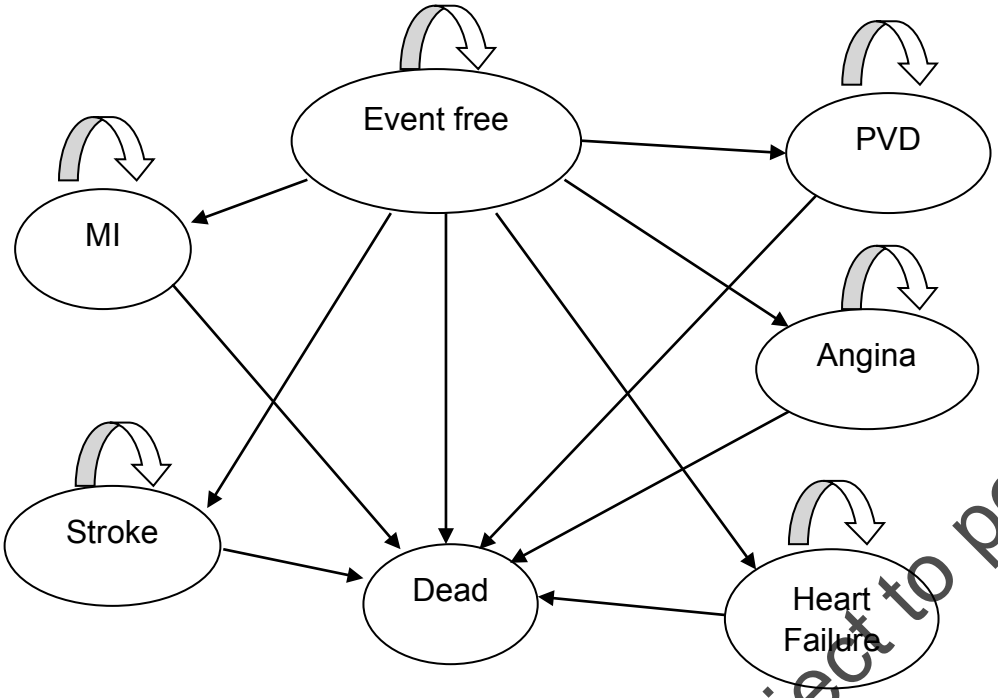
	Cost difference vs. current practice	QALY difference vs. current practice	Most CE strategy* and ICER for polypill
Base case	1,255	0.062	Current practice (£20,404)
Sensitivity analysis			
Cost of polypill doubled	3,533	0.062	Current practice (£57,457)
Cost of polypill halved	115	0.062	Polypill (£1,877)
Cost of polypill reduced £57/year	-668	0.062	Polypill (dominates)
Decreased take up of polypill (25% take polypill)	420	0.018	Current practice (£23,303)
Change cost of CV events.			
CV events increase by 30%	1,145	0.062	Polypill (£19.351)
CV events decrease by 30%	1,365	0.062	Current practice (£22,196)
Quality of life reduction with polypill by 1%	1,255	0.001	Current practice (£130,817)
Reduction in polypill effectiveness:			
Antihypertensive effect reduced (statin effect fixed): 50%	1,354	0.043	Current practice (£31,373)
25%	1,304	0.052	Current practice (£24,944)
Statins effect reduced (antihypertensive effect fixed) by 25%	1,276	0.057	Current practice (£22,457)
Antihypertensive and statin effect reduced by 25%	1,326	0.047	Current practice (£28,012)
Study population restricted to people with uncontrolled risk factors at baseline†	1,089	0.081	Polypill (£13,385)
Alternative time horizon			
20 years	1,794	0.190	Polypill (£9,465)
30 years	2,012	0.293	Polypill (£6,860)
Lifetime	2,044	0.315	Polypill (£6,487)

* CE at a £20,000/QALY gained threshold; † i.e. >20% ten year cardiovascular risk and not on a statin, and/or with systolic blood pressure > 140 mmHg

Table 5: Optimal price of polypill

(CE= <£20,000/QALY gained),. Base case price £365.25

Subgroup	Annual cost of polypill where the polypill is CE vs optimal guideline care (£)	Annual cost of polypill where the polypill is CE vs current practice (£)
Male		
40-49	175	215
50-59	210	285
60-69	207	361
70-74	187	408
75+	165	542
Female		
40-49	152	167
50-59	173	211
60-69	193	244
70-74	204	282
75+	185	324



Web Figure 1 Model health states

Web Table A Baseline patient sub-group characteristics by age, sex and guideline category

Men, age-group (mean age) [BP in mmHg]	Mean (SD) 10 year CV risk (%)	Mean (SD) Systolic BP [BP in mmHg]	Mean (SD) no. AHT drugs	Proportion at baseline (%)
40-49 (45.0) n=273				
On statins, <=140 SBP	8.4 (4.9)	125.6 (10.1)	-	15.4
On statins, >140 SBP	12.1 (6.4)	151.6 (15.2)	-	3.3
On statins & AHT, <=140 SBP	7.0 (3.2)	128.2 (10.2)	1.78 (0.70)	14.7
On statins & AHT, >140 SBP	12.4 (9.5)	150.7 (12.2)	1.55 (0.83)	10.6
On AHT, <=140 SBP, 10y CVD <20%	8.5 (3.6)	131.4 (7.6)	1.62 (0.74)	33.3
On AHT, <=140 SBP, 10y CVD 20%+	23.6 (1.0)	139.5 (0.7)	1.50 (0.81)	0.7
On AHT, >140 SBP, 10y CVD <20%	11.7 (3.9)	153.1 (11.1)	1.58 (0.69)	19.4
On AHT, >140 SBP, 10y CVD 20%+	24.0 (4.8)	168.6 (17.1)	2.14 (0.69)	2.6
50-59 (54.5), n=481				
On statins, <=140 SBP	14.3 (7.1)	127.6 (9.8)	-	12.3
On statins, >140 SBP	22.1 (7.7)	149.1 (6.3)	-	3.9
On statins & AHT, <=140 SBP	12.9 (6.4)	128.3 (8.9)	1.72 (0.78)	20.8
On statins & AHT, >140 SBP	19.8 (7.1)	151.1 (10.5)	1.95 (0.85)	12.1
On AHT, <=140 SBP, 10y CVD <20%	12.5 (3.6)	130.0 (7.9)	1.63 (0.72)	26.8
On AHT, <=140 SBP, 10y CVD 20%+	24.2 (4.5)	132.2 (6.5)	1.56 (0.51)	5.2
On AHT, >140 SBP, 10y CVD <20%	15.1 (2.8)	149.3 (16.3)	1.63 (0.80)	11.6
On AHT, >140 SBP, 10y CVD 20%+	25.3 (5.3)	157.8 (14.3)	1.66 (0.73)	7.3

Men, age-group (mean age)	Mean 10 year CV risk (%)	Mean (SD) Systolic BP	Mean (SD) no. AHT drugs	Proportion at baseline (%)
60-69 (64.2), n=653				
On statins, <=140 SBP	20.5 (8.7)	128.9 (10.7)	-	12.4
On statins, >140 SBP	25.8 (8.5)	152.0 (9.1)	-	4.4
On statins & AHT, <=140 SBP	19.1 (6.4)	130.7 (8.1)	1.81 (0.79)	22.2
On statins & AHT, >140 SBP	26.5 (9.0)	151.8 (12.3)	1.77 (0.72)	16.1
On AHT, <=140 SBP, 10y CVD <20%	15.8 (3.2)	130.2 (9.3)	1.65 (0.74)	12.9
On AHT, <=140 SBP, 10y CVD 20%+	25.5 (5.1)	133.1 (7.4)	1.58 (0.65)	11.0
On AHT, >140 SBP, 10y CVD <20%	1.7 (1.9)	145.3 (2.9)	1.83 (0.76)	4.5
On AHT, >140 SBP, 10y CVD 20%+	29.1 (6.3)	153.4 (10.1)	1.8 (0.86)	16.5
70-74 (71.8), n=266				
On statins, <=140 SBP	24.5 (7.1)	129.5 (9.3)	-	8.7
On statins, >140 SBP	26.7 (3.4)	148.0 (6.3)	-	3.0
On statins & AHT, <=140 SBP	23.5 (5.5)	130.0 (8.2)	1.90 (0.74)	18.8
On statins & AHT, >140 SBP	30.2 (8.2)	150.3 (8.9)	1.69 (0.75)	24.4
On AHT, <=140 SBP, 10y CVD <20%	17.3 (2.1)	122.3 (12.1)	1.82 (0.87)	4.1
On AHT, <=140 SBP, 10y CVD 20%+	26.3 (5.7)	132.4 (6.4)	1.63 (0.73)	20.3
On AHT, >140 SBP, 10y CVD <20%	-	-	-	0
On AHT, >140 SBP, 10y CVD 20%+	31.2 (6.2)	149.6 (8.1)	1.69 (0.79)	20.7

Men, age-group (mean age)	Mean 10 year CV risk (%)	Mean (SD) Systolic BP	Mean (SD) no. AHT drugs	Proportion at baseline (%)
75+ (80.3), n=126				
On statins, <=140 SBP	23.4 (3.1)	126.7 (12.8)	-	1.8
On statins, >140 SBP	33.2 (9.7)	151.7 (8.9)	-	2.9
On statins & AHT, <=140 SBP	25.5 (6.9)	127.1 (10.3)	1.59 (0.74)	15.7
On statins & AHT, >140 SBP	34.8 (5.8)	153.1 (11.3)	2.00 (0.77)	12.2
On AHT, <=140 SBP, 10y CVD <20%	18.7 (0.4)	120.5 (27.6)	3.00 (0.00)	0.6
On AHT, <=140 SBP, 10y CVD 20%+	31.3 (6.6)	131.1 (8.8)	1.77 (0.79)	30.2
On AHT, >140 SBP, 10y CVD <20%	-	-	-	0
On AHT, >140 SBP, 10y CVD 20%+	39.1 (7.8)	152.5 (11.9)	1.68 (0.72)	36.6

SBP: Systolic Blood Pressure; AHT: Anti-Hypertensive Treatment; CV: Cardiovascular; CVD: Cardiovascular Disease

Women, age-group (mean age)	Mean (SD) 10 year CV risk	Mean (SD) Systolic BP	Mean (SD) no. AHT drugs	Proportion at baseline (%)
40-49 (45.6), n=223				
On statins, <=140 SBP	4.8 (2.8)	122.1 (11.2)	-	11.7
On statins, >140 SBP	4.6 (2.2)	151.0 (9.5)	-	1.3
On statins & AHT, <=140 SBP	4.6 (3.2)	123.9 (10.4)	1.56 (0.96)	7.2
On statins & AHT, >140 SBP	5.8 (2.3)	150.4 (6.9)	1.60 (0.55)	2.2
On AHT, <=140 SBP, 10y CVD <20%	4.4 (2.7)	126.7 (10.2)	1.34 (0.56)	53.4
On AHT, <=140 SBP, 10y CVD 20%+	-	-	-	0
On AHT, >140 SBP, 10y CVD <20%	8.4 (4.4)	154.4 (13.7)	1.54 (0.73)	23.3
On AHT, >140 SBP, 10y CVD 20%+	23.7 (4.3)	153.0 (15.6)	1.00 (0.00)	0.9
50-59 (55.1), n=463				
On statins, <=140 SBP	8.1 (4.1)	125.8 (9.5)	-	13.0
On statins, >140 SBP	12.8 (6.4)	149.4 (7.7)	-	3.5
On statins & AHT, <=140 SBP	7.9 (3.9)	128.3 (9.2)	1.58 (0.59)	17.9
On statins & AHT, >140 SBP	10.9 (4.7)	152.1 (11.8)	1.68 (0.65)	8.9
On AHT, <=140 SBP, 10y CVD <20%	7.4 (3.3)	128.0 (9.4)	1.59 (0.68)	33.9
On AHT, <=140 SBP, 10y CVD 20%+	23.4 (2.2)	140.0 (0.0)	1.00 (0.00)	0.4
On AHT, >140 SBP, 10y CVD <20%	11.2 (3.8)	152.2 (10.8)	1.56 (0.67)	19.4
On AHT, >140 SBP, 10y CVD 20%+	25.2 (3.6)	167.7 (12.7)	1.71 (0.83)	3.0

Women, age-group (mean age)	Mean (SD) 10 year CV risk	Mean (SD) Systolic BP	Mean (SD) no. AHT drugs	Proportion at baseline (%)
60-69 (64.4), n=733				
On statins, <=140 SBP	9.7 (4.7)	127.9 (10.6)	-	9.7
On statins, >140 SBP	15.3 (5.7)	151.7 (12.1)	-	4.8
On statins & AHT, <=140 SBP	11.1 (4.5)	129.1 (9.1)	1.67 (0.75)	21.2
On statins & AHT, >140 SBP	15.9 (7.0)	152.1 (10.9)	1.70 (0.82)	15.4
On AHT, <=140 SBP, 10y CVD <20%	10.9 (3.7)	129.2 (10.4)	1.71 (0.73)	28.9
On AHT, <=140 SBP, 10y CVD 20%+	23.1 (3.0)	136.9 (2.9)	1.92 (0.79)	1.6
On AHT, >140 SBP, 10y CVD <20%	14.0 (2.9)	149.9 (8.1)	1.70 (0.72)	13.8
On AHT, >140 SBP, 10y CVD 20%+	23.7 (3.3)	158.9 (16.9)	1.65 (0.81)	4.6
70-74 (71.9), n=353				
On statins, <=140 SBP	13.0 (3.9)	129.0 (9.1)	-	6.0
On statins, >140 SBP	24.8 (8.1)	157.3 (13.1)	-	4.8
On statins & AHT, <=140 SBP	13.1 (4.4)	131.6 (8.1)	1.99 (0.84)	21.8
On statins & AHT, >140 SBP	19.1 (6.5)	149.9 (7.9)	1.81 (0.76)	17.8
On AHT, <=140 SBP, 10y CVD <20%	13.7 (3.6)	131.4 (8.8)	1.76 (0.74)	20.4
On AHT, <=140 SBP, 10y CVD 20%+	24.3 (2.7)	132.6 (4.5)	1.71 (0.76)	2.0
On AHT, >140 SBP, 10y CVD <20%	16.5 (2.6)	146.6 (4.1)	1.69 (0.74)	17.3
On AHT, >140 SBP, 10y CVD 20%+	25.0 (5.0)	156.0 (13.4)	1.74 (0.66)	9.9

Women, age-group (mean age)	Mean (SD) 10 year CV risk	Mean (SD) Systolic BP	Mean (SD) no. AHT drugs	Proportion at baseline (%)
75+ (81.2), n=702				
On statins, <=140 SBP	16.0 (7.6)	125.6 (13.0)	-	4.7
On statins, >140 SBP	20.3 (7.3)	153.2 (10.7)		3.0
On statins & AHT, <=140 SBP	15.6 (5.2)	130.6 (9.5)	1.90 (0.78)	18.2
On statins & AHT, >140 SBP	22.6 (6.3)	152.7 (11.1)	1.86 (0.72)	16.8
On AHT, <=140 SBP, 10y CVD <20%	16.1 (2.6)	130.2 (8.4)	1.64 (0.74)	15.5
On AHT, <=140 SBP, 10y CVD 20%+	24.2 (3.6)	135.1 (6.2)	1.62 (0.83)	9.7
On AHT, >140 SBP, 10y CVD <20%	17.3 (1.6)	146.2 (13.9)	1.70 (0.69)	5.7
On AHT, >140 SBP, 10y CVD 20%+	27.8 (6.6)	156.7 (14.9)	1.71 (0.77)	26.4

SBP: Systolic Blood Pressure; AHT: Anti-Hypertensive Treatment; CV: Cardiovascular; CVD: Cardiovascular Disease

Web Table B Sensitivity analysis: Men. Polypill price halved

Age group	Strategy	Mean cost (£)	Mean QALYs	Incremental cost	Incremental QALYs	ICER (£ per QALY gained)	Polypill vs current practice	
							ICER (£ per QALY gained)	Probability polypill cost-effective at £20,000/QALY
40-49	Current practice	1,625	7.202					
	Treat to target	1,634	7.216	8	0.014	604		
	Polypill to all	1,957	7.229	323	0.014	23,917	12,043	98%
50-59	Current practice	2,008	6.740					
	Treat to target	2,013	6.765	5	0.025	182		
	Polypill to all	2,212	6.784	199	0.019	10,489	4,635	100%
60-69	Treat to target	2,315	6.524					
	Current practice	2,343	6.477	28	-0.047	Dominated		
	Polypill to all	2,459	6.539	143	0.015	9,690	1,877	100%
70-74	Treat to target	2,429	5.916					
	Current practice	2,457	5.853	28	-0.063	Dominated		
	Polypill to all	2,527	5.922	98	0.006	16,190	1,012	100%
75+	Treat to target	2,320	4.782					
	Polypill to all	2,385	4.781	65	-0.001	Dominated	Dominates	100%
	Current practice	2,395	4.692	75	-0.091	Dominated		

Web Table C Sensitivity analysis: Women Polypill price halved

Age group	Strategy	Mean cost (£)	Mean QALYs	Incremental cost	Incremental QALYs	ICER (£ per QALY gained)	Polypill vs current practice	
							ICER (£ per QALY gained)	Probability polypill cost-effective at £20,000/QALY
40-49	Current practice	1,325	7.077					
	Treat to target	1,343	7.083	18	0.006	2,994		
	Polypill to all	1,752	7.093	409	0.010	41,846	26,880	13%
50-59	Current practice	1,586	6.675					
	Treat to target	1,599	6.688	13	0.013	950		
	Polypill to all	1,920	6.701	321	0.013	24,918	12,689	97%
60-69	Current practice	1,805	6.513					
	Treat to target	1,829	6.530	23	0.018	1,304		
	Polypill to all	2,070	6.546	242	0.015	15,677	7,955	100%
70-74	Current practice	1,985	5.982					
	Treat to target	2,042	6.009	57	0.027	2,105		
	Polypill to all	2,169	6.022	128	0.013	9,826	4,604	100%
75+	Current practice	1,880	4.733					
	Treat to target	1,947	4.774	66	0.041	1,606		
	Polypill to all	2,030	4.779	84	0.005	17,349	3,251	100%

Patient Feedback about a Primary Prevention Polypill Trial: Questionnaire Survey

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Originally we intended to use the preparatory work as described throughout section 2 to design and carry out a pilot RCT that would determine the feasibility and acceptability of performing an RCT to test the cost effectiveness of using a polypill strategy. The intention was to carry out an individual randomised trial of treating to target levels of BP and cholesterol as compared to using fixed doses of statins and BP lowering agents (Polypill strategy). The polypill comprised: simvastatin 40mg; hydrochlorothiazide 12.5mg; lisinopril 5mg; amlodipine 2.5mg. The trial was due to recruit from January to March 2013. However, in October 2012 the Medicines and Healthcare Products Regulatory Agency (MHRA) published a recommendation that the maximum dose of simvastatin in patients also receiving amlodipine should be 20mg per day rather than the usual 40mg dose.[85] This meant that the polypill that was sourced for this study could no longer be used, and there was insufficient time remaining on the grant to enable us to source an alternative and gain the necessary regulatory approvals. Therefore, with agreement of the funders, it was decided that instead a questionnaire study would be carried out with the aim of gaining patient feedback about the proposed study design, thus allowing us to explore the issue of acceptability of the trial and its associated documentation (as opposed to the issue of the acceptability of a polypill more generally – see section 2.3.2) Some of the more practical issues that need to be considered when running a trial, for example, storage, supply and distribution of trial drugs, would not be directly addressed through a questionnaire. However, during the design phase of the planned pilot RCT, many of these issues were addressed and implementation plans determined. Therefore, this preparatory work, combined with the information gleaned in the questionnaire study, will inform the design of a future trial.

Background

One factor critical to the success of an RCT examining a polypill approach is an understanding of the factors that make people and practitioners keen or reluctant to initiate a polypill strategy. However, another factor that can influence the acceptability of a trial is the information that is given to patients and the impact that this has on their understanding, anxiety and willingness to participate.[86] [87] Easier to read information sheets result in lower anxiety and higher satisfaction when compared with standard consent information[86] and also lead to improved understanding of the study purpose and procedures.[87] Phrasing used in information giving, and the information provided both have an impact on recruitment; therefore it is important that trial information sheets are acceptable to patients.[88]

The proposed polypill trial may be particularly sensitive to the format and content of the information given to patients, because it is a trial testing both a new drug format and a new concept. Therefore, the aim of this questionnaire study is to gain feedback from patients about the proposed RCT and its patient information sheets, which can be used to inform the design of a future trial.

Methods

An information sheet for a hypothetical polypill trial for primary prevention of CVD and a questionnaire asking for feedback and comments about the content of the information sheet were developed. An anonymised electronic search was carried out in one practice in the West Midlands using MIQUEST programming. This search identified patients who were aged 50-74 and with unknown CV risk (these are the eligibility criteria for the polypill primary prevention study). People were considered to have an unknown CV risk if they fulfilled the following criteria:

- No BP and/or total cholesterol measurement in the last year AND not on an anti-hypertensive or cholesterol lowering agent

OR

- On an anti-hypertensive but not on a cholesterol lowering and with no total cholesterol measurement available for the last year

OR

- On a cholesterol lowering agent, but not on a BP lowering agent, with no BP measurement available for the last year

Patients considered unsuitable to contact (i.e. those with a terminal illness) were removed from the list by the GP. The information sheet and questionnaire were sent to eligible patients, together with a short covering letter explaining the purpose of the questionnaire, and a pre-paid envelope for the questionnaires to be returned to the study team at the University of Birmingham.

The questionnaire asked questions such as: would you take part in a clinical trial such as this; what do you think of the information sheet; can you suggest any improvements to the information; and do you have any other comments regarding a polypill trial. Demographic data (gender; age group; ethnicity) was also collected on the questionnaire.

Quantitative analysis was carried out using SPSS version 21. Ages were grouped into 50-59; 60-69; and 70-74. Ethnic group was collected on the questionnaire using criteria defined in the Office for National Statistics ethnic group index.[89] For analysis, these were grouped into the English/Welsh/Scottish/Northern Irish/British category, and all other ethnicities. Free text reasons given for not wishing to take part in a trial were coded as: side effects; not wanting to take unnecessary medications; concerns/queries/confusion about the study; and other (including not wishing to take part in research per se, preferring other approaches to CVD prevention, atypical blood pressure readings). Free text answers were also analysed qualitatively to enable identification of thoughts and attitudes of people that can be incorporated into the design of future polypill trials.

Results

A total of 53 of 527 people returned completed questionnaires (response rate 10%). Table 1 gives an overview of the respondents' demographics.

Table 1: Respondent Demographics

Characteristic	Total Returning Questionnaire n (%)	P Value*
Gender		
Male	25 (47)	
Female	28 (53)	0.774
Age Group		
50-59	26 (49)	
60-69	19 (36)	
70-74	8 (15)	0.361
Ethnicity^		
United Kingdom	46 (87)	
All other ethnicity	7 (13)	

*Testing difference in characteristics between responders and non-responders.

^Differences between responders and non-responders could not be calculated because ethnic group was only available for responders.

25(48%) of responders said, having read the information sheet, that they would agree to participate in the trial. One participant was undecided. A higher proportion of men than women agreed that they would take part in the trial (see figure 1), while a higher proportion of people in the younger age group agreed that they would participate. (See figure 2)

Figure 8: Willingness to participate by gender

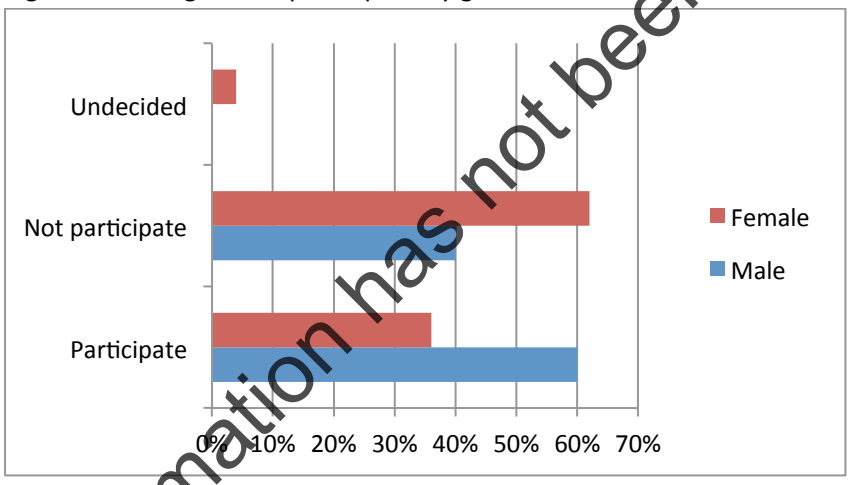
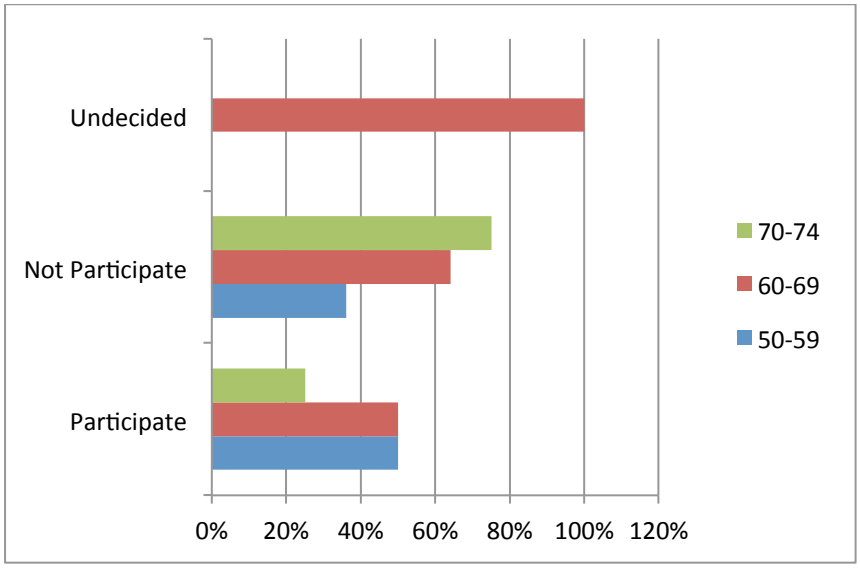


Figure 9: Willingness to participate by age group



Reasons for refusal to participate

Reasons given for reluctance to participate in a polypill trial are given in table 2

Table 2: Reasons given for not agreeing to participate in a polypill trial

Reason Given	N (%)
Side Effects	3(12)
Do not wish to take unnecessary medication	12 (46)
Concerns/uncertainties/queries about the study	5 (19)
Other	6 (23)

<u>Concerns about taking medication</u>

The most common reason for not wanting to participate was concern about taking medication. For some this was because they perceived the medication to be unnecessary.

"I don't think that taking pills when you don't have to is good"

Questionnaire 32

"I do not like the idea of taking unnecessary medication"

Questionnaire 3

The patient who is undecided about whether or not they would participate also expressed concerns about taking unnecessary medication.

"Don't like taking medication when not required"

Questionnaire 21

For others, their reluctance stems from the fact that they are already taking other medications, and they were concerned that additional pills would interfere with these.

I already take a carefully balanced amount of medication and don't want to risk the stability of my condition by taking anything else"

Questionnaire 26

"I already have to take various pills… other pills could interfere with my present ones!"

Questionnaire 23

However, the majority of people citing this as a reason to not participate state that they are reluctant to take medication because they are not currently taking anything and would like to continue that way.

"I am fortunate that…I take no medication. Therefore I would be reluctant to take the pills"

Questionnaire 8

"I am currently very healthy and take no medication for anything so would not wish to take any"

Questionnaire 29

One person who had stated that they were not willing to participate because they currently take no medications also stated that they did not like the idea of randomly allocated drugs.

"I would not be happy taking random medication… it is not really clear if 'fit' people would be asked to trial the polypill on a random basis"

Questionnaire 20

Side effects of the medication

Concern about side effects was also given as a factor that would deter people from participation in the trial, with one person citing a specific side effect as their main concern.

"because dizziness is a side effect of the polypill"

Questionnaire 19

"do not like the sound of side effects when I don't have problems"

Questionnaire 6

Other Reasons

People gave a number of other reasons for not wishing to take part in a trial of this nature, ranging from specific personal circumstances, to views about the polypill itself or trials in general.

"My blood pressure readings….are atypically high…. Limited benefit as my risk factors have been assessed recently"

Questionnaire 25

"I am not a fan of the polypill it has a dailymail feel to it"

Questionnaire 5

"not enthusiastic about being experimented on"

Questionnaire 9

One patient said that they were not willing to participate because they *"do not know enough about this subject to evaluate"* (Questionnaire 31).

A number of patients who indicated that they would take part in the trial added a proviso to their decision. One person said that they would need more information about clinic availability because of work commitments:

"Its fine for people who have flexible working hours… I doubt if the clinic hours would suit me and why should I lose a whole shift just to take part in it. Apart from that I would like to take part"

Questionnaire 58

Another said that they were due to be away for a month and would therefore need to delay their trial entry.

"I am away for a month…. I would not want to take anything which might have side effects in that time"

Questionnaire 38

Suggested improvements for the information sheet

A number of comments and suggestions were made about the information sheet. Interestingly, the two people who said that they felt the information was *"very informative"* (Questionnaires 26 and 32) both said they would not be interested in taking part in a study.

A number of people made some very specific comments about the information sheet, and parts that either seemed unclear to them, or did not give them information that they felt they needed. One person who did not wish to participate, questioned the explanation in the information sheet about the purpose of the study

"Under what do better means: I presume it means blood pressure and cholesterol are lowered, but don't you know that anyway? Is the new factor using the drugs in combination?"

Questionnaire 25

Another patient, who did say they would take part in a trial, queried the meaning of the same section, saying *"first question….what does this mean?"* (Questionnaire 41). However, this person still went on to say that they felt this was an *"interesting and important area of research".*

Other people felt that they would like more information about the drugs included in the polypill and the expected side effects. One person said they would be *"interested to know how the components of the polypill work"* (Questionnaire 40), while another asked *"What is the polypill… is it being used in any other country, what does it consist of, is it safe?"* (Questionnaire 43). One stated that they felt that *"drug names and doses should be provided. A better list of side effects and their frequency should be given"* (Questionnaire 5).

Others asked for further information about how the polypill would affect their current medication, or clarification where they currently take no drugs.

"what of other medication that I take. Will it affect the polypill?"

Questionnaire 30

"advice for people like myself who do not take any medication"

Questionnaire 15

One patient did not understand what constitutes usual care and would like more information about that. This person stated that they had never had their blood pressure or cholesterol checked and said

"I am not aware of the details of the 'usual care'. How is this carried out?"

Questionnaire 3

Other Comments

The questionnaire gave people opportunity to provide further comments about the proposed polypill trial. Most used this to add further detail about the information sheets, but some patients did provide general comments about the concept of the trial or the polypill itself. Unsurprisingly there were mixed views. One person thought it was a *"good idea"* (Questionnaire 3) while another described it as *"an interesting and important area of research."* (Questionnaire 32). However, another person was less enthusiastic and did not *"consider it a priority for NIHR funding"* (Questionnaire 5).

The idea of giving the polypill to everyone was not liked by everyone, with one person stating that they felt it was not *"a good idea to give someone a pill in case….is it not better to identify high risk patients and treat them?"*(Questionnaire 32). Despite this opinion, however, this patient also said that they would agree to trial participation.

Patterns

More women than men cited concerns about side effects of the drugs; no men at all gave this as a reason for not participating. Similarly, more women than men were concerned about taking unnecessary medication, with 12 women and only 2 men giving this as a reason. Two men however, said that they did not wish to take part in research per se, or had particular concerns about the polypill, whereas no women cited this reason. There were no patterns evident with regard to age or ethnicity.

Discussion

Despite the low response rate, this study has provided us with some useful insights into people's attitude towards a polypill trial, and some useful feedback about the design of any future polypill trials. There were no significant differences between those who would participate and those who would not with regard to gender or age, thus ensuring that the views of people with a range of these characteristics were captured. Just under 50% of responders indicated that they would participate in the trial if offered entry, which is in line with the recruitment rate of eligible patients in other RCTs[90] and provides some basis for estimation of potential recruitment rates. Beyond this there is little

quantitative data that can inform the design of future trials. However, the qualitative data collected provided us with a range of useful information.

The one patient who returned a questionnaire saying they would not consider participation, but who clarified this by stating that they were actually unsure, indicates that people who do not have the information they need, or who do not understand what they have been given, may actually default to refusal as opposed to contacting the study team to address their concerns. Recruitment to trials is often difficult,[91 92] and this problem may be exacerbated in a trial testing both a new drug format and a new concept (as is the case with a polypill). Evidence has demonstrated that the information given to patients during the consent process for research can influence their willingness to participate.[93] Therefore, it is in the research team's interest to ensure that patients are given the information they require to make an informed choice for refusal. [94]The responses to this questionnaire indicate that there are a number of potential areas where this issue could be addressed in the patient information sheet.

Firstly, many patients who did not wish to participate did not wish to do so because of the need for taking what they perceive as unnecessary medication. The polypill approach (giving pills instead of offering a health check) is a new concept for many people, and it is possible that increased understanding of the reasons why this new approach means the drugs may not be unnecessary could potentially overcome the reluctance of some to consider participation. Similarly, people who said they did not wish to take part because they do not currently take any medication and wish to stay that way may also benefit from a better understanding of the preventative role of the polypill. Therefore, in order to ensure that recruitment to a trial is optimised, consideration should be given during the design phase as to how much and what information should be given to patients about the value or necessity of preventative medication, taking into account the issues raised by respondents in this study.

Other people did not wish to take part because they are concerned about the impact polypill may have on their existing medications. No one provided detail about what drugs they are currently taking, so it is possible that the polypill may actually be in place of existing medication for some people (ie those already taking a statin or an anti-hypertensive). One patient did like the idea of taking one pill instead of many, so consideration should be given to highlighting this issue in the information sheet and to clarify the fact that their concerns will be addressed during the study recruitment clinic appointment. This will help to ensure that people are aware that participation may not mean extra medication, which in turn could help to minimise the number of patients who decide not to participate due to any reluctance to ask further questions.

Another reason given for non-participation was concern about the potential side effects of the medications in the polypill. The information sheet warns people of potential side effects, and specifically highlights dizziness, but gives no more detail. One respondent said that they would like a more comprehensive list of side effects together with information about their frequency, which could potentially be included in the information sheet. However, only a small number of respondents cited side effects as a concern (3 respondents) so this may not be a big problem. Over emphasis on these negatives may therefore serve to deter otherwise interested people; the research team should carefully consider whether it would be appropriate to provide this level of detail in the initial contact before amending the information sheet to reflect this comment.

Some of the reasons given for non-willingness to participate are not areas where it would be possible, or even appropriate, in some cases, to try and influence, for example, where patients do not wish to take part in research per se. There were, however, a number of people who were willing to take part in a trial but who wanted more information about the availability of clinics outside of normal working hours. It is likely, therefore, that other people would refuse participation because they would assume that there would not be the flexibility available to attend study appointments at a time that does not disrupt their work patterns or interfere with other responsibilities. When designing a trial, therefore, it would be advisable to ensure that clinic times can be as flexible as possible, with evening and weekend appointments available wherever possible. Furthermore, information sheets should emphasise that the research team will endeavour to organise appointments at a time convenient to the patient, thus ensuring that people do not refuse participation where they may otherwise be interested in taking part.

Suggested improvements for the information sheets covered some of the reasons why patients refused participation. For example, suggested improvements in detail provided about side effects, or the provision of additional information about potential interactions with other drugs. One patient did not understand what was meant by the term 'usual care', although this was described to some extent in the information sheet. If one person has not understood this section, it is likely that other people will also not understand; it would be worth-while to ensure that this crucial information is worded in a way that is understood by everyone.

Other patients asked for more information about what is in the polypill and whether its safety has been tested. This may be an area that should be addressed in more detail in the information sheet: trials of drugs that have not been tested in humans are likely to carry far higher risks than later phase studies such as this one.[95] Although the information sheet explains that the drugs contained within the polypill have been used in standard care for some time, patients may be put off by the perceived level of risk if they mistakenly believe that polypill is an untested drug. Providing detail about the drugs included in the polypill may also help to address this; they are common drugs so it is likely that many people will have already heard of them. Furthermore, this information may help to overcome the barrier posed by people not wishing to take extra medication, if they are already taking one of the polypill's components as part of their current care.

Strengths and Weaknesses

The main weakness of this study is the poor response rate and the low number of questionnaires that were returned: the small sample could be the reason why there are no significant findings in the quantitative analysis. However, while it would have been useful to identify significant differences in attitudes between, for example, men and women, the primary aim of this study was to gain feedback and input from people who would be potentially eligible for a trial to ensure that the design and information removes any unnecessary barriers to recruitment, by providing people. The questionnaires received had a good mix of gender and age, and also represented the views of some different ethnic groups, albeit in small numbers. Therefore, the qualitative nature of the questions asked means that, despite the low response, the study aim has still been addressed.

The low response rate may also indicate the reality of the proportion of people who would respond to an invitation to a primary prevention trial of a polypill in people with unknown cardiovascular risk. This would enable trialists to conservatively estimate the number of sites and/or patients they would

need to approach to achieve recruitment targets. However, if the trial was carried out in a different patient population, those at high risk of CVD for example, there may be more motivation for people to respond; it is possible that more people in this category would understand the preventative nature of the pill, and fewer would have concerns about taking medication. It is possible, therefore, that high risk patients would be the most appropriate population in which to trial the polypill in the first instance.

The insight gained from this study into the information that patients want about research that they are invited to participate is likely to be useful when designing the information sheet for a polypill trial. Some of the suggestions, for example, clarity around the flexibility of study appointments, are sensible and would be easy to incorporate without overburdening patients. However, a balance needs to be struck between giving patients adequate information to make a decision about whether to consider participation, and giving them so much information that they are overwhelmed or cannot understand it. Teams should consider carefully how much information to include about study drugs or side effects in the initial contact with patients, because it may be more appropriate to discuss this level of detail during the informed consent discussion. Once the information sheet is drafted it is very useful for as many potential patients as possible to comment upon the content before it is finalised, to ensure that consensus can be reached about the optimum balance of information to incorporate.

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Work programme 2

Cost-effectiveness of self-management of blood pressure in hypertensive patients over 70 years with sub-optimal control and established cardiovascular disease or additional CV risk diseases (TASMIN-SR)

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Abstract

Background: A previous economic analysis of self-management, that is, self-monitoring with self-titration of antihypertensive mediation evaluated cost-effectiveness among patients with uncomplicated hypertension. This study considered cost-effectiveness of self-management in those with raised blood pressure plus diabetes, chronic kidney disease and/or previous cardiovascular disease.

Design and methods: A Markov model-based economic evaluation was undertaken to estimate the long-term cost-effectiveness of self-management of blood pressure in a cohort of 70-year old 'high risk' patients, compared with usual care. The model used the results of the TASMIN-SR trial. A cost-utility analysis was undertaken from a UK health and social care perspective, taking into account lifetime costs of treatment, cardiovascular events and quality-adjusted life years (QALYs). A sub-group analysis ran the model separately for men and women. Deterministic sensitivity analyses examined the effect of different time horizons and reduced effectiveness of self-management.

Results: Base-case results indicated that self-management was cost-effective compared with usual care, resulting in more QALYs (0.21) and cost savings (-£830) per patient. There was a 99% chance of the intervention being cost-effective at a willingness to pay threshold of £20,000 per QALY gained. Similar results were found for separate cohorts of men and women. The results were robust to sensitivity analyses, provided that the blood pressure lowering effect of self-management was maintained for more than a year.

Conclusion: Self-management of blood pressure in 'high risk' people with poorly controlled hypertension not only reduces blood pressure, compared with usual care, but also represents a cost-effective use of health care resources.

Word count: 249

Background

Hypertension is a leading risk factor for cardiovascular mortality and morbidity worldwide.[1, 2] Despite evidence of cost saving from antihypertensive treatment,[3] and improvements in blood pressure monitoring, management and treatment, [3, 4] significant numbers of people remain inadequately controlled hence new models of care are required.[5] Self-management of hypertension, where an individual self-monitors their own blood pressure and adjusts their own medication has been shown to lead to significantly lower blood pressure in hypertension, including in those with higher cardiovascular risk.[6, 7]

The only economic analysis of self-management in the control of hypertension to date demonstrated that tele-monitoring with self-titration in uncomplicated hypertension was highly cost effective with incremental cost-effectiveness ratios (ICERs) below £5,000 per quality-adjusted life year (QALY) gained for men and women, when modelled over patient lifetime.[8] However subgroup analysis in the main trial suggested that the intervention might not be as effective in those with significant co-morbidities, although patient numbers for this sub-group were small.[7] Therefore, the TASMIN-SR trial was undertaken to determine the effect of self-monitoring with self-titration of anti-hypertensive medication on systolic blood pressure (BP) among hypertensive patients with sub-optimal control and pre-existing cardiovascular disease, diabetes and/or chronic kidney disease, compared with usual care. A model-based probabilistic cost-utility analysis was undertaken as part of this study to assess the long-term cost-effectiveness of the self-management intervention in a 'high risk' patient population, compared with usual care.

Methods

A Markov cohort model, built in TreeAge Pro (TreeAge Software Inc, Williamstown, MA, USA), was developed to estimate the long-term cost-effectiveness of self-management of BP compared with

usual care, in patients with hypertension and a history of stroke, coronary heart disease (CHD), diabetes or chronic kidney disease (CKD). The analysis used the results of the TASMIN-SR trial on blood pressure, extrapolating these to long-term risk of cardiovascular endpoints [see below]. Full details of the trial methods and results have been described in detail elsewhere.[6, 9] The model was run over a lifetime (30 year) time horizon using a six-month time cycle, with results presented from a UK National Health Service (NHS) and Personal Social Services (PSS) perspective.

Study population

The base case analysis considered a cohort of 70 year old patients (39% female) with sub-optimal hypertension, BP ≥ 130/80 mmHg at baseline, combined with a history of stroke, CHD, diabetes or CKD.[6] Patients had at least one of four main underlying conditions (diabetes, stroke, CHD and CKD), to be eligible with 15 possible combinations of high risk conditions in total. Further details of the combined risk conditions are available in the supplemental online document, eTable 2.

Interventions

Patients randomised to usual care booked an appointment for a routine BP pressure check and medication review with the study general practitioner (GP). Thereafter, usual care consisted of the participants seeing their GP and or nurse for routine BP measurement and adjustment of medication at the discretion of the health professional. Patients randomised to self-management were trained to self-monitor BP and to self-titrate their anti-hypertensive medication following a predetermined plan, in two or three sessions, each lasting around an hour. Following training, patients adjusted their anti-hypertensive medication based on their monthly self-monitored BP readings.[9]

Model structure

A patient entered the model in the "high risk" health state and could move to another health state if they suffered one of three possible cardiovascular (CV) events (stroke, myocardial infarction (MI), unstable angina (UA)), or died from other causes (figure 1). After a CV event, individuals could

survive from that event or die within the first 6 months. Those that survived an event subsequently moved to a chronic health state for that condition until death, with no recurrences of CV events. For each chronic health state, an ongoing health care cost was applied every time cycle and quality of life was permanently reduced. Movement between health states was defined by transition probabilities, which represented the risk of experiencing an event within each six-month time cycle.

Model parameters

Patient level data from the TASMIN-SR trial were used to reflect the CV disease history of patients entering the Markov model. The probabilities of suffering a stroke, MI or developing UA were obtained from published literature for hypertensive patients with each of the high risk conditions [10-14] (Table 1). Where the model required probabilities that were not available in the literature (for given age group, gender or combination of high risk conditions), missing values were estimated through extrapolation (see supplemental online document). For patients presenting with two or more high risk conditions, the probability of an event was calculated as the sum of the two individual risk probabilities. Further detailed calculations are available in the supplemental online document, etables 1 and 2.

Systolic BP reductions recorded in the trial at 6 months (11.4mmHg and 5.5mmHg for the intervention and control arms) and at 12 months (15.0mmHg and 5.8mmHg for the intervention and control arms) were extrapolated to age-related risk reductions for coronary heart disease (CHD, comprising both MI and UA) and stroke, using Law et al [15] (Table 1). Relative risks for CHD and stroke related to 6 and 12 month BP reductions are reported in Table 1. The model assumed that blood pressure remained static for the first six month cycle of the model, then reduced as per the 6 month trial results for the second model cycle followed by the 12 month trial reductions thereafter with the between groups differences assumed constant in the base case. The probabilities of death from MI and stroke within a year of the event are reported in Table 1 and applied to the first year after an

event (first two cycles in the model). Life tables were used to determine overall mortality, dependent on age and gender. [16]

Resource use and costs

Costs are reported in UK pounds at 2011/12 prices. Resource use related to ongoing BP monitoring in primary care, self-management and prescription of anti-hypertensives was obtained from the TASMIN-SR trial at 12 months follow-up. For self-management, equipment and training costs were annuitized at an annual rate of 3.5% and based on a lifetime of five years. [17] Replacement costs for the equipment and costs of additional training were included at five yearly intervals -every 10 cycles- over the lifetime of the model (supplemental online document, eTable 3). Equipment used by individuals who died within any five year interval was assumed to be discarded. Unit costs were applied to resource use and mean patient costs per six months were calculated for both randomised groups, and applied to the initial high risk health state. Costs for acute and chronic CV event states were obtained from published studies. [18-21] A summary of all costs included in the model is shown in Table 1.

Utility values

The primary outcome measure was quality adjusted life years (QALYs). All utility scores used in the model are shown in Table 1. The utility values for the starting 'high risk' health state were obtained from the TASMIN-SR trial where the overall mean EQ-5D score for hypertensive patients at baseline was used to estimate utilities. This was adjusted for age group using weights calculated from Ara et al, [22] which allowed the overall reduction in quality of life with increasing age to be incorporated in the model. Acute events were assumed to happen approximately three months into a six-month cycle and individuals stayed in that acute state for three months before moving into a chronic state. Therefore utilities for the acute state were applied mid-way through the six-month cycle and chronic

health state utilities were applied at the start of the subsequent cycle (table 1). Health state utilities for CV events were applied multiplicatively to the age-related 'high risk' health state utility values.

Analysis

A cost-utility analysis was undertaken from a UK NHS and Personal Social Services (PSS) perspective.. For the base-case analysis, fifteen separate cost-effectiveness analyses were run, one for each combination of high risk conditions assessed in the model. The final cost-effectiveness results correspond to the trial population-weighted average of costs and quality adjusted life years (QALYs) and are reported in terms of the incremental cost per QALY gained. [23] Analyses were also separately run for men and women. Costs and outcomes were discounted at an annual rate of 3.5%. [24]

Uncertainty in the model results was assessed using sensitivity analyses. Deterministic sensitivity analysis was undertaken around key parameters and assumptions. The time horizon for the model was varied from 30 years (lifetime) to between 1 year and 20 years, to determine whether the intervention was cost effective in the shorter term. The assumption regarding the long-term effectiveness of the intervention was tested by assessing the impact of limiting the additional effect on BP lowering to years of self-management 1, 2, 5 and 10. Additional sensitivity analyses altered long term cardiovascular event costs by 30% (up and down). Finally, all analyses were re-run using the un-adjusted trial data which showed marginally smaller reductions in BP (11.4 mmHg and 5.8 mmHg for the intervention and control arms at 6 months and 14.9 mmHg and 6.0 mmHg respectively at 12 months). Where possible, data were entered into the model as distributions in order that a probabilistic sensitivity analysis (PSA) could be undertaken to incorporate parameter uncertainty. Gamma distributions were fitted to all costs obtained from the TASMIN-SR trial and beta distributions were applied to the utility values. The parameters used for these distributions are shown in Table 1. The PSA was run with 10,000 simulations and cost-effectiveness planes and cost-effectiveness acceptability curves (CEACs) constructed, to estimate the probability of self-management being cost effective at different willingness-to-pay thresholds. [17]

Results

In the base case analysis, self-management of BP was dominant compared to usual care, being cheaper and more effective (Table 2). Self-management was associated with mean cost savings of £830 per patient for the total population (self-management £7,357 vs. usual care £8,187) and a gain of 0.21 QALYs (6.25 vs. 6.03, respectively). This dominance was demonstrated for both men and women (Table 2). In the cost-effectiveness plane (Figure 2), all results are in the north-east and south-east quadrants indicating that self-management is always more effective but with greater uncertainty around the difference in costs. The cost-effectiveness acceptability curve (CEAC) shows that the probability of self-management of BP being cost effective compared with usual care was at least 99% if decision makers were willing to pay £20,000 per QALY gained. At a lower threshold of £10,000 per QALY, the probability of the intervention being cost-effective compared with usual care was still high at 97% (Figure 2).

A sensitivity analysis of time horizon demonstrated that self-management is dominant if the horizon is two years or more (Table 3). Similarly, if the impact of self-management on blood pressure is time limited, the cost-effectiveness is reduced – but the intervention is still cost-effective provided that the effect is sustained for one year (first two cycles) (Table 4). Other sensitivity analyses (costs and reduced impact on blood pressure) did not change the overall results (supplemental online document, etables 4-6).

Discussion

This is the first study to present results of the cost-effectiveness of self-management of BP compared with usual care in a high risk population with sub-optimally managed hypertension and significant cardiovascular comorbidity. The base-case analysis suggests that self-management of BP

is cost-effective and is likely to be dominant (i.e., it is less costly and produces more QALYs) compared to usual care.

The main driver of this result is the estimated decline in the risk of cardiovascular events associated with the observed additional BP lowering achieved with self-management, and this explanation also holds for the greater benefit seen for men. This result was robust to sensitivity analysis unless the time horizon was reduced below two years or the observed BP lowering effect of self-management did not continue beyond a year.

Relationship with other literature

Previous economic studies have evaluated the cost-effectiveness of self-monitoring rather than self-management (self-monitoring plus self-titration of anti-hypertensives) and only one previous economic analysis of self-management has been undertaken (TASMINH2)[8], which found self-management to be cost-effective (£1,624 and £4,923 per QALY gained for men and women respectively).[8] In this analysis, we found self-management to be even more cost effective, reflecting the higher number of cardiovascular events predicted to have been prevented in the higher risk population, and the slightly greater reductions in blood pressure that were observed in the TASMIN-SR trial.

Strengths and limitations

This study used cost and outcome data of trial participants6 who may differ from similar patients not taking part in the trial for instance being more adherent and healthier. 25 The strongly positive results however suggest that such an intervention would be cost-effective even in a less compliant population. The costs of long-term and acute care were taken from estimates in the literature and a number of assumptions were made about the annual probabilities of cardiovascular events by risk conditions based on best published information. A key assumption was that of the prolonged effectiveness of the intervention. In both TASMINH2 and TASMIN-SR, the difference in BP reduction

between trial arms continued to diverge between 6 and 12 months suggesting that the effect may be maintained over time. Indeed, an 18 month post trial follow up of the HSM self-management trial found that blood pressure continued to diverge over time suggesting our assumption of maintenance of effect may even be conservative. [26] The sensitivity analyses showed that even if blood pressure differences lasted only one further year and then returned to the effectiveness of usual care, self-management is still likely to be cost effective. For simplicity, the model did not include subsequent cardiovascular events. Given that the main driver of costs was events and the main driver of events was blood pressure, it would be expected that a model including secondary and subsequent events would show self-management to be even more cost-effective than usual care. Finally, an assumption has been made regarding the differential effect of blood pressure lowering between the intervention and control groups. Systematic reviews suggests that lowering blood pressure below 140/90 mmHg is as effective as lowering blood pressure to 140/90 mm Hg,[27] but it is fair to say that the evidence of benefit is stronger in stroke and diabetes than in CHD or CKD.[10, 28-30]

Clinical implications

These results suggest that the benefits of blood pressure reduction seen in the trial can be achieved in a highly cost-effective manner. The up-front costs of implementation of self-management of hypertension in high risk groups are relatively modest (£14.6 equipment and £20.0 training) and are soon repaid by future maintenance of quality of life and reductions in costs from reduced cardiovascular events. The very high likelihood of cost effectiveness from both this and the previous analyses suggests that self-management is a strong candidate for implementation.

Conclusions

The results of this model-based economic evaluation suggest that self-management of hypertension in high risk patients is a cost effective strategy in the short and long term, resulting in QALY gains and cost-savings. Self-management of blood pressure in high risk patients represents an important new addition to the management of hypertension in primary care.

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Conflict of interest

RJM has received research equipment from Omron and Lloyds Pharmacies.

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Table 1 Model parameters

Parameter	Value	Source
Reduction in systolic blood pressure at 12 months (mmHg)		TASMIN-SR trial[6]
Self-management	15.0	
Usual care	5.8	
Reduction in systolic blood pressure at 6 months (mmHg)		TASMIN-SR trial[6]
Self-management	11.4	
Usual care	5.5	
Annual transition probabilities		
CVD events for patients with diabetes mellitus (DM)		NICE Diabetes guidelines, Appendix D1[12]
Stroke		
60-69 years old	0.0196	
70-79 years old	0.0262	
80-89 years old	0.0293	
Myocardial infarction (MI)		
60-69 years old	0.0089	
70-79 years old	0.0100	
80-89 years old	0.0111	
Unstable angina (UA)		
60-69 years old	0.0041	
70-79 years old	0.0047	
80-89 years old	0.0052	
CVD events for patients with chronic kidney disease (CKD)		Kerr et al (2012)[11]
Stroke		
60-69 years old	0.0072	
70-79 years old	0.0147	
80-89 years old	0.0189	
MI		
60-69 years old	0.0051	

70-79 years old	0.0113	
80-89 years old	0.0171	
UA		
60-69 years old	0.0024	
70-79 years old	0.0054	
80-89 years old	0.0081	
CVD events for patients with a previous stroke		PROGRESS (1999) & NICE, Lipid modification guidelines[10, 14]
Stroke		
60-69 years old	0.0348	
70-79 years old	0.0589	
80-89 years old	0.0713	
MI		
60-69 years old	0.0139	
70-79 years old	0.0232	
80-89 years old	0.0232	
UA		
60-69 years old	0.0139	
70-79 years old	0.0232	
80-89 years old	0.0232	
CVD events for patients with coronary heart disease (CHD)		NICE, Lipid modification guidelines[14] and NICE Hypertension guidelines[4]
Stroke		
60-69 years old	0.0359	
70-79 years old	0.0588	
80-89 years old	0.0713	
MI		
60-69 years old	0.0666	
70-79 years old	0.1112	
80-89 years old	0.1112	
UA		
60-69 years old	0.0528	
70-79 years old	0.0881	

80-89 years old	0.0881	
Age-related relative risks at 12 months		TASMIN-SR trial & Law et al (2009)[6, 15]
MI and UA - self management		
60-69 years old	0.63 (0.60, 0.66)	
70-79 years old	0.68 (0.64, 0.71)	
80-89 years old	0.74 (0.70, 0.78)	
Stroke - self management		
60-69 years old	0.53 (0.49, 0.57)	
70-79 years old	0.59 (0.55, 0.64)	
80-89 years old	0.74 (0.69, 0.79)	
MI and UA - usual care		
60-69 years old	0.83 (0.81,0.84)	
70-79 years old	0.85 (0.84,0.87)	
80-89 years old	0.89 (0.87,0.90)	
Stroke - usual care		
60-69 years old	0.77 (0.75, 0.79)	
70-79 years old	0.81 (0.79, 0.83)	
80-89 years old	0.89 (0.86, 0.91)	
Age-related relative risks at 6 months		TASMIN-SR trial & Law et al (2009) [6, 15]
MI and UA - self management		
60-69 years old	0.71 (0.68, 0.73)	
70-79 years old	0.75 (0.72, 0.77)	
80-89 years old	0.80 (0.76, 0.83)	
Stroke - self management		
60-69 years old	0.62 (0.59, 0.66)	
70-79 years old	0.68 (0.64, 0.71)	
80-89 years old	0.80 (0.76, 0.84)	
MI and UA - usual care		
60-69 years old	0.83 (0.82,0.85)	
70-79 years old	0.86 (0.85,0.87)	
80-89 years old	0.89 (0.87,0.91)	
Stroke - usual care		

60-69 years old	0.77 (0.75, 0.80)	
70-79 years old	0.81 (0.80, 0.84)	
80-89 years old	0.89 (0.87, 0.91)	
Probability of death for those who have suffered an event		
Fatal stroke	0.23	Bamford et al (1990)[31]
Fatal myocardial infarction		ONS, Deaths registry (2011) & Kerr et al (2012) [11, 32]
65-74 years old	0.23	
75-84 years old	0.39	
85 and over	0.52	
Costs (2011/12 UK £)		
Cost for the initial state (UK £) [a]		TASMIN-SR trial, Curtis L (2012) & BNF 2012 [6, 33, 34]
Self-management (including the cost of the intervention)[b]	183	
Usual care	125	
Costs of acute disease one-off cost (UK £)		
Stroke	11,020	Youman et al (2003)[20]
MI	5,487	Palmer et al (2004)[21]
Unstable Angina	3,292	Assumed 60% of MI
Costs for long-term (chronic) disease per year (UK £)		
Stroke	2,721	Youman et al (2003)[20]
MI	572	Cooper et al (2008)[19]
Unstable Angina	572	Cooper et al (2008) [19]
Utilities		
Utilities for initial health state		
Self-management and usual care		TASMIN-SR Trial[6]
65-74 years old	0.81	
75-84 years old	0.74	
85 and over	0.71	

Utilities for acute events		Cooper et al (2008) [19]
Unstable angina	0.77	
Myocardial Infarction	0.76	
Stroke	0.63	
Utilities for long term (chronic) disease		Cooper et al (2008) [19]
Unstable angina	0.88	
Myocardial Infarction	0.88	
Stroke	0.63	
Dead	0.00	by definition

[a] Total costs included annual costs of drugs per patient, average GP and PN cost of consultation(s) and the costs of the intervention (equipment and training). The cost difference between self-monitoring and usual care was driven by the cost of the intervention.

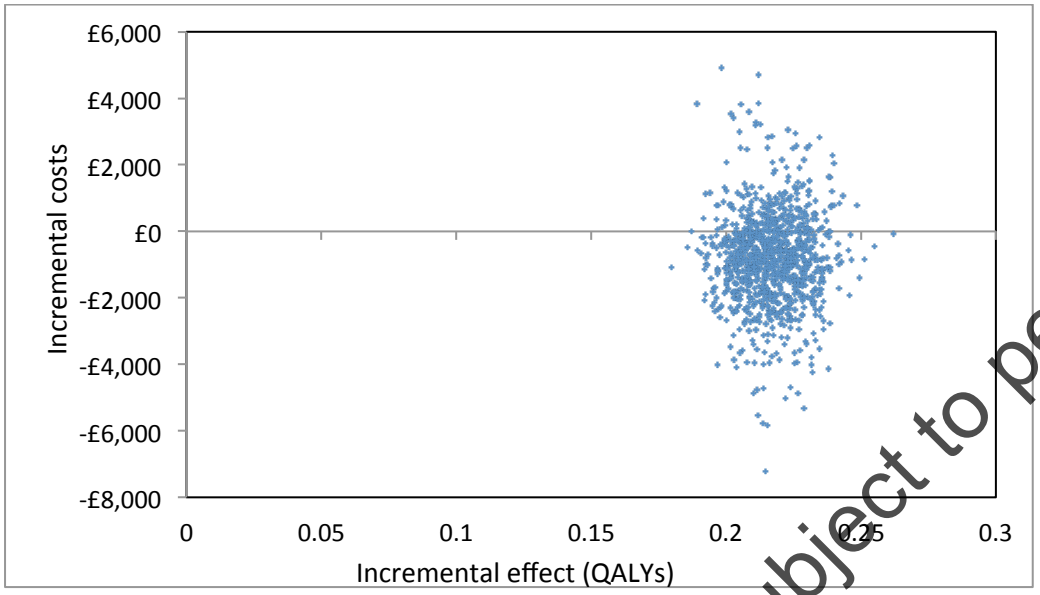
[b] For greater detail on the annuitized costs for equipment and training see supplemental online document

Table 2 Results of cost-effectiveness analysis

	Costs (£)	QALYs	Incremental cost (£)	Incremental QALYs	ICER (£ per QALY)
Total population					
Usual care	8,187	6.0326			
Self-management	7,357	6.2466	-830	0.2139	Dominant
Women					
Usual care	7,338	6.2467			
Self-management	6,579	6.4456	-759	0.1988	Dominant
Men					
Usual care	8,654	5.9035			
Self-management	7,791	6.1257	-864	0.2221	Dominant

Figure 2 Base case results: incremental cost effectiveness plane and cost effectiveness acceptability curve

Base case incremental cost-effectiveness plane, comparing self-management against usual care



Base case cost-effectiveness acceptability curve (CEAC) for self-monitoring of hypertension

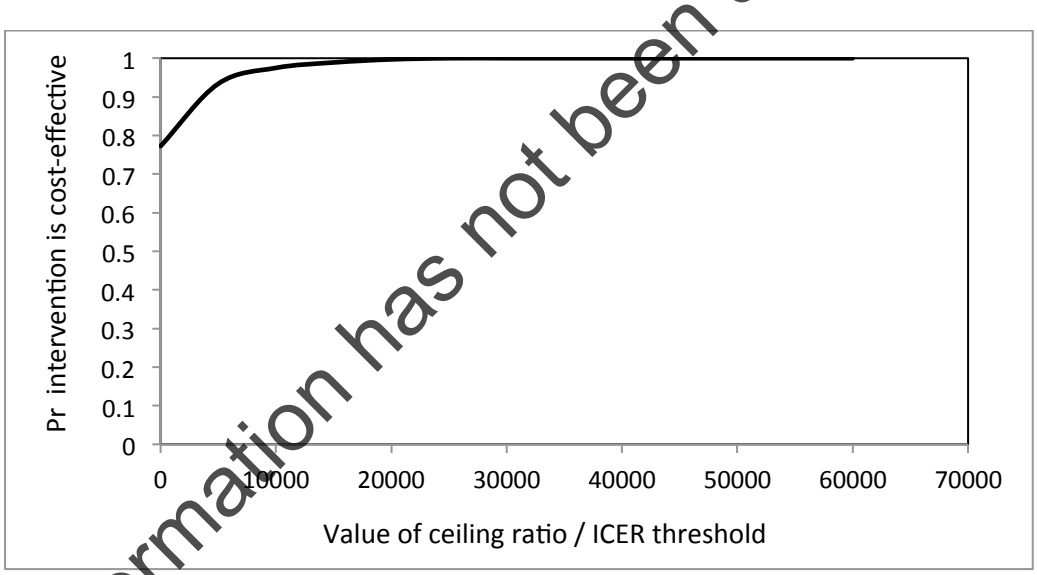


Table 3 Sensitivity analyses: results of cost-effectiveness analysis by time horizon

	Costs	QALYs	Incremental cost	Incremental QALYs	ICER
20-year					
Usual care	7,709	5.8830			
Self-management	6,919	6.0975	-789	0.2145	Dominant
10-year					
Usual care	5,242	4.7756			
Self-management	4,675	4.9252	-567	0.1496	Dominant
5-year					
Usual care	2,882	3.1178			
Self-management	2,554	3.1742	-328	0.0564	Dominant
3-year					
Usual care	1,690	2.0859			
Self-management	1,535	2.1044	-155	0.0186	Dominant
2-year					
Usual care	1,116	1.4651			
Self-management	1,056	1.4718	-59	0.0067	Dominant
1-year					
Usual care	603	0.7729			
Self-management	625	0.7736	22	0.0006	34,791

Table 4 Sensitivity analyses: results of cost-effectiveness analysis by reducing the additional effect of self-management to BP lowering at four different time points

Time horizon	Costs (£)	QALYs	Incremental cost (£)	Incremental QALYs	ICER (£ per QALY)
10 years					
Usual care	8,187	6.0326			
Self-management	7,530	6.2242	-657	0.1916	Dominant
5 years					
Usual care	8,187	6.0326			
Self-management	7,876	6.1623	-311	0.1297	Dominant
2 years (or equivalently, first year after the trial)					
Usual care	8,187	6.0326			
Self-management	8,259	6.0757	71	0.0430	1,660
1 year (within the trial or first year of the intervention)					
Usual care	8,187	6.0326			
Self-management	8,382	6.0454	195	0.0127	15,341

Supplemental online document

Distribution of primary CVD events (named stroke, MI or UA)

Patient level data from TASMIN-SR indicated that the 'high risk history' of patients entering the model was best reflected through presence or absence of four main underlying conditions (diabetes, stroke, Coronary Heart Disease - CHD and Chronic Kidney Disease - CKD). This gives 16 possibilities (2×2×2×2) of underlying conditions. Since all patients had at least one of the four main conditions the group "none of these" was omitted, leaving fifteen different groups.

The risks associated to each of three possible cardiovascular events (stroke, Myocardial Infarction - MI or Unstable Angina - UA) for high risk condition patients within a year were calculated by age ranges, gender and for the total population:

1. Risks associated to the four main high risk conditions were identified in various sources. [10-14] Data were not always available per age ranges or gender, in which case these risks were applied directly to the four relevant risk groups.
2. When the probability of an event (Stroke, MI or UA) was not available stratified by age group, the following assumption was made: the average relationship between available probabilities of an event by age ranges was used to calculate missing values. Table 1 shows the available data for the annual risk of stroke for a 65 years old person.

eTable 1 Risk of stroke for given existing condition

Age group	Diabetes (stratified data available)	CKD (stratified data available)	Stroke (missing values in blue)
65	0.0196	0.0072	0.0348*
75	0.0262	0.0147	to be estimated
85	0.0298	0.0189	to be estimated

* Probability of a 65 years old patient with a history of stroke of having a stroke within a year

To estimate the probability of a repeat stroke for a 75 year old patient with a history of (previous) stroke, the relative risk (compared to age 65) was estimated as the average of the relative risks for the other two existing conditions, that is

$$\frac{1}{2}\left(\frac{0.0262}{0.0196}+\frac{0.0147}{0.0072}\right)=1.6925.$$

Multiplying 0.0348 by 1.6925 gives an estimated risk of 0.0589 for a 75 year old patient. Similar calculations for an 85 patient give an estimated risk of 0.0713.

3. Annual transition probabilities of having an unstable angina or a myocardial infarction per age ranges in a population with diabetes were estimated based on the NICE Type 2 Diabetes guidelines.[12] The following assumptions were adopted: i) baseline risk of CVD for a 65-year old non-diabetic is 0.02; ii) this risk increases 0.0003 per a one year increase in age in males and 0.0002 in females; iii) the risk of CVD in diabetics compared to non-diabetics is 2.5 fold; and iv) the proportion of MI and UA population in relation to the total CVD population remains the same during the lifetime.

4. Risks induced by patient's underlying conditions are additive.
5. For risk groups reflecting the presence in a given patient of two or more high risk conditions, assumptions to calculate the risk of an event (stroke, MI or UA) were made: the probability of an event (stroke) will be the sum of the individual probabilities of the event for the existing conditions. Using data from Table 1 above as an example, the risk of stroke for a 65-year old patient with a history of (previous) diabetes (DM) and Chronic Kidney Disease (CKD) was estimated as,

$$Risk\ Stroke\ 65\ yrs = [1 - (1 - DM) * (1 - CKD)]$$

Risk Stroke 65 yrs = [1-(1-0.0196)*(1-0.0072)]

Risk Stroke 65yrs = [1-(0.9804)*(0.9928)]

Risk Stroke 65yrs = [1-0.9733]

Risk Stroke 65yrs = 0.0267

6. The probability of an event (stroke, MI or UA) stratified by gender and age group was only available for the high risk condition Chronic Kidney Disease (CKD). [11] For other high risk conditions for which data stratified by gender was not available, assumptions were adopted: i) within the population the proportion of men and women are the same; ii) the risk ratio men to women was assumed to be the same as per individuals without underlying conditions; iii) risk ratios male to female for a one year risk of stroke, MI and UA were estimated from table 1, TASMINH2, [8] from where the one year risk ratio (RR) male/female of stroke was estimated to be 1.8 and the one year RR male/female of MI and UA was estimated to be 2.0. Risks by gender were estimated from the following relationship:

The risk in a population with underlying conditions of developing a Stroke (TP)

TP = (RR*F/2) + (F/2)

Where RR is the one year male/female risk ratio of having a stroke; F is the risk for a female of developing a stroke per age range. Solving the equation for F, we have:

F = (2*TP) / (RR + 1)

For example, the risk for a 65 years female with previous history of diabetes of developing stroke within a year was estimated as:

F = (2*0.0196) / (1.8+1)

F = 0.0140

7. Since the cycle length of the TASMIN-SR model is six months, annual transition probabilities needed to be converted into six-month transition probabilities following standard practice[35]:

Annual transition probabilities were transformed into instant six-month rates:

$$R = - [\ln (1-P)] / t$$

Where R is the instant 6-month rate, P is the annual probability of the event and t is the time period of interest. Rates were then transformed back into probabilities:

6-month probability = 1 – Exp (- R * 1), where R is 6-month rate

Table 2 shows all the estimated 6-month probabilities of cardiovascular events by high risk conditions for the total population, by gender and age ranges.

eTable 2 Six-month probabilities of cardiovascular events by risk conditions, age and gender

Risk condition*	Stroke			MI			UA		
	65	75	85	65	75	85	65	75	85
Total									
Risk 1	0.0098	0.0132	0.0150	0.0045	0.0050	0.0056	0.0021	0.0024	0.0026
Risk 2	0.0036	0.0074	0.0095	0.0026	0.0057	0.0086	0.0012	0.0027	0.0040
Risk 3	0.0176	0.0299	0.0363	0.0070	0.0117	0.0117	0.0070	0.0117	0.0117
Risk 4	0.0176	0.0298	0.0363	0.0339	0.0572	0.0572	0.0208	0.0451	0.0451
Risk 5	0.0134	0.0205	0.0244	0.0070	0.0107	0.0141	0.0033	0.0050	0.0066
Risk 6	0.0211	0.0370	0.0455	0.0095	0.0173	0.0202	0.0082	0.0143	0.0157
Risk 7	0.0211	0.0370	0.0455	0.0363	0.0626	0.0653	0.0279	0.0476	0.0489
Risk 8	0.0272	0.0427	0.0508	0.0114	0.0166	0.0172	0.0090	0.0140	0.0142
Risk 9	0.0272	0.0426	0.0508	0.0382	0.0620	0.0625	0.0288	0.0473	0.0476
Risk 10	0.0348	0.0588	0.0713	0.0406	0.0682	0.0682	0.0335	0.0562	0.0562
Risk 11	0.0307	0.0497	0.0598	0.0139	0.0222	0.0256	0.0102	0.0166	0.0182
Risk 12	0.0307	0.0497	0.0598	0.0406	0.0673	0.0705	0.0299	0.0499	0.0514
Risk 13	0.0443	0.0712	0.0853	0.0449	0.0729	0.0734	0.0355	0.0584	0.0587
Risk 14	0.0383	0.0658	0.0802	0.0431	0.0735	0.0762	0.0347	0.0587	0.0600
Risk 15	0.0478	0.0781	0.0940	0.0473	0.0782	0.0814	0.0367	0.0610	0.0625
Male									
Risk 1	0.0113	0.0152	0.0173	0.0051	0.0058	0.0064	0.0024	0.0027	0.0030
Risk 2	0.0042	0.0076	0.0091	0.0039	0.0079	0.0111	0.0019	0.0037	0.0052
Risk 3	0.0195	0.0333	0.0405	0.0078	0.0130	0.0130	0.0078	0.0130	0.0130
Risk 4	0.0202	0.0344	0.0419	0.0391	0.0661	0.0661	0.0308	0.0520	0.0520
Risk 5	0.0155	0.0226	0.0262	0.0090	0.0137	0.0175	0.0042	0.0064	0.0082

Risk 6	0.0237	0.0406	0.0492	0.0117	0.0208	0.0239	0.0096	0.0167	0.0181
Risk 7	0.0244	0.0417	0.0506	0.0428	0.0735	0.0765	0.0326	0.0556	0.0570
Risk 8	0.0306	0.0479	0.0570	0.0128	0.0187	0.0193	0.0101	0.0156	0.0159
Risk 9	0.0313	0.0490	0.0584	0.0440	0.0715	0.0721	0.0331	0.0546	0.0549
Risk 10	0.0393	0.0665	0.0806	0.0465	0.0782	0.0782	0.0383	0.0643	0.0643
Risk 11	0.0347	0.0551	0.0656	0.0167	0.0265	0.0302	0.0119	0.0193	0.0211
Risk 12	0.0354	0.0563	0.0670	0.0477	0.0788	0.0824	0.0349	0.0581	0.0598
Risk 13	0.0502	0.0807	0.0965	0.0514	0.0835	0.0841	0.0406	0.0668	0.0671
Risk 14	0.0434	0.0736	0.0890	0.0503	0.0855	0.0885	0.0401	0.0678	0.0692
Risk 15	0.0542	0.0876	0.1047	0.0551	0.0908	0.0943	0.0424	0.0703	0.0720
Female									
Risk 1	0.0075	0.0101	0.0115	0.0034	0.0039	0.0043	0.0016	0.0018	0.0020
Risk 2	0.0033	0.0073	0.0097	0.0018	0.0046	0.0077	0.0009	0.0022	0.0036
Risk 3	0.0130	0.0220	0.0268	0.0052	0.0086	0.0086	0.0052	0.0086	0.0086
Risk 4	0.0134	0.0228	0.0277	0.0258	0.0435	0.0435	0.0205	0.0343	0.0343
Risk 5	0.0108	0.0173	0.0210	0.0052	0.0084	0.0119	0.0024	0.0040	0.0056
Risk 6	0.0162	0.0292	0.0362	0.0070	0.0132	0.0162	0.0060	0.0108	0.0122
Risk 7	0.0167	0.0299	0.0371	0.0276	0.0479	0.0509	0.0213	0.0364	0.0378
Risk 8	0.0204	0.0319	0.0380	0.0085	0.0125	0.0129	0.0067	0.0104	0.0106
Risk 9	0.0209	0.0327	0.0388	0.0292	0.0472	0.0476	0.0220	0.0361	0.0363
Risk 10	0.0262	0.0444	0.0537	0.0309	0.0518	0.0518	0.0255	0.0427	0.0427
Risk 11	0.0236	0.0390	0.0473	0.0104	0.0170	0.0204	0.0076	0.0126	0.0142
Risk 12	0.0241	0.0397	0.0481	0.0309	0.0516	0.0549	0.0228	0.0382	0.0398
Risk 13	0.0336	0.0540	0.0646	0.0342	0.0555	0.0558	0.0270	0.0444	0.0446
Risk 14	0.0294	0.0513	0.0629	0.0327	0.0562	0.0591	0.0264	0.0447	0.0461
Risk 15	0.0367	0.0609	0.0736	0.0359	0.0598	0.0631	0.0279	0.0465	0.0480

Notation:

1. DM = diabetes mellitus; CKD = chronic kidney disease; ST = stroke and CHD = coronary heart disease
2. Risk 1=DM; Risk 2=CKD; Risk 3=ST; Risk 4=CHD; Risk 5= DM-CKD; Risk 6= CKD-ST; Risk 7= CKD-CHD; Risk 8= DM-ST; Risk 9= DM + CHD; Risk 10= CHD-ST; Risk 11= DM-CKD-ST; Risk 12= DM-CKD-CHD; Risk 13= DM-ST-CHD; Risk 14= CKD-ST-CHD, and Risk 15= DM-ST-CHD-CKD

* Relative risks for which information was not available were imputed

† Relative risks for two or more conditions (Risk groups 5 to 15) are equivalent to the sum of the individual risk conditions

Sources: PROGRESS (2001); NICE guidelines on diabetes; NICE guidelines on lipid modification; Kerr et al, (2012)

Quality of life utilities

Utilities in the model for stroke, MI and unstable angina (UtilityAngina, UtilityStroke and UtilityMI) are the resultant of multiplying:

Utility multipliers for CVD (from Cooper et al, table 14, Lipid Modification guidelines) * Absolute utility by age (Non-CVD population) * time in acute state (assumption is half cycle or 0.5) * Mult_dist (PSA)

eTable 3 Costs of equipment and training

Costs 2013	Equipment	Main training costs[a]	Total intervention costs
VAT	0.200		
Equipment (cost per monitor)	55.0		
capital outlay (K)	66.0	90.0	156.0
Interest/Discount rate (r)	0.035	0.035	0.035
Useful life of equipment (n years)	5	5	5
Equivalent annual cost (£)	14.6	19.9	34.6[b]

[a] Training costs assumed each patient required 2 training face-to-face sessions by a practice nurse

[b] Annuitized costs for equipment and training

eTable 4 Un-adjusted results of cost-effectiveness Analysis

	Costs (£)	QALYs	Incremental cost (£)	Incremental QALYs	ICER (£ per QALY)
Total population					
Usual care	8,169	6.0370			
Self-management	7,381	6.2415	-787	0.2045	Dominant
Female					
Usual care	7,321	6.2507			
Self-management	6,601	6.4408	-719	0.1901	Dominant
Male					
Usual care	8,635	5.9081			
Self-management	7,816	6.1203	-819	0.2122	Dominant

eTable 5 Un-adjusted results of sensitivity analysis: results of cost-effectiveness analysis by time horizon

	Costs	QALYs	Incremental cost	Incremental QALYs	ICER
20-year					
Usual care	7,691	5.8873			
Self-management	6,942	6.0923	-749	0.2050	Dominant
10-year					
Usual care	5,227	4.7793			
Self-management	4,693	4.9217	-534	0.1424	Dominant
5-year					
Usual care	2,868	3.1198			
Self-management	2,566	3.1732	-302	0.0533	Dominant
3-year					
Usual care	1,680	2.0865			
Self-management	1,541	2.1041	-140	0.0177	Dominant
2-year					
Usual care	1,111	1.4653			
Self-management	1,059	1.4718	-52	0.0064	Dominant
1-year					

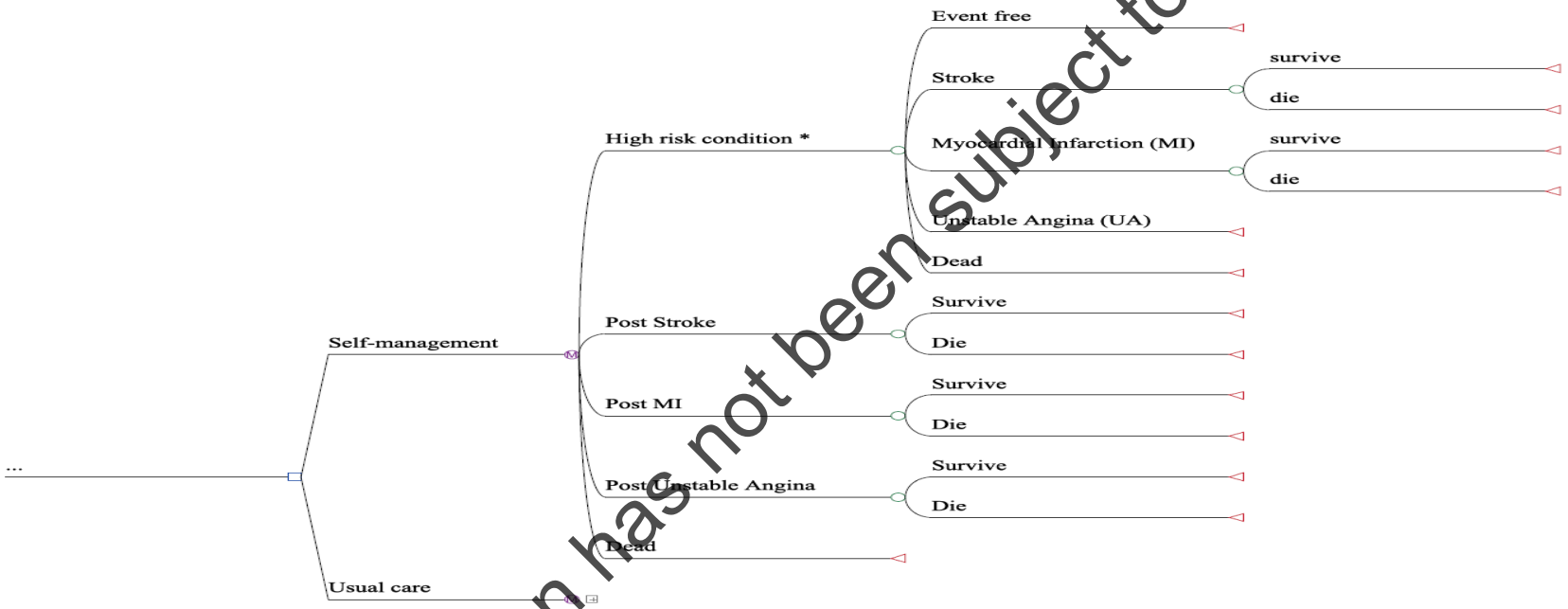
Usual care	603	0.7729			
Self-management	625	0.7736	22	0.0006	34,791

Note: un-adjusted results of CE for 1-year time horizon did not change as compared to the adjusted results because the age-related risk reductions remained the same at 6M

eTable 6 Un-adjusted results of sensitivity analysis: results of cost-effectiveness analysis by reducing the effect of BP lowering

	Costs (£)	QALYs	Incremental cost (£)	Incremental QALYs	ICER (£ per QALY)
10-year					
Usual care	8,169	6.0370			
Self-management	7,546	6.2202	-622	0.1832	Dominant
5-year					
Usual care	8,169	6.0370			
Self-management	7,890	6.1596	-278	0.1227	Dominant
2-year					
Usual care	8,169	6.0370			
Self-management	8,364	6.0497	195	0.0127	15,313

Figure 1 Markov model structure



* In the Markov model patients can enter through any of fifteen combinations of high risk conditions Note: The Markov model is displayed for the self-management strategy only however, the model is identical for the usual care strategy.

RCT for Secondary Prevention: Patient Experiences of Trial Participation

Authors:S Greenfield; C Schwartz; RJ McManus

Paper in preparation.

This section discusses the qualitative study that was embedded in the secondary prevention randomised controlled trial (TASMIN-SR).

Background

Increasing use is being made of novel methods to capture patient experience. What patients say when given the opportunity to freely express their views [1,2] can be useful for finding out about their experience of taking part in a study or their views about the study intervention. This type of information may not be revealed by trial documentation and hence never drawn to the researchers' attention and not taken into account.[3] Such data can be collected for example by leaving a blank page at the end of a questionnaire for respondents to add additional comments,[4] by analysing any comments respondents write in the margin of a questionnaire[5] or by using postcards for people to express their views by drawing pictures.[6] At 12 month follow up, participants in TASMIN-SR, a trial of self-management of blood pressure (BP) compared to usual care were given a blank postcard and asked to write a few sentences about their experience of the trial. An analysis of their comments was undertaken to find out more about patient experiences and views about participating in the trial.

Methods

Trial intervention

Patients in the TASMIN-SR trial were aged over 35 and had a history of stroke, coronary heart disease, diabetes or chronic kidney disease. They had poorly controlled hypertension (clinic blood pressure greater than 130/80) which was managed in primary care. They were recruited through the UK Primary Care Research Network and were individually randomised either to usual care or self-management.[7] Patients were asked to attend for two further follow-up clinics (6- and 12-months) and at the 12 month visit were given a blank postcard and asked to write a few sentences about their experience of the trial.

Analysis

All comments written by respondents on the postcards were extracted and transcribed. They were independently read by SG and themes and sub-categories were identified by highlighting relevant text.[8] A selection of postcards were read by CS and themes discussed by the trial team to confirm theme development (25). Extracts of text for each theme are used to reflect the range of issues raised and a numerical summary of the themes and subcategories is also shown (Table 1), to aid interpretation and contextualisation of the range of issues.[3] The patient number is shown at the end of each section of text.

Table 1: Summary of Postcard themes and sub-categories n=148

Theme/sub-categories	Total no. of respondents who mentioned
Reasons for taking part	
Altruism	34
Medical factors	7
General feelings about taking part	
Positive	
Staff helpful	52
Personal satisfaction	49
Personal benefit	43
Want to know trial results	12
Negative	
Preference for medical management	2
Negative views about medication	2
Unsure about value of trial	2
Comments about the treatment programme	
Benefits of taking part	
Patient empowerment	
BP	14
Greater understanding of BP	23
Benefits of monitoring process	18
Benefits around medication	4
Lifestyle re-evaluation	
Lifestyle in general	24
Diet	33
Exercise	11
Weight	4
Problems/negative issues around taking part	
Unable to complete due to other medical conditions/personal circumstances	9
Didn't motivate to lifestyle change	5
Medication side effects	2
Comments about the carrying out the treatment programme	
Paperwork	
Format	11
Content	49
Lifestyle questions	13
BP measurement	
Taking BP	10
BP readings	9
Timing of BP measurements	11
Home versus clinic BP	28
Medication change	
Side effects	6
process	6
medication beliefs and behaviour	4

Results

Postcards were completed by a total of 149/450 respondents one of which stated the respondent had no comments (response rate 32.9%). Four main themes each with subcategories emerged from the analysis of the open comments (Table 1). These were; reasons for taking part in the study, general feelings about taking part (positive and negative) comments about the treatment programme (benefits of taking part, problems and negative issues about taking part) and comments about carrying out the treatment programme (paperwork, BP measurement, Lifestyle questions, medication change).

Reasons for taking part in the study

The most common reason given by patients for taking part could be described as altruism i.e. in the hope that their participation could help future work on hypertension.

"I have been pleased to be a participant in the TASMINH SR Trial over the last 12 months and hope that analysis of the results will be useful in the entire management and reduction in levels of hypertension" 01325

and ultimately benefit other patients.

"..hope my contribution may help your research-the results I hope will be of greater benefit to present and future generations…"
00316

Other patients saw it as an opportunity to feed back their views and experiences of their own treatment to the NHS.

"I appreciate having my opinion asked about the treatment I receive and the medication I am given, even though I am not in a position to do anything about it personally. Collectively however the NHS may listen. If nutrition was taught in schools I think we would have a healthier nation" 00865

Personal or family experience of illness also acted as a motivator for patients to try and protect both their individual health and that of other family members.

"My father was in his sixties when he died so I think there may be a inherit factor. I had a very bad turn some years ago like a mini stroke. It is paramount that I keep healthy in order to care for my dear wife who has osteoporosis" 85018

General feelings about taking part in the study

There were a large number of positive comments about taking part in the study, most often mentioned was the helpfulness of the trial staff.

"My mentor was very pleasant made one feel at ease the way she has conducted my test made me feel it was well worth while" 00089

Many participants wrote about the personal satisfaction or personal benefits they felt had come from their participation.

"I would just like to say thank you for taking the time to study my blood pressure" 819

"*Although it is quite time consuming I found this project helpful…Usually I felt GPs were not interested in seeing a patient 'just' because of BP queries! So in that respect it has been invaluable*"

00907

Twelve participants had thought about what the trial would eventually lead to and expressed a wish to see the trial results.

"I would like a glimpse of the published paper regarding the study as a whole. A title/author would do as I can then access it through the Internet." 01437

Very few participants wrote negative comments about taking part. Where they did these related either to a preference for medical rather than self-management on their condition.

"*I dropped out of the TASMINH-SR study because I found taking my own blood pressure somewhat stressful. I hope a doctor or nurse will always be available to do it*" 01016

or that they simply had strong views about medication.

"*I do not agree with self-medication*" 00003

"…I have a feeling that over medication does occur-maybe I should stop reading Dr Le Fanu in the 'Telegraph'" 00770

Participant comments about the treatment programme

Again most of the comments under this heading were positive. They could be divided into three categories the first of which related to **patient empowerment** either in terms of improved health or in managing the patient's condition.

I have felt much better during my participation and have been able to lead a much higher quality of life 01175

It made me feel in control in managing my blood pressure 199

Some patients felt that their understanding of BP had increased and they had been spurred on to find out more about it for themselves

I found the blood pressure survey interesting as it made me go into it more, looked it up on the computer and made me aware of how important the blood pressure is. I tell my friends and others of how important it is to look and see their blood pressure and try to bring it down and discuss it with their GP 01606

..it has highlighted examples of what I think affects my blood pressure…I certainly understand the terms high and low blood pressure and its readings. It has also made me aware of trying to relax more 01554

Another patient described how despite having a previous history of high blood pressure, it was the trial which had been the trigger to reducing it.

..whenever I had my blood pressure checked prior to this project I was always being told that my readings were too high (in the 140 range and even 150/90). Nothing was done about this problem other than advice to control my weight and exercise. Participating in this project with the facility of medication changes, I had three changes, has reduced my blood pressure from 140/84 at the start of the project to 129/75 today… 00912

A large number of comments suggested that in addition to the direct aims of lowering BP participation in the trial had motivated participants to rethink **other aspects of their lifestyle**.

Taking part in the TASMINH trial has caused me to re-evaluate my lifestyle. I feel that I am very active for my age-only my back problem stops me from doing more. Whilst my diet is not bad, I feel there is room for improvement and will try to eat more fruit, veg and fish
00040

The programme and writing the diaries was helpful and made me realise I do not eat enough fruit and fish and don't do enough exercise 01467

A small number of patients ex-pressed their **regret** that they had been unable to complete the trial due to other medical problems.

I found it interesting to see the blood pressure readings gradually reducing with the changes every two months of the tablets. This process was disrupted when I was admitted to the QE Hospital with deep vein thrombosis and the hospital changed my blood pressure tablets…
00021

..I increased my medication and if my life had not been disrupted I would have had better results…

01095

Others however felt they had not needed or been motivated to make any lifestyle changes as a result of the trial.

My weight stayed pretty much the same as I had already altered my diet when first diagnosed with blood pressure some 4 years ago so for me it would have been more interesting if I could have done it then 01560

Two patients felt that the medication had caused them to have problematic side effects.

..severe side effects from medication. This included swollen ankles and knee plus couching. For a final change my doctor prescribed candestartan cilexetil and this has had no after effects on my blood

01034

Trial procedures and paperwork

There were many comments about the trial paperwork. Many patients felt that having to complete regular paperwork was repetitive and boring.

Thought the diary was sometimes a little too predictable and could have been more adventurous in the way it was presented. I found it uninteresting 00917

However for some this repetition was felt to be beneficial as it had highlighted important factors about their lifestyle and they were able to see a pattern emerging.

Keeping the diary over the 6 month period brought to my attention how consistent my daily diet is. As a result I may try to vary it a little more. I will also try to improve on the 'healthy food' intake

00757

Many who mentioned the content of the paperwork felt that it was informative and comprehensive but others felt that there were some important issues relating to lifestyle which were not included.

Questions relating to fat intake made no reference to cheese consumption-in my case my greatest weakness! 0023

Carrying out self-monitoring and self-management

Whilst some patients found no problems in taking their own blood pressure, others found that despite being concerned at the start, over time they became more accustomed to doing so. Being able to see concrete evidence in terms of a visible drop in blood pressure reinforced this.

…but as the months passed by it became easier and then as my blood pressure dropped I felt better about the whole thing... 0132

From my point of view it has been interesting to try and interpret some of the recordings, in that why after a 5 minute wait the second reading has been higher than the first reading! Perhaps it was the anticipation that the second reading would always be lower than the first reading, and the anticipation that it would change from an amber reading to a green reading where the first reading was only slightly into the Amber area.. 01436

I might be incorrect but my experience of having a high BP was altered by when I took my medication. If I did not take it at least 1 hour before taking a BP reading, the reading was generally at amber. I suggest the timing of the two (BP testing and medication times) be recorded in your next BP survey 01151

Although some patients felt more reassured by taking their own blood pressure at home, others did not feel that the physical location of where the measurement was taken could make any difference to the reading.

I had my blood pressure taken each time at the doctor's surgery and don't believe the results would have been any different if I'd had them taken at home 797

Six patients pointed out that they had suffered from side effects as a result of having to change medications during the trial.

It has been a long 12 months but I'm now on the correct prescription losartan potassium 100mg lorvacs XL1.5mg 01337

Six patients commented on the process of adjusting their own medication. One who had found this difficult described how she had not carried medication changes out.

…However I felt the two monthly changes of medication difficult and on the advice of my GP I ignored them… 00731

Another highlighted the complexity of the process.

Handling the medication changes I found I had to have my wits about me 00573

Some patients can feel concerned when they have to take multiple medications and for some, these concerns were heightened by the medication change process.

I think the turning point was when I didn't need the changes in medication as I was concerned different medications might clash with what I was already required to take 032

Discussion

Use of postcards for patients to freely write about their experiences of taking part in a trial of self-management compared to usual care proved to be a useful method of collecting qualitative data. 148 patients, one third of those for whom 12 month primary outcome data was available took the opportunity to comment, far more than are generally included in qualitative sub-studies. Most participants commented fully, in many cases filling both sides of the postcard. The data suggested that many patients may have gained additional benefits from participation in the trial over and above any quantitative reduction in BP. These could range from the personal satisfaction of taking part, feeling more involved in and better able to cope with their own care, gaining greater understanding about hypertension to being aware of the need to change and changing components of their lifestyle. The large number of comments made about the trial paperwork and what patients like or find problematic can help with the design of future trials in this topic area.

Limitations of this approach to data collection are that only the views of respondents who chose to complete a postcard are included. These may be people who had definite opinions about the topic area and those who chose not to respond may have had other views. Given that the data depends upon a written response to a written question, it does not include views of respondents for whom this method was problematic. The vast majority of comments were positive. This may mean that patients were reluctant to be critical, but the participants had finished the trial at this stage and the range and depth of comments received suggest that they valued the chance to write about their experiences of participation.

The use of an open question to seek participant opinion at the end of a series of closed questions is an opportunity to gain additional or perhaps unexpected information about a topic.[3] In this study the postcard comments performed a similar function as they gave greater insight into patient beliefs and behaviours around the TASMIN-SR trial which can help to complement and facilitate broader understanding of the trial results. Compared with our previous approach of one to one interviews in the TASMINH2 trial of self-management in hypertension,[9] the postcard methodology allowed much greater coverage of the range of views but was unable to probe particular areas of concern in more detail. There were distinct parallels in terms of recurrent themes of increasing patient empowerment and understanding regarding blood pressure. Participants in both studies raised some concerns regarding the process of self-management and this needs to be considered in future

work. The postcard system allowed new data regarding trial processes to emerge, particularly with respect to the collection of health behaviour data which were contained in the patient diaries. Similarly it captured information regarding the influence on behaviour of the intervention that may not have been captured otherwise. The open nature of the postcard responses meant that no new data on regarding ongoing plans for self-management were gained.

The current study included patients at higher risk of cardiovascular disease than previously included in self-management studies. The themes of increased knowledge and empowerment also emerged in a qualitative study of stroke patients who self-monitored without planned self-titration[10] In that study, several patients reported "experimenting" with self-titration and the perceived risk of further stroke seemed to drive at least some of the reported enthusiasm. Focus groups held as part of a small pilot study of self-titration using a web-based tool revealed largely positive views of the principle of self-titration which was thought to influence awareness of treatment, patient engagement and motivation whilst being more convenient. However, subsequent pilot results were disappointing with both technical and patient engagement problems.[11]

Overall, in combination with the positive trial results, these qualitative data support the adoption of self-management of hypertension in stroke and other high risk groups. Patients were generally enthusiastic about the trial with some reservations about the data collection instruments and the process of self-titration.

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Work programme 3

Randomised controlled trial of different systolic blood pressure targets for people with a history of stroke or transient ischaemic attack: the PAST-BP (Prevention After Stroke – Blood Pressure) study.

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Abstract

Objectives: Blood pressure lowering is effective at reducing risk of stroke recurrence in people who have had a cerebrovascular event, but it is uncertain how low blood pressure should be lowered in this population. We assessed whether using intensive blood pressure targets would lead to lower blood pressure in a community population of people with prevalent cerebrovascular disease.

Design: Open label randomised controlled trial.

Setting: 99 General Practices in England, with participants recruited 2009-2011.

Participants: People with a history of stroke or transient ischaemic attack whose systolic blood pressure was ≥ 125 mmHg.

Interventions: Intensive systolic blood pressure target (130mmHg or 10mmHg reduction from baseline if this was < 140 mmHg) or a standard target (140mmHg). Apart from the different target, patients in both arms were actively managed in the same way with regular reviews by the primary care team.

Main outcome measure: Change in systolic blood pressure between baseline and twelve months.

Results: 529 patients, mean age 72, were enrolled, 266 to the intensive target arm and 263 to the standard target arm, of whom 379 were included in the primary analysis (182, 68% intensive arm; 197, 75% standard arm). 84 patients withdrew from the study during the follow up period (52 intensive arm; 32 standard arm). Mean systolic blood pressure dropped by 16.1mmHg to 127.4mmHg in the intensive target arm and by 12.8mmHg to 129.4mmmHg in the standard arm (difference between groups 2.9 mmHg, 95% confidence interval (0.2 to 5.7); p = 0.03).

Conclusions: Aiming for a 130mmHg or lower target for systolic blood pressure in people with cerebrovascular disease in primary care rather than a 140mmHg target leads to a small additional reduction in blood pressure. Active management of systolic blood pressure in this population using a 140mmHg target leads to a clinically important reduction in blood pressure.

Trial Registration: ISRCTN29062286.

Introduction

Stroke accounts for about 10% of deaths internationally, and for over 4% of direct health care costs in developed countries.[96] If other resources, such as lost productivity, benefits payments and informal care costs are taken into account, the total costs double – for example in the United Kingdom annual care costs are around £4.4 billion, but total costs are £9 billion per annum.[97] Over 20% of strokes are recurrent events,[98] and if one also takes into account prior history of transient ischaemic attack (TIA), this figure rises to about 30%.[96] Therefore, secondary prevention has a major potential role to play in reducing both morbidity and costs of stroke care. Hypertension is a key risk factor for stroke. A 20 mm Hg difference in usual systolic blood pressure is associated with a 60% lower risk of death from stroke in someone aged 50 to 70, and a 50% lower risk in someone aged 70 to 79.[99]

The PROGRESS trial demonstrated that treatment to lower blood pressure in people who have had a stroke or TIA reduces risk of further stroke.[100] However, there is debate over how to apply this evidence in clinical practice.[101 102] In particular, there is uncertainty over how intensively to lower blood pressure in people who have had a stroke or TIA.[103] A post hoc observational analysis of the PROFESS trial found that people with recent ischaemic stroke whose systolic blood pressure was less than 130mmHg had a higher risk of vascular events.[104] Conversely, in PROGRESS participants whose baseline systolic blood pressure was 120-140mmHg who were randomised to combination therapy had significantly reduced stroke risk.[105] The SPS3 trial of different blood pressure targets in younger (mean age 63) patients with recent lacunar stroke found a non-significant 19% reduction in risk of stroke after one year in people treated with a systolic blood pressure target of less than 130 mmHg as compared to a 130-149mmHg target.[106] Recent guidelines have drawn different conclusions from the evidence base, with the European guidelines recommending a target systolic blood pressure of 140mmHg (or higher) [107] and British guidelines a target of 130mmHg.[108]

In view of these controversies, the Prevention After Stroke- Blood Pressure (PAST-BP) study compared two different targets for blood pressure lowering after stroke or TIA in people recruited from a prevalent primary care population. The aim was to determine whether setting a more intensive target in primary care would lead to a lower blood pressure, as a prelude to a trial powered to detect whether such a strategy would lead to a reduction in stroke recurrence.

Methods

Participants

The methods used in PAST-BP have been reported in detail elsewhere.[109] PAST-BP was an individually randomised trial in which participants were allocated either to an intensive blood pressure target (<130mmHg or a 10mmHg reduction if baseline pressure <140mmHg) or a standard target (<140 mmHg). Patients were recruited from 106 General Practices (of whom 99 contributed at least one patient) in England during 2009-2011. Patients were considered for inclusion if they were on the practice TIA/stroke register. They were excluded if: their baseline systolic blood pressure was less than 125 mmHg; they were already on 3 or more antihypertensives; they had >20mmHg postural change in systolic blood pressure on standing; they were already being treated to a 130mmHg systolic blood pressure target; they were unable to provide informed consent; or there was insufficient corroborative evidence that they had had a stroke or TIA. Potentially eligible participants were identified using a search of the General Practice clinical computer system. A general practitioner reviewed this list to exclude patients for whom a study invitation would be inappropriate. The remainder were sent a letter inviting them to attend a study clinic appointment held at their General Practice by a research nurse, where written informed consent was obtained. Ethical approval was provided by the Warwickshire Research Ethics Committee (reference 08/H1211/121).

Randomisation and masking

Randomisation was performed by the central study team at the University of Birmingham and was minimised on the basis of age, sex, diabetes mellitus, atrial fibrillation, baseline systolic blood pressure and general practice. Treatment allocation was ascertained by the research nurse either by telephone or online.

Neither participants nor clinicians were blinded to treatment allocation. The primary outcome measure (blood pressure) was obtained using automated sphygmomanometers and measured by a research nurse who was not otherwise involved in the patient's care.

Procedures

Patients randomised to the intensive arm were given a target systolic blood pressure of 130mmHg, or a target reduction of 10mmHg if their baseline blood pressure was between 125 and 140 mmHg. The target in the standard arm was 140 mmHg irrespective of baseline blood pressure. Apart from the different blood pressure targets, the management of blood pressure was the same in both groups, and was carried out by a practice nurse (to monitor blood pressure) and a general practitioner (responsible for modifying blood pressure treatment). Patients whose systolic blood pressure at baseline was above target (everyone in the intensive arm, and those patients in the standard arm whose blood pressure was greater than 140 mmHg) had their antihypertensive therapy reviewed by their General Practitioner. A practice nurse would see all patients at three month intervals (if their blood pressure was below target when previously measured) or at a one month interval (if previous blood pressure was above target), and refer to the general practitioner if the blood pressure was above target. No down-titration of therapy was performed if blood pressure was below target. General practitioners were provided with treatment protocols that reflected the national guidelines for blood pressure lowering in operation at the time of the trial.[110] In both arms of the trial, the general practitioners had access to a computer based algorithm that actively suggested drugs and dosage if the participant was above target. Follow up ceased if the participant had a major cardiovascular event.

The primary outcome was change in systolic blood pressure between baseline and one year. Participants had blood pressure measured by a research nurse (separate from the practice nurse measurement described above) at baseline, six and twelve months. Blood pressure was measured using a British Hypertension Society validated automated electronic monitor supplied and validated for the study.[111] Blood pressure was measured in a standardised way, with the patient seated for five minutes and then six measurements taken at minute intervals. The primary outcome was the average of the second and third measurements.

Secondary measures of blood pressure included diastolic blood pressure at six and twelve months, systolic blood pressure at six months, and proportion achieving target blood pressures at twelve months. For the systolic blood pressure we also calculated the means of readings 2 to 6 and 5 to 6 to look for any differential effects with regard to habituation to blood pressure measurement.

Clinical events were identified through review of the general practice record at twelve months. These comprised: major cardiovascular events (composite of fatal and nonfatal stroke, myocardial infarction, fatal coronary heart disease or other cardiovascular death), emergency hospital admissions and deaths. Participants were flagged for mortality at the NHS Central Register. Side effects were assessed through the use of standard questionnaires.[109]

Statistical analysis

We estimated that a sample size of 305 patients in each group would detect a 5 mmHg difference in systolic blood pressure between groups with 90% power at a significant level of 5% assuming a standard deviation of 17.5 mmHg, 10% loss to follow up, 5% mortality and 10% major vascular events.[100 102] For the primary analysis, mixed models were used, adjusting for baseline blood pressure, age group (<80 years, ≥80 years), gender, diabetes mellitus, atrial fibrillation and practice (as a random effect). The principal analysis was a complete case analysis. We also explored the potential effects of missing values by the use of three approaches: multiple imputation, group mean and by last available value. Subgroup analyses were pre-specified for diabetes mellitus, atrial

fibrillation and age group. In addition, we performed a sub-group analysis by baseline systolic blood pressure (<140mmHg, ≥140mmHg). The number of consultations, treatment changes and side effects were compared using generalised mixed modelling, adjusting for the same variables as the primary outcome. For clinical events, we calculated hazard ratios and their 95% confidence interval using Cox proportional hazards modelling adjusting for the same covariates mentioned previously. We checked the proportional hazard assumption with Schoenfeld residual plots and by including interaction terms in the model (for each term by time). For all clinical event analyses, patients were censored at the time of the first event relevant to that analysis. Thus, if a patient had more than one emergency hospital admission, only the first one would be counted. Analysis was undertaken using SAS 9.2 and Stata 12.

Results

Figure 1 shows the trial profile. 529 patients from 99 general practices (range 1 – 16 per practice) entered the trial. 84 patients withdrew from the trial in the twelve months following randomisation (52, 20% in the intensive target arm and 32, 12% in the standard target arm, p =0.02). Primary outcome data were available for 379 participants at one year follow up (182, 68% in the intensive target arm and 197, 75% in the standard target arm). All patients were followed up for clinical events and deaths. Table 1 shows baseline patient characteristics. About a quarter of participants were on no blood pressure lowering treatment at randomisation (76 in intensive arm; 63 in standard arm). For half of participants, the index event was a TIA. Just under 20% of participants reported at least moderate disability (modified Rankin score of three or more). There were no important differences in characteristics between participants who did and did not have blood pressure recorded at twelve months.

The intensive target arm was associated with significantly more consultations with the general practitioner and practice nurse for blood pressure control than the standard target arm (median

visits 2 versus 1, p < 0.0001 and 3 versus 2, p = 0.002 respectively). This higher consultation rate led to more intensifications of blood pressure treatment (458 versus 278, p < 0.0001), and more changes due to side effects (77 versus 30, p < 0.0001). However, patients were also less likely to have their blood pressure treatment increased after review by the general practitioner when the blood pressure was above target in the intensive arm (109 versus 57, p = 0.005) (table 2). At the end of the study, the number of antihypertensive drugs that patients were on in both arms had increased by a similar amount (mean number of antihypertensive drugs 2.1 in intensive arm and 1.9 in standard arm, p = 0.13).

Treatment to a more intensive target was associated with a significantly greater reduction in systolic blood pressure at twelve months (primary outcome) (table 3). Systolic blood pressure was reduced by 16mmHg in the intensive target arm and by 13mmHg in the standard target arm. This difference persisted if it was calculated using the mean of the 5th and 6th reading: -3.2 mmHg, 95%CI -5.8 to -0.64) or the mean of the 2nd to 6th reading: -3.3mmHg, 95% CI -5.8 to -0.67) (see web appendix table i). Taking account of the missing values had different impact depending upon the method used (see web appendix table ii). Using multiple imputation the effect size was -3.2mmHg, 95% CI -5.7 to -0.65, using the group mean it was -2.3 mmHg, 95% CI -4.3 to -0.32 and using the last value carried forward -1.8mmHg, 95% CI -4.2 to 0.57. Blood pressure target at one year was achieved in 93 (51.1%) patients in the intensive arm. Proportions achieving a systolic blood pressure of less than 140 mmHg were similar in the two arms (150/182, 82.4% versus 161/197, 81.7%, p = 0.59). There was no evidence of a significant difference in effectiveness of using an intensive blood pressure target in any patient sub-group (figure 2).

There was one major cardiovascular event in the intensive target arm (a non-fatal myocardial infarction), and five in the standard care arm (3 strokes; 1 non-fatal myocardial infarction and 1 cardiovascular death) (HR 0.19, 95% CI 0.02 to 1.87, p = 0.16). There were two deaths in the intensive target arm and one in the standard target arm. Risk of emergency admission was 12.8% per annum in the intensive target arm and 7.8% per annum in the standard target arm (HR 1.56,

95%CI 0.84 to 2.93, p = 0.16). Two admissions in each arm were related to falls. Apart from TIA (responsible for five admissions in the standard target arm and three admissions in the intensive target arm) and stroke, no single diagnosis accounted for more than two admissions. Table 4 shows the commonest symptoms at twelve months by treatment allocation. There were no significant differences between the two groups.

Discussion

Statement of principal findings

We found that aiming for a target systolic blood pressure of 130 mmHg or lower in a primary care population with prevalent cerebrovascular disease led to a lower systolic blood pressure than if a 140 mmHg target was aimed for, but the difference was small – about 3mmHg and was associated with increased workload – an extra consultation each for GPs and nurses per year. The intensive target arm was not associated with more side effects as measured at follow up, but there were more changes to treatment because of side effects during the trial. More people withdrew consent for the trial from the intensive target arm, and this might have reflected unwillingness to persevere with the increased medication regime. Perhaps the most important finding was the greater than 10mmHg reductions in mean systolic blood pressure in both arms of the study, so that over 80% of participants in each arm had achieved a blood pressure of < 140mmHg by the end of the trial, as compared to less than 50% at baseline.

Strengths and weaknesses of the study

Blood pressure at twelve months was not available for 28% of patients randomised. This reflected a high number of patient withdrawals from the study, with some differential loss to follow up in the intensive target arm. However, if missing values were imputed using multiple imputation – the most robust method -the difference in achieved blood pressure between arms at one year was very

similar to that observed. Only 4% of patients on general practice stroke/TIA registers participated in the trial. Participants had a low prevalence of disability for a prevalent cerebrovascular disease population, were younger than typical patients in primary care with a history of cerebrovascular disease and over-represented people with a history of TIA only.[102] It is likely therefore that the more intensive target would have been even harder to achieve if the trial population was more representative of people with prevalent cerebrovascular disease. The outcome measure was unblinded, but obtained using an automated sphygmomanometer by a nurse not directly involved in the participant's care, so systematic recording bias is unlikely.

The standard target arm in PAST-BP was actively managed, with support of a computer based algorithm that suggested medication changes rather than simply receiving 'usual care'. If we had used a more passive management strategy in the comparison group, we may have achieved a greater separation in systolic blood pressure between arms. In another blood pressure lowering study of patients with increased cardiovascular risk undertaken by our group in the same timeframe, the standard care control arm dropped by 6mmHg from a similar baseline compared to 13mmHg in the current study.[112] We used an active control as we wanted to ascertain the impact of setting different blood pressure targets, and to avoid confounding that would be introduced by having different management strategies in the two arms.

Comparison with other studies and interpretation

The change in mean blood pressure that we observed in the intensive target arm was very similar to that observed in the <130mmHg target arm of the SPS3 trial, with both PAST-BP and SPS3 achieving a mean systolic blood pressure in the intensive arm of 127 mmHg after one year.[106] However, the comparison arms had different achieved blood pressures (PAST-BP 129 mmHg versus SPS3 138 mmHg). This reflects the more conservative target in the higher target arm of SPS3 (140-159mmHg

as opposed to <140mmHg), and that antihypertensive therapy was reduced if blood pressure fell below target.

Most of the observed reduction in blood pressure is likely to have been mediated by increased use of antihypertensive drugs, which on average went up from 1 to 2 drugs per person over the year of the study in both arms of the trial. Alternative explanations are that there was habituation to blood pressure measurement leading to reduced white coat effect, or that there was regression dilution bias. However, in a blood pressure monitoring trial in a similar post-stroke population with similar mean baseline systolic blood pressure, no fall in blood pressure was observed in the control group over a twelve month period,[113] and in the SPS3 trial (also with similar mean baseline systolic blood pressure to PAST-BP) there was a fall of just 4 mmHg in the 140 mmHg target arm over the study period.[106] This suggests that the fall of 13 mmHg observed in the standard target arm of PAST-BP is unlikely to be primarily due to effects of regression dilution or habituation to measurement.

Only 51% of patients in the intensive target arm of PAST-BP achieved their target blood pressure. Both patient wishes and general practitioner decision making led to treatment not being intensified when blood pressure was above target (table 2), and 10% of the intensive arm withdrew from the trial because they did not want their blood pressure medication increased. Although reported side effects and symptoms were similar in the two arms, and serious adverse events were infrequent (two admissions for falls in each arm), significantly more changes to treatment needed to be made because of side effects in the intensive target arm.

Implications

Using a systolic blood pressure target of < 130 mmHg or lower for people with prevalent cerebrovascular disease in primary care will lead to lower blood pressure than an actively managed < 140 mmHg target, but the difference in achieved blood pressure is small. Clinically important reductions in blood pressure can be achieved with active management to a < 140 mmHg target –

13mmHg equates to more than 40% stroke risk reduction and more than 20% CHD risk reduction.[114] Active management of blood pressure after stroke/TIA therefore appears more important than the target that is set. The difficulty in achieving lower targets, the increased workload and extra medication changes required because of side effects suggest that primary care should focus on achieving the more conservative <140mmHg target in this population. Given this conclusion, and the relatively small difference in blood pressure achieved between arms, we did not feel that a study powered to detect a difference in cardiovascular end-points using an intensive target in primary care was warranted.

Panel: What this paper adds

What is already know on this subject

- Lowering blood pressure after stroke is associated with lower risk of stroke recurrence, but there is uncertainty over what the target blood pressure should be
- One trial in people with recent lacunar stroke found that a systolic blood pressure target of < 130mmHg was associated with a non-significant reduction in stroke compared to a target of 130-149mmHg
- No trials have been carried out in primary care settings of different blood pressure targets after stroke

What this study adds

- Patients set a target of 115 - 130mmHg achieved lower systolic blood pressures than those set a target of < 140mmHg, but the difference was small (3mmHg) in the context of the reduction in blood pressure observed in both arms (13mmHg and 16mmHg).
- Active management of blood pressure after stroke/TIA is more important than the target that is set.

Details of Contributors

JM, RMcM, SG & FDRH had the original idea and gained the funding. KF, JM, RMcM, CT, UM, SV, SG & FDRH contributed todeveloped the protocol. AR conducted the primary data analysis. KF & SV were responsible for the data collection. JM wrote the first draft of the paper. All authors subsequently refined the manuscript and approved the final version. JM is the study guarantor. JM affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; and that no important aspects of the study have been omitted. There are no discrepancies from our original plans for this study.

All authors have full access to all of the data (including statistical reports and tables) in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis.

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	All participants		Participants with systolic blood pressure recorded at 12 months	
	Intensive target	Standard target	Intensive target	Standard target
	n=266	n=263	n=182	n=197
Age (years)	71.9 (9.1)	71.7 (9.4)	72.6 (8.3)	71.9 (9.5)
Men	157 (59.0)	156 (59.3)	104 (57.2)	125 (63.5)
White ethnicity	260 (97.7)	259 (98.5)	180 (98.8)	194 (98.5)
Current smoker	25 (9.4)	33 (12.6)	15 (8.3)	27 (13.9)
Systolic blood pressure	142.9 (14.0)	142.2 (13.4)	143.5 (13.5)	142.2 (12.9)
<140mmHg	128 (48.1)	129 (49.1)	79 (43.4)	98 (49.8)
>=140mmHg	138 (51.9)	134 (50.9)	103 (56.6)	99 (50.3)
Diastolic blood pressure	79.9 (10.0)	80.4 (9.8)	78.8 (9.3)	80.7 (10.1)
Diabetes mellitus	26 (9.8)	25 (9.5)	19 (10.4)	21 (10.7)
Atrial Fibrillation	28 (10.5)	27 (10.3)	21 (11.5)	22 (11.2)
Coronary heart disease	41 (15.4)	46 (17.5)	28 (15.4)	35 (17.8)
Chronic kidney disease	26 (9.8)	30 (11.4)	19 (10.4)	23 (11.7)
Heart failure	2 (0.8)	7 (2.7)	1 (0.6)	6 (3.1)
Peripheral vascular disease	11 (4.1)	11 (4.2)	7 (3.9)	6 (3.1)
Stroke	130 (48.9)	122 (46.4)	85 (46.7)	95 (48.2)
TIA only	135 (50.8)	141 (53.6)	97 (53.3)	102 (51.8)
Number of antihypertensive drugs	1.0 (0.8)	1.1 (0.8)	1.1 (0.8)	1.1 (0.8)
Number of other drugs	4.5 (2.5)	4.6 (2.6)	4.5 (2.5)	4.6 (2.6)
Total number of drugs	5.6 (2.8)	5.7 (2.7)	5.6 (2.7)	5.7 (2.7)
Modified Rankin scale†				
0 or 1	135 (50.8)	125 (47.5)	98 (53.8)	84 (42.6)
2	65 (24.4)	69 (26.2)	42 (23.1)	57 (28.9)
3 or 4	47 (17.7)	51 (19.4)	29 (15.9)	42 (21.3)

Table 1: Baseline characteristics

Data are mean (SD) or number (%); †Data missing for 19 patients in intensive arm and 18 in standard arm (all participants) and for 13 patients in intensive arm and 14 in standard arm (participants with 12 month systolic blood pressure).

	Intensive target (n=109)	Standard target (n=57)
Other blood pressure readings (e.g. home readings) taken into account	17	20
Patient did not want treatment intensified	22	13
Decision taken to re-measure blood pressure at future time	19	12
Symptoms attributed to blood pressure medication	24	5
Blood pressure only just above target	14	2
Patient had not been taking pills	9	5
Blood pressure reading attributed to patient anxiety	3	8
Changes to drug therapy already made	4	2
Postural hypotension	3	2
Awaiting specialist advice/ test results	5	-
Intercurrent illness	3	-
Patient too old for further increases in therapy	1	2
Change in lifestyle advocated rather than change in medication	-	1

Table 2: Reasons given by general practitioner for not increasing blood pressure medication after patient referred by practice nurse with blood pressure above target

A reason was given for 164 of 166 non-intensification decisions. Numbers add up to more than 164 as in some cases two reasons were given.

	Mean blood pressure (mm Hg)			Mean difference from baseline (mm Hg)		Effect size (mm Hg, 95% CI)†	
	Baseline	6 months	12 months	6 months	12 months	6 months	12 months
	Systolic blood pressure						
Intensive target‡	143.5 (13.5)	125.7 (14.5)	127.4 (14.8)	-17.3 (16.7)	-16.1 (15.0)	-4.12 (-6.84 to -1.40)	-2.94 (-5.68 to -0.21)
Standard target*	142.2 (12.9)	129.3 (14.6)	129.4 (14.8)	-12.7 (16.7)	-12.8 (17.2)	..	..
	Diastolic blood pressure						
Intensive target‡	78.8 (9.3)	73.1 (10.3)	72.0 (9.0)	-6.5 (10.7)	-6.8 (9.1)	-1.14 (-2.86 to 0.58)	-1.63 (-3.10 to -0.15)
Standard target*	80.7 (10.1)	74.6 (9.8)	74.4 (8.9)	-6.1 (9.7)	-6.3 (9.4)	..	..

Table 3: Systolic and diastolic blood pressure in intensive target and standard target groups

Data are mean (standard deviation)

†Adjusted for baseline blood pressure, age group (<80, ≥80), gender, diabetes mellitus, atrial fibrillation and general practice (random effect)

‡Blood pressure data for 193 intensive target patients at six months and 182 at twelve months

*Blood pressure data for 198 standard target patients at six months and 197 at twelve months

	Intensive target arm	Standard target arm	P value
Pain	93/163 (57%)	89/173 (51%)	0.48
Breathlessness	53/148 (36%)	49/158 (31%)	0.53
Fatigue	75/149 (50%)	88/163 (54%)	0.36
Stiff joints	93/162 (57%)	99/176 (56%)	0.80
Sore eyes	35/148 (24%)	24/158 (15%)	0.08
Wheeziness	32/163 (20%)	28/175 (16%)	0.46
Headaches	27/151 (18%)	36/165 (22%)	0.22
Sleep difficulties	56/150 (37%)	66/163 (40%)	0.39
Dizziness	45/164 (27%)	39/173 (23%)	0.42
Loss of strength	44/148 (30%)	51/162 (31%)	0.52
Loss of libido	47/160 (29%)	50/171 (29%)	0.83
Impotence	29/129 (22%)	31/145 (21%)	0.54
Pins and needles	54/163 (33%)	44/176 (25%)	0.11
Cough	40/144 (28%)	49/160 (31%)	0.57
Swelling of legs/ankles	51/162 (31%)	49/177 (28%)	0.70
Dry mouth	34/147 (23%)	36/161 (22%)	0.95

Table 4: Most frequent symptoms at 12 months

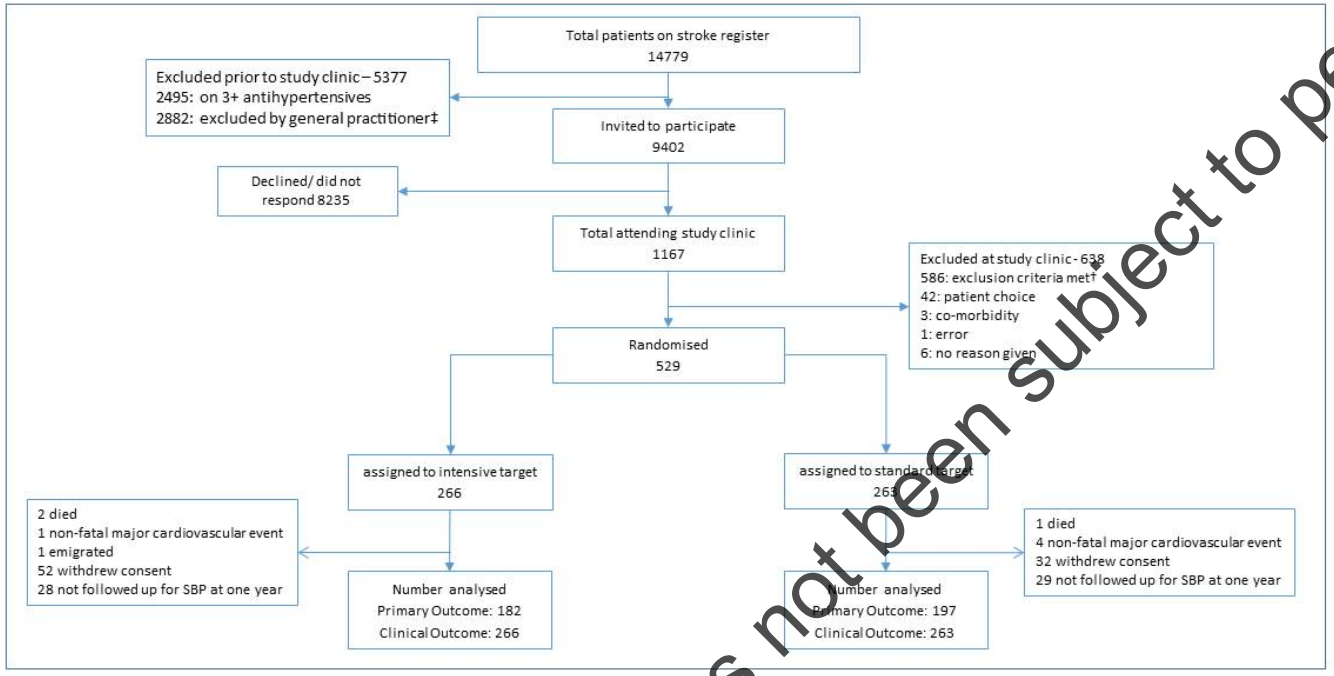

Figure 1: Trial profile

‡ Reasons given: patient was housebound or in a nursing home (957, 33%); would be unable to provide consent (338, 12%); co-morbidity (216, 7%); blood pressure too low (199, 7%); at risk of falling (164, 6%); insufficient evidence of stroke/TIA (98, 3%); already being treated to 130 mmHg target (71, 2%); other patient factors (69, 2%); patient choice (54, 2%); terminally ill (48, 2%); deceased or left practice (41, 1%); participating in another trial (9). In 618 (21%) cases, no reason was given. †blood pressure < 125mmHg 447; lack of corroborative evidence of stroke/TIA 60; on 3 or more antihypertensives 51; orthostatic hypotension 22; already being treated to lower BP target 4; unable to provide informed consent 2. SBP: Systolic Blood Pressure

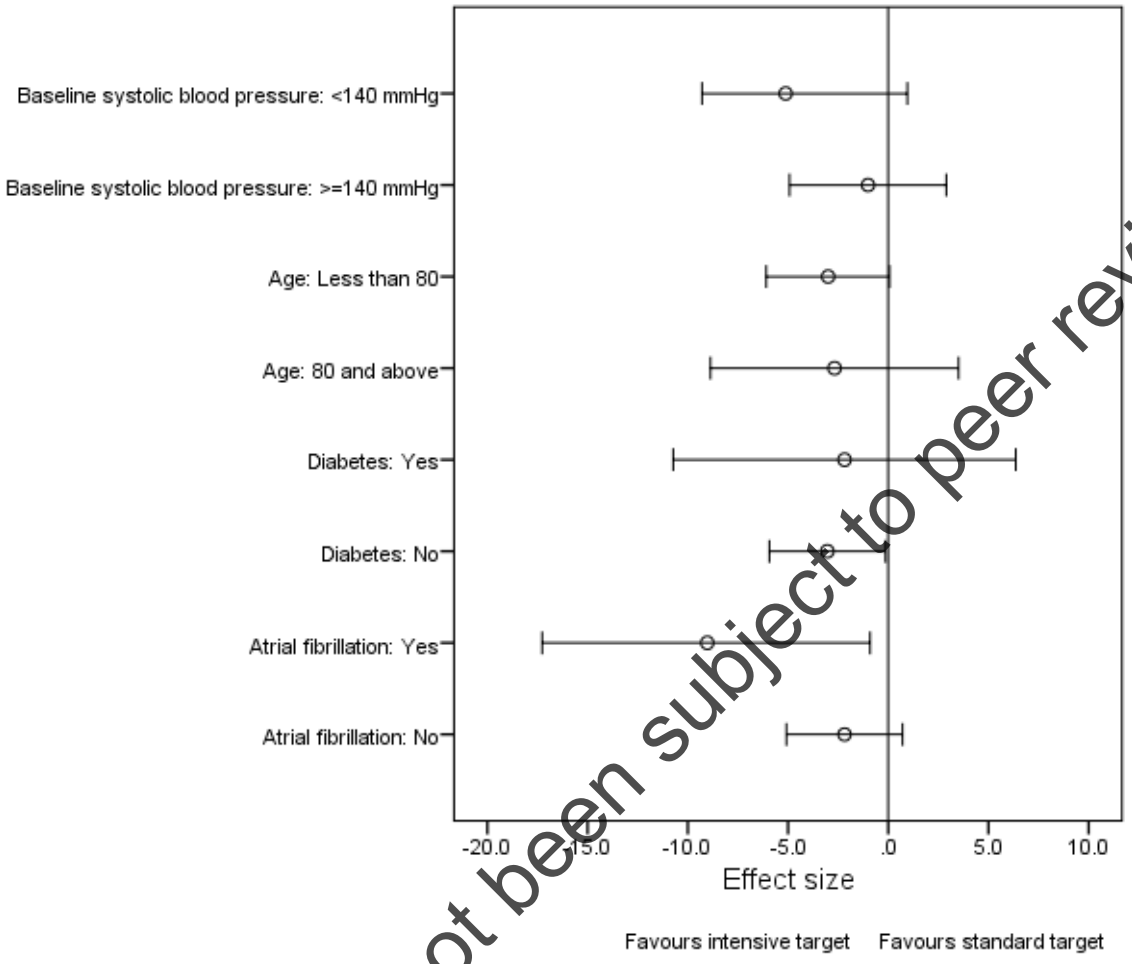

Figure 2 Effect of intensive versus standard target on systolic BP at twelve months for different patient sub-groups

Adjusted for baseline blood pressure, age group (<80, ≥80), gender, diabetes mellitus, atrial fibrillation and general practice (random effect)

Intensive Blood Pressure Lowering: Understanding and beliefs about the relationship between blood pressure and stroke and understanding and views about BP management – a qualitative study

Authors: Satnam Virdee; Kate Fletcher; Sheila Greenfield; Jonathan Mant; Richard McManus

Background

The aim of PAST-BP was to determine whether more intensive blood pressure targets for people with a stroke or TIA in a pragmatic primary care setting will lead to a lower blood pressure. Achieving more intensive targets often requires administering multiple antihypertensives to patients. However, there is evidence suggesting that as drug numbers and procedural complexity increase so does non-adherence.[1,2] There is also research demonstrating that a partnership between the patient and HCP in reaching a decision on when, how and why to use medicines (sometimes described as concordance)[3] plays a positive role in medication adherence.[4,5]

The aim of the qualitative interview study was to explore whether there were any barriers to more intensive blood pressure lowering. Hence both health care professionals HCPs and patients were interviewed about their experiences of taking part in the trial.

Methods

The trial methodology and main results have been described previously. In summary, 529 patients were randomised to the intensive target arm (BP target 130mmHg systolic, or 10mmHg reduction in systolic BP if baseline BP < 140) or standard arm (BP target 140 mmHg systolic).

Participants and sampling

Health care professional sampling

72 HCPs (46 general practitioners and 26 practice nurses) across 42 Birmingham, Black Country and Warwickshire practices in the PAST BP trial were selected and invited by letter to participate in the interview study. 5 general practitioners and 3 practice nurses across 7 practices agreed to participate.

Patient sampling

Patients across 29 Birmingham, Black Country and Warwickshire practices were purposively sampled on a range of characteristics to take part in the interview study. They were selected on the basis of study arm (control or intervention), with a further group chosen from those who declined to take part in the trial after attending the baseline clinic. Within each group, participants were further selected on the basis of gender, ethnicity, age and whether they had had a stroke or TIA. An attempt was made to ensure there were similar numbers of participants across all categories.

44 trial participants were approached by letter and 6 standard and 7 intervention patients agreed to take part in the interview study. 6 participants who had refused to consent to the trial were contacted in writing and 4 agreed to participate.

Interviews

Semi-structured interviews were used to investigate respondent views because they offer an opportunity for in-depth exploration of personal perspectives, detailed understanding and chance for clarification.[6] The interview guide was developed through a discussion by research team members (SKV, SMG, KF and JM) and covered: concordance and adherence; experience of taking part in the trial; and HCP views on intensive blood pressure targets.

All interviews were carried out by one of the authors (SKV) between August 2010 to October 2012. Signed informed consent was obtained before the interview. HCP interviews were carried out at the practice and patient interviews in their home. Interviews lasted between 20-45 minutes, were audio recorded and transcribed verbatim.

Analysis

Transcripts were checked against the recording for accuracy. Throughout the analytic process each transcript was compared with others to develop conceptualisations of the relations between various pieces of data and key areas.[7] Interviews ceased when 3 of the authors (SKV, SMG and KF) agreed saturation had been achieved. Transcripts were read independently by SKV, SMG and KF and the subthemes identified in each key area.[8] These were discussed by the study team and a thematic coding framework was developed to code each transcript systematically. NVivo 10 software was used to aid data organisation.

Results

Participants

There were more general practitioners than practice nurses (table 1). All practice nurses and almost all HCPs were female.

There were similar numbers of patients in the standard and intervention arms, although there were fewer participants from the declined group (table 2). There were slightly more male than female patients. Most were White British and only 2 from a minority ethnic group (1 White British and 1 Pakistani British). Patients were aged between 52 and 83 years, with the majority of participants aged between 60 and 79. There were comparable numbers who had experienced either a stroke or TIA.

Key areas

In order to facilitate a comparison of comments and contextualise subthemes, findings are presented within each of the three key areas: concordance and adherence with antihypertensive medication; experience of PAST BP trial; and HCP attitude towards intensive blood pressure targets. The number of respondents discussing each subtheme is reported[9] to help contextualise the findings and facilitate a comparison between respondents. Interview extracts representative of each subtheme are given.

Concordance and adherence with antihypertensive medication

HCP views

All HCPs (8) claimed that treatment decisions regarding antihypertensive medication following a stroke/TIA was a process of explanation, understanding and negotiation with the patient. It was believed that this led to most patients being adherent with medication.

"I always ask a patient's permission to start medication because they're not going to just take it when you suggest it to them. I will ask them if they're happy. I think you have to involve the patient". HCP 1

"Often patients don't want to start medication and often it's a negotiation. I will tell them this is your blood pressure, this is the information and these are your risks. If they won't start on medication I'll say well come back in a month and we'll see what your blood pressure's doing, and do it gradually that way". *HCP 8*

Half of all respondents (4) highlighted that many patients did not like being on long term medication and were worried about side-effects. For some patients this led to poor adherence.

"Some patients aren't too keen on the idea of being on medication long term, especially because blood pressure gives no symptoms, and that's even more the case if they get side-effects from the medication". HCP 6

"Some people are not very keen to go on drug treatment if they perceive that the drugs are likely to give them side-effects and restrict their lifestyle". HCP 4

Many interviewees (4) also mentioned that several patients preferred to attempt lifestyle changes before resorting to medication.

"There are a lot of people that to try changing their lifestyle first. Then they get to a point where they realise that they've got to go on medication". HCP 3

Patient views

Most patients (14) said their involvement in antihypertensive treatment decisions was limited to an explanation and information, the level of which was felt sufficient.

"There was little involvement, but I was happy with the information I was given. I didn't need any more because the practice was very thorough". P13

"I seem to recall the GP went into some depth about the medication, and yes I was quite happy with it". P16

In fact, some (5) thought too much information would cause unnecessary worry.

"I wouldn't have liked any more information. It would probably put you off taking them if you had too much information". P6

Others (3) however claimed that no explanation of their medication was provided and they either had to request one or seek further information themselves.

"They didn't really explain the medication in any detail. I had to find out for myself more precisely why I was taking it. It would have been nice to have been given a slightly more detailed explanation".

P5

All patients (17) agreed that the actual decision to start treatment was made by the HCP which they preferred as they trusted their doctor and regarded them as the expert.

"I wouldn't have wanted to be involved as I've got confidence in my doctor and if he tells me that's what I need fair enough". P2

"The doctors are the professionals, they know what they're doing, I trust them. So I don't need to be involved". P3

All respondents (17) believed that starting medication was necessary and that it had benefitted them in terms of preventing further problems.

"I saw that I had no choice but to take the medication. If I don't take them, it [a stroke] could happen again. I could die I suppose". P9

"The medication was necessary. I don't mind taking pills if it's for a good cause, I didn't want any more TIA's". P15

"The tablets have helped otherwise my blood pressure wouldn't be so low". P3

"The tablets have been beneficial as I've not had another mini stroke". P7

However, a minority (3) also expressed serious concerns over side-effects and long term use.

"The only concern I've had is the cocktail of tablets and the interactions between them". P2

"I was quite horrified when I found out the medication was for life. P11

Despite their reluctance, reported adherence amongst all (17) patients was found to be excellent: they all claimed to take their medication regularly and only occasionally missing a dose.

"I take them [medication] *religiously every day. I don't really miss a dose because my husband puts them all out of a morning".* P8

"I take my tablets every morning. I only occasionally miss a dose which worries me". P11

Experience of PAST BP trial

HCP experience

HCPs gave various reasons for their practice taking part in the PAST BP trial. The most common ones included: for the long-term benefit of patients; to further research knowledge and understanding of the condition; and because the research question was worthwhile and interesting.

"We're all for furthering knowledge and so we're quite happy to participate in something that is eventually going to benefit somebody somewhere". HCP1

"The fact that it's a worthwhile trial and that it might benefit my patients in the long run was the reason we took part". HCP 6

The majority of interviewees (7) were in agreement that the intensive blood pressure targets were a struggle to achieve because of increasing side-effects, particularly hypotension.

"I think for the ones whose blood pressure has already been quite low, getting it down below 10mmHG has been a bit of a struggle with extra side-effects". HCP 5

"It's been slightly more difficult for those with lower targets. You start to find that they get these hypotensive episodes". HCP 6

Furthermore, many (4) questioned the protocol of adding additional medication or increasing the dosage just to bring the blood pressure down by a further 1-2mmHg to achieve the target.

"When you've got somebody who's just a little bit over target, you're sort of thinking do we want to give them any more medication just to drag this down a little bit more?" HCP4

All interviewees (8) thought that the study led to only a small increase in workload because there were so few patients recruited.

"Because we had so few patients, I don't think it really impacted on our workload very much" HCP3

"I've probably had a little bit of an increase in the workload because I've been doing extra paperwork, but it's not been labour intensive at all". HCP4

Half (4) believed the study led to better control of blood pressure for those in the trial. Two highlighted that the trial raised their awareness of blood pressure control in general.

"There have been benefits of the trial for the patients, because some of their pressures are better controlled". HCP2

"The trial has made us more clinically aware of blood pressure control. We perhaps accept too high numbers whereas actually we could be thinking about lower numbers". HCP2

Some respondents (3) found the trial to be well organised and felt they received a lot of support from the research study team, whereas others (3) said they experienced problems with the trial in terms of a lack of communication from the study team.

"We've had a great deal of support from the University staff and I think without them we might have struggled to keep people to the algorithm. But they've been very good" HCP4

"I didn't know it was a year's trial. When it finished I actually found out from the patients that it had finished. Nobody contacted me to let me know things had finished" HCP1

Despite this, all HCPs (8) claimed they would take part in the trial again.

"We would take part in the trial again; I wouldn't see no reason why not". HCP2

"Yes, we would take part again, without a doubt" HCP4

Patient experience

Although all patients (17) claimed that the PAST BP trial was explained to them clearly, for many (14) their understanding of the study was poor.

"It was all very clear. I was given a lot of information to read". P1

"It was explained clearly. It was all pretty straightforward" P7

"I didn't know that I would have to wear the monitor and go home for 24 hours. That was a bit of a pain" P10

"The study was obviously to see the effects of the medication on different people. Actually, I'm not quite sure what the idea was" P15

Trial participants (13) gave two main reasons for taking part in the study: to contribute to research that will help other stroke patients; and to receive monitoring thereby providing reassurance regarding their health.

"I thought I would do it if it would help someone. Even if it didn't help me it would help someone else in the future" P12

"I thought if someone's going to keep an eye on me, that's good. Its peace of mind" P3

The concern of additional medication was the leading reason for non-trial participants (4) failing to consent to the study.

"I definitely didn't want to be put on more medication, so I said if I can go in the group where I don't have to take more medication, fine. But if I then have to take more medication I'm not prepared to do that"

P15

Most respondents (11) believed they had personally benefited from participating in terms of: raising their awareness of blood pressure control; giving them assurance of their health though monitoring; a feeling of contributing to research that will help others; providing them with social contact with the study team; and lowering their blood pressure further.

"Its made me aware to watch my blood pressure and be careful" P3

"One of the benefits is that somebody's keeping an eye on my blood pressure which can't be a bad thing" P2

"It gives that feeling that I've perhaps contributed to something. I've done my social duty" P9

"Now I'm retired, it's a way of making sure you move about, you get out and you're not sat at home every day. I know it was only every three months but whoever I went to see, we had a chat about different things and I just enjoyed it" P11

"It's done its job; it's bought my blood pressure down to 130 and it was 164 in the beginning" P10

Several (5) felt there was a lack of feedback from the study team regarding the results of the 24 hour blood pressure monitor investigation. Despite this, all interviewees felt the trial was worthwhile and would take part again.

"I've had no feedback. I would have expected some sort of note to say your blood pressure is high, low, indifferent, whatever, but there was nothing" P2

"When I had that 24 hour monitor and I took it back, I was expecting some feedback of what it was like over the 24 hour period and when was it high and when was it low. I didn't know the outcome" P3

"Because it's going to benefit others and me, I would go in the trial again" P1

"If it's going to help others in the future then yes I would take part again" P13

HCP attitude towards intensive blood pressure targets

All HCPs (8) expressed reservations over the feasibility of setting intensive blood pressure targets for patients, particularly older patients. This was due to side-effects such as dizziness and postural hypotension from additional or increased dosages of medication.

"Up to a point lower blood pressure is better, but it's going to be difficult to squeeze that extra bit out really. And then there's the potential for side-effects because of more medication. It's not a win-win situation" HCP2

"I have a few apprehensions about it because generally that group's an older group and I worry a lot about polypharmacy and the risk of falls and side-effects" HCP5

It was also felt intensive targets would be difficult to achieve for patients whose blood pressure was resistant to medication. All respondents believed intensive blood pressure targets would need to offer a balance between side-effects and long term benefit for patients.

"The side-effects of the medication have to be weighed up against the benefits of having lower blood pressure" HCP4

"It's good to be aggressive about blood pressure treatment in people with pathology such as TIA's and strokes, but I think you still have to get this balance right though because you can over treat and then people don't feel well" HCP6

Discussion

Summary of main findings

Although HCPs believed treatment decisions concerning antihypertensive medication were made concordantly, for patients their involvement appeared to be limited to being given an explanation. However, it seemed they preferred to leave treatment decisions to the experts. Patients also thought starting medication following their stroke/TIA was necessary and beneficial and reported excellent adherence to their drug regime, despite some concerns over side-effects.

Both HCPs and patients took part in the PAST BP trial for altruistic reasons: primarily to benefit stroke patients. Patients that refused to consent to the study did so due to concerns over taking additional medication. Those patients that did take part claimed to have benefitted from participating.

HCPs had reservations over the feasibility of intensive blood pressure targets due to potential side-effects. In the trial, they found the intensive targets a struggle to achieve and many questioned adding additional medication or increasing dosages just to bring patient blood pressure down by a minimal amount.

Comparison with existing literature

Our finding where patients prefer to leave treatment decisions to the doctor is well documented in other studies.[10,11] It seems patients do not want the additional responsibility and would rather the professionals decide for them. However, since our patients were largely over 60 years this finding may be more common among the older population.

Research has shown about a third to half of hypertensive patients do not adhere to their blood pressure medication.[12,13] Our study however found reported adherence to be optimal. This difference may be accounted for by the fact that average rates of adherence in clinical trials is often high due to the attention study participants receive and the selection of patients.[14] The discrepancy may also be because patient reported adherence is often overestimated.

Some of the patients in our study expressed concerns over side-effects but continued with treatment because of the perceived benefits: a finding consistent with previous research.[15,16]

Strengths and limitations

A strength of the study is that all interviews were carried out by a single researcher thus maintaining consistency.[17] However, since the researcher was non-medical, interviewee responses may have been different if the researcher had been a clinician.

The qualitative approach adopted by the study allowed an in-depth exploration of attitudes not possible in quantitative surveys. Although the aim of qualitative research is not to be generalisable,[18] the patient sample was representative across trial arms, gender and whether they had had a stroke or TIA. The participating practices were also representative of the 42 practices initially approached to take part in the study. Both sample sizes were also sufficient to achieve saturation.[19]

The way patients claimed to adhere to treatment changes in the trial is not necessarily what they would do in reality. Equally, the medication changes made by HCPs as part of the study may not be what they would actually do if lower blood pressure targets were set.

Implications

This study suggests that setting intensive blood pressure targets for patients is not considered feasible by HCPs due to the potential for side-effects. Patients too appear to express concerns over side-effects from extra medication. If intensive blood pressure targets result in additional medication and potentially more side-effects, it could lead to an even lower level of adherence. Therefore, although intensive targets may offer long term benefits for patients, these benefits are only possible if the medication is well tolerated and acceptable to patients. It seems a balance between long term benefit and potential side-effects is needed if intensive blood pressure targets are to be established.

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Intensive Blood Pressure Lowering: Cost-effectiveness analysis of intensive blood pressure lowering in people with cerebrovascular disease in primary care

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This section contains the cost effectiveness analysis that explored whether the potential benefits associated with intensive blood pressure lowering might be outweighed by potential adverse effects on quality of life and costs.

Background

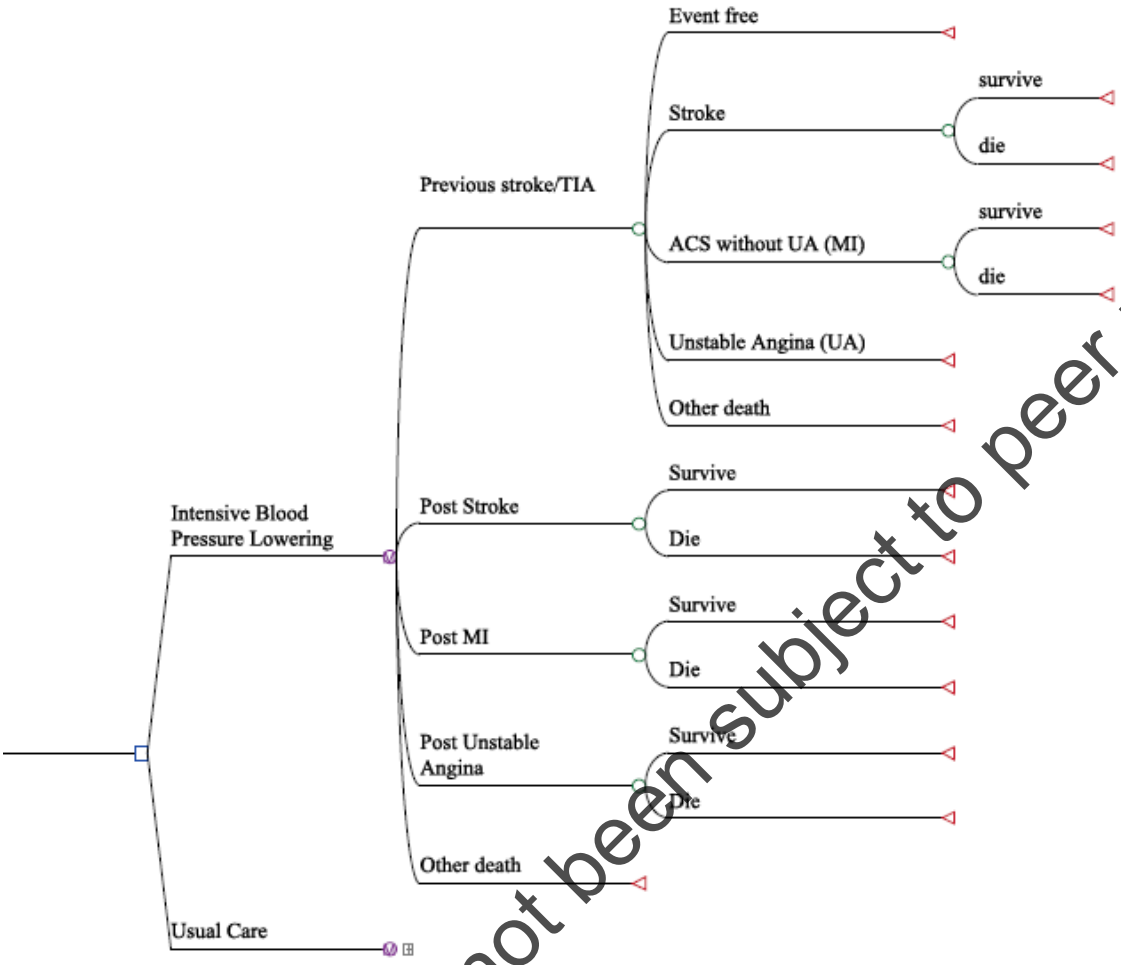
There is controversy over how intensively to lower blood pressure in people who have had a stroke. For this reason, the Prevention After Stroke – Blood Pressure (PAST-BP) randomised controlled trial was carried out, to compare two different targets for blood pressure lowering after stroke or TIA in people recruited from a prevalent primary care population . In this trial, participants were recruited from stroke/TIA registers in English general practices during 2009-2011 and randomised to an intensive blood pressure target (<130mmHg or a 10mmHg reduction if baseline pressure <140mmHg) or a standard systolic blood pressure target (<140 mmHg). Over one year, mean systolic blood pressure dropped by 16.1mmHg in the intensive target arm and by 12.8mmHg in the standard arm (difference between groups 2.9mmHg, p = 0.03). Here, we report the results of an analysis utilising the results of the PAST BP trial and the literature to determine the cost effectiveness of aiming for intensive blood pressure lowering targets after stroke/TIA in a primary care population.

Methods

A Markov model was constructed to estimate the long-term cost-effectiveness, in terms of the cost per quality adjusted life year (QALY) gained, of intensive target and standard target strategies for blood pressure lowering in people with cerebrovascular disease. The model was developed using TreeAge Pro Suite 2012 software. The analysis was conducted from a UK National Health Service (NHS) and Personal Social Services (PSS) perspective.

The model had a time cycle of one year with a 30-year time horizon and the base-case analysis considered a cohort similar to that recruited to the PAST BP trial (aged 70 years old, 41 % female). A patient started the model in a "previous stroke/TIA" health state and could move to one of three possible new health states (new stroke, myocardial infarction (MI) or unstable angina, UA) or die. Movements between health states were defined by transition probabilities, which represented the risk of experiencing an event within the one year time cycle. Long term costs and health outcomes were assessed by attaching estimates of resource use and health outcomes to the model health states. QALYs were calculated by multiplying life expectancy by the utility associated with a given outcome. Cost-effectiveness was expressed as cost per additional QALY gained. The structure of the Markov model is shown in Figure 1.

Figure 1: Markov model



Note: The Markov model in this figure is only being displayed for the "Intensive Blood Pressure Lowering" strategy. The standard target strategy is identical. Similarly, the model is identical at every node ending with green circles. Final outcomes (shown as red triangles) are survival and death.

Individual patient level data were used from the PAST-BP trial, supplemented by the best available estimates from published sources (tables 1 and 2).

Model structure and inputs

The cohort started in the initial health state 'previous stroke/TIA', and patients could remain in the 'previous stroke/TIA' state if they were event free or moved to another health state if they experienced a cardiovascular (CV) event or died (Figure 1). Office for National Statistics' Life tables were used to determine overall mortality dependent on age and gender, adjusted by CVD mortality.1[355] Death was attributed to either stroke, MI or other causes. After a CV event, individuals could survive from the event or die, with death from an event occurring within a year. Individuals that survived a CV event moved to the chronic health state for that event, where annual costs were incurred and quality of life was lower than in the 'previous stroke/TIA' state (Table 1). Individuals in a chronic health state were assumed to remain in that state for the rest of their lives unless they died within the time horizon for the model.

Table 1: Parameters used in the Markov model

Parameter	Value	Distribution	Source
Unit costs £			
GP consultations	33.00		Curtis L, 2012
PN consultations	11.25		Curtis L, 2012
Annual cost of consultation per patient (UK £) - Intensive BP lowering			
GP consultations	86		PAST-BP Trial
PN consultations	35		PAST-BP Trial
Annual cost of consultation per patient (UK £) - standard target			
GP consultations	50		PAST-BP Trial
PN consultations	29		PAST-BP Trial
Average cost of hypertensive drugs per patient £ per year			
Intensive BP lowering	23		BNF 2013
Standard target	20		BNF 2013
Cost for the initial state £ per year			
Intensive BP lowering	144	Gamma	Curtis L. 2012 & BNF 2013
Standard target	100	Gamma	Curtis L. 2012 & BNF 2013
Costs of acute disease £ one-off cost			
Stroke	11020	Gamma	Youman et al (2003)
MI	5487	Gamma	Palmer et al, 2002
Unstable Angina	3292	Gamma	Assumed 60% of MI
Costs for long-term (chronic) disease £ per year			
Stroke	2721	Gamma	Youman et al (2003)
MI	572	Gamma	Cooper et al (2008)
Unstable Angina	572	Gamma	Cooper et al (2008)
Utilities for the initial health state			ScHARR, HEDS 10/11
Intensive BP lowering			
65-74 years old	0.78	Beta	
75-84 years old	0.71	Beta	
85 and over	0.69	Beta	
Utilities for acute disease			Cooper et al (2008)
Unstable angina (UA)	0.77	Beta	
Myocardial Infarction (MI)	0.76	Beta	
Stroke	0.63	Beta	

Table 1 (cont)

Parameter	Value	Distribution	Source
Utilities for long term (chronic) disease			
Unstable angina (UA)	0.88	Beta	Cooper et al (2008)
Myocardial Infarction (MI)	0.88	Beta	
Stroke	0.63	Beta	
Annual event probabilities			
Stroke			Progress, (2001)
65-74 years old	0.03		
75-84 years old	0.06		
85 and more	0.07		
Myocardial Infarction (MI)			NICE, Lipid modification Guidelines
65-74 years old	0.01		
75-84 years old	0.01		
85 and more	0.02		
Unstable Angina (UA)			NICE, Lipid modification Guidelines
65-74 years old	0.01		
75-84 years old	0.02		
85 and more	0.02		
Probability of death from an event			
Fatal stroke	0.19		Ward et al (2007)
Fatal myocardial infarction (MI)			
65-74 years old	0.39		Ward et al (2007)
75-84 years old	0.29		Ward et al (2007)
85 and more	0.23		Ward et al (2007) 11(14)

* Annual cost of drugs was calculated on the basis of commonest drug and dose per drug group per arm at 6 and 12 months

† Total costs included costs of drugs and costs of general practice (GP) and practice nurse (PN) consultations

Annual transition probabilities determining the risk of a stroke/TIA were based on the results of the PROGRESS trial.2[10] Age-related risk reduction for coronary heart disease (CHD) and stroke associated with subsequent reductions in systolic BP observed in the PAST-BP trial were obtained from Law et al (Table 2)3[102] The risk reduction for CHD was applied to both MI and UA. The probability of each CV event occurring, the risks of dying from stroke or MI and the increased risk of death once in a chronic health state incorporated in the model are shown in Table 1. Outcomes were discounted at the standard annual rate of 3.5%.4[319]

Table 2: Estimates of age-related risk reductions

Description	Standard target	Intensive BP lowering	Source
Stroke			
60-69	0.59 (0.55, 0.63)	0.52 (0.47, 0.56)	Law et al & PAST-BP
70-79	0.65 (0.61, 0.68)	0.58 (0.54, 0.63)	Law et al & PAST-BP
80-89	0.78 (0.73, 0.82)	0.74 (0.68, 0.78)	Law et al & PAST-BP
Myocardial infarction & Unstable Angina			
60-69	0.68 (0.65, 0.70)	0.62 (0.59, 0.65)	Law et al & PAST-BP
70-79	0.72 (0.69, 0.75)	0.68 (0.63, 0.70)	Law et al & PAST-BP
80-89	0.78 (0.74, 0.81)	0.74 (0.69, 0.77)	Law et al & PAST-BP

Resource use and costs

Costs are reported in UK pounds at 2011-12 unit prices, and were discounted at 3.5% per annum as recommended by NICE.4[319] Resource use and costs per patient were obtained from the PAST-BP trial and applied to the initial health state in the model. Costs for acute and chronic states were obtained from published sources.5-8[157,159-161] Costs considered over the lifetime of the model included the cost of antihypertensive drugs, consultation costs and subsequent cardiovascular events. A summary of all costs included in the model is shown in Table 2.

Utility values

All utility scores are shown in Table 1. The starting utilities for the initial health state in the model were obtained from Ara et al.9[359] The occurrence of acute events were assumed to happen approximately six months into a one year cycle; individuals stayed in that acute state for six months before transitioning into a chronic state. Utilities for the acute state were applied mid-way through the one-year cycle and those for the chronic state at the start of the next cycle following an acute event. Future health state utilities were estimated by multiplying the starting quality of life with that of the new health state. We have assumed that different intensity of blood pressure management had no effect on quality of life.10[280]

Analysis

Probabilistic analyses were used in the base case based on 10,000 Monte Carlo simulations. A gamma distribution was fitted to the costs obtained from the PAST-BP trial. Beta distributions were used to model the probability of dying from any of the cardiovascular events as well as the uncertainty around the utility values. A cost-effectiveness plane and a cost-effectiveness acceptability curve (CEAC) were constructed. The plane shows the relationship between the incremental cost and incremental effect of intensive BP lowering relative to standard target while the CEAC depicts the probability of intensive BP lowering being more cost-effective compared to standard target at different willingness-to-pay thresholds.

Uncertainty in the results of the model was assessed through sensitivity analyses. These involved varying the time horizon for the model until the intensive BP lowering strategy was not cost-effective. Time horizon was chosen to represent a plausible range within which the cost-effectiveness of the intervention could be assessed.

Results

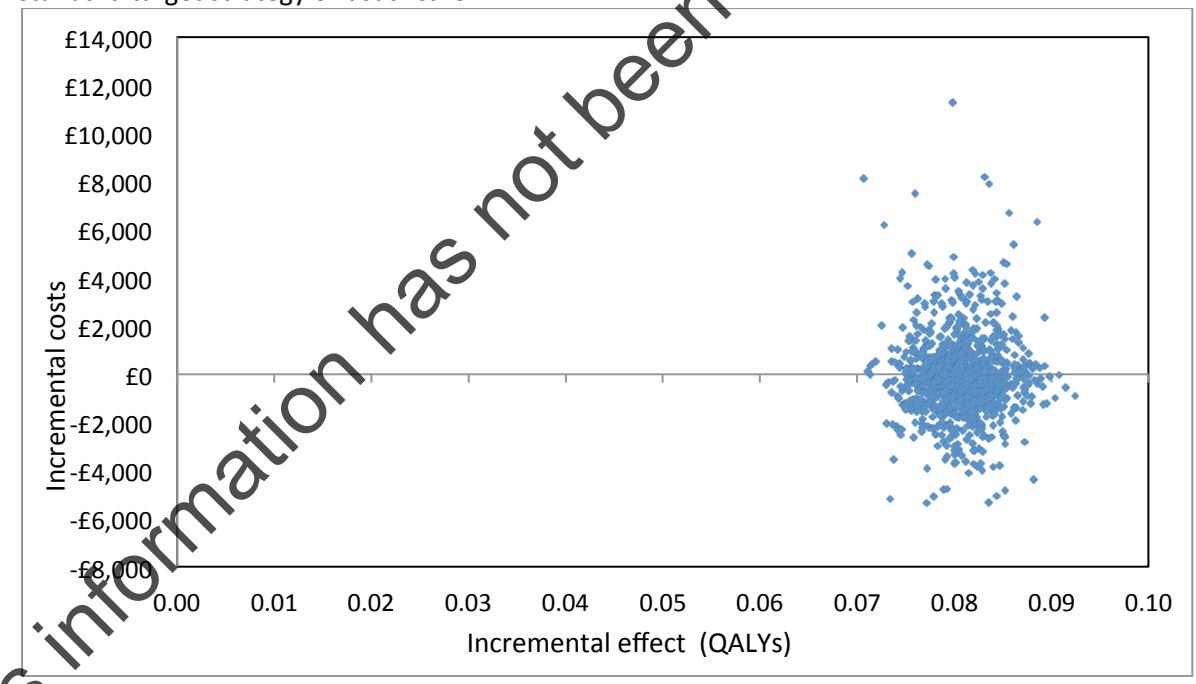
The base-case lifetime costs and QALYs, are presented in Table 3. Compared to a standard BP target of 140 SBP, intensive BP lowering of hypertension was in a position of dominance, being cheaper and more effective, and therefore is the treatment of choice. Intensive BP lowering was associated with average cost savings per patient of £130 and an additional 0.08 QALYs.

Table 3: Lifetime costs and outcomes per patient

	Costs (£)	QALYs	Incremental cost (£)	Incremental QALYs	ICER (£ per QALY)
Standard target	10,253	8.06			
Intensive BP lowering	10,123	8.14	- 130	0.08	Dominant

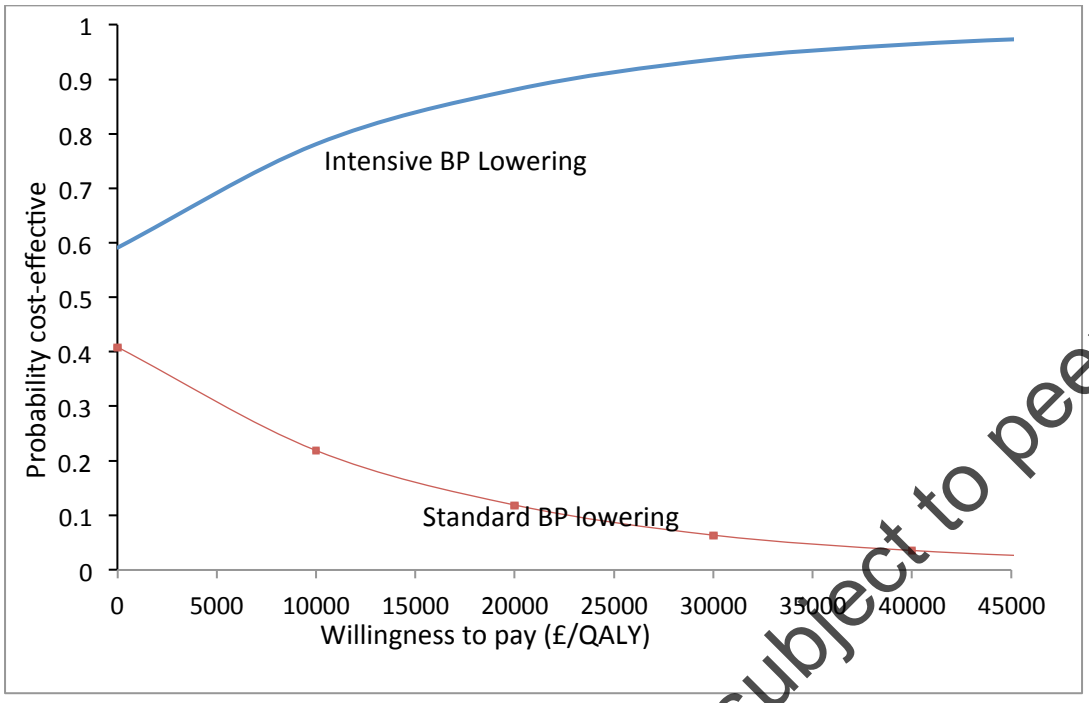
Figure 2 presents the cost-effectiveness plane comparing intensive BP lowering to standard target when distributional uncertainty was incorporated. The plane shows the joint distribution of the mean incremental costs and mean incremental effects (QALY gains) with most of the results between the north-east and south-east quadrant, indicating that overall, intensive BP lowering is more effective but with a large amount of uncertainty around the difference in costs

Figure 2: Incremental cost-effectiveness plane comparing the intensive BP lowering strategy vs. standard target strategy or usual care



The CEAC was calculated from the joint density of incremental costs and incremental QALYs (Figure 3). The CEAC shows that if a healthcare commissioner has a willingness-to-pay of zero, 60% of the model replications indicated that intensive BP lowering was cost-effective and where the commissioner was willing to pay £20,000 per QALY gained, the likelihood of cost-effectiveness was 88 per cent (figure 3).

Figure 3: Cost-effectiveness acceptability curve (CEAC) for the intensive BP lowering model showing the probability that the intervention is cost-effective



Sensitivity analysis was undertaken by varying the time horizon of the model, using two approaches. Firstly, model was run for the time horizons of 20, 10, 7 and 6 years exploring when the intensive BP lowering strategy was no longer a dominant strategy. The model was also run for time horizons of 6, 3, 2 and 1 year to explore when the intervention was no longer cost-effective at a threshold of £20,000 per QALY. The results of cost-effectiveness analysis of varying the time horizon of the model are shown in Table 4. Intensive BP lowering was cost-effective, at a threshold of £20,000 per QALY, starting in the second year of treatment. Similarly the intensive target strategy becomes the dominant strategy after 6 years of the intervention (Table 4).

Table 84: Sensitivity analysis: time horizon

	Costs (£)	QALYs	Incremental cost (£)	Incremental effectiveness QALYs	ICER(£/QALY)
20 years					
Standard target	9,219	7.68			
Intensive target	9,091	7.75	-127	0.071	Dominant
10 years					
Standard target	4,990	5.62			
Intensive target	4,936	5.65	-54	0.032	Dominant
7 years					
Standard target	3,234	4.41			
Intensive target	3,227	4.42	-8	0.017	Dominant
6 years					
Standard target	2,639	3.92			
Intensive target	2,647	3.93	8	0.013	638
3 years					
Standard target	1,177	2.18			
Intensive target	1,203	2.18	26	0.003	8,269
2 years					
Standard target	762	1.51			
Intensive target	784	1.51	22	0.001	19,112
1 year life time					
Standard target	368	0.78			
Intensive target	382	0.78	13	0.000	356,876

Discussion

Our analysis suggests that aiming for an intensive systolic blood pressure target of 130mmHg or lower in people with a history of stroke or TIA in primary care is cost effective provided that a separation in blood pressure between intensive and standard care is maintained for at least two years. Indeed, over the long term (six years or more), using an intensive target is the dominant strategy, being more effective and lower cost, with the costs of treating fewer cardiovascular events off-setting the increased costs associated with delivering a more intensive target. These results are sensitive to the time horizon used. If the difference in blood pressure is not maintained beyond twelve months, then aiming for this target is not cost effective. The SPS3 trial, which involved different targets for blood pressure in people with a history of lacunar stroke, did find that differences between arms were maintained up to eight years after randomisation11[365] While the SPS3 trial was not set in primary care, and involved a different younger group of people with cerebrovascular disease than PAST-BP, this provides some evidence that it is reasonable to expect long term differences in blood pressure to persist.

PAST-BP was not powered to detect differences in clinical end points between arms, and so we estimated the impact of observed blood pressure reductions by applying these to the results of a systematic literature review.3[102] While this review was not restricted to people with previous stroke, the relative reductions in cardiovascular risk associated with reduction in blood pressure appears to be similar in people with and without existing cerebrovascular disease.12[7] However, in the only other trial of different targets for blood pressure after cerebrovascular disease – the SPS3 trial - an 11mmHg difference in systolic blood pressure between arms was only associated with a non-significant 19% reduction in the risk of stroke.11[365] This result is in contrast to the 28% reduction in stroke risk associated with a 9mmHg reduction in PROGRESS,2[10] and the confidence intervals of the effect on stroke risk in SPS3 were wide.

Our results are consistent with the results of a cost-effectiveness analysis based on the PROGRESS trial, which found treating people with cerebrovascular disease was cost-effective, with a cost per QALY of £6,927 over four years.13[379] Whereas our analysis found long term treatment to be dominant, in the PROGRESS trial, using the perindopril regimen remained more expensive than standard care in the long term. This is probably because the costs of the relevant drugs have dropped by about 90% since the PROGRESS economic analysis was performed: for example, perindopril now costs £1.72 per month, as opposed to £10.95 as applied in 2005.13,14[379,380]

Conclusion

This analysis suggests that it is cost-effective to aim to achieve even the moderate reductions of 3mmHg in blood pressure that are associated with targeting a systolic blood pressure target of 130mmHg or less as compared to a target of less than 140mmHg in people with cerebrovascular disease in primary care. In the absence of side effects of treatment, it may therefore be appropriate to aim for a more intensive target than 140mmHg in individual patients. However, the difficulty in achieving a target such as 130mmHg suggests that the focus of attention in the community should primarily be on actively managing patients with stroke to achieve a target of less than 140mmHg rather than 'failing' with more ambitious targets.

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