Appendices

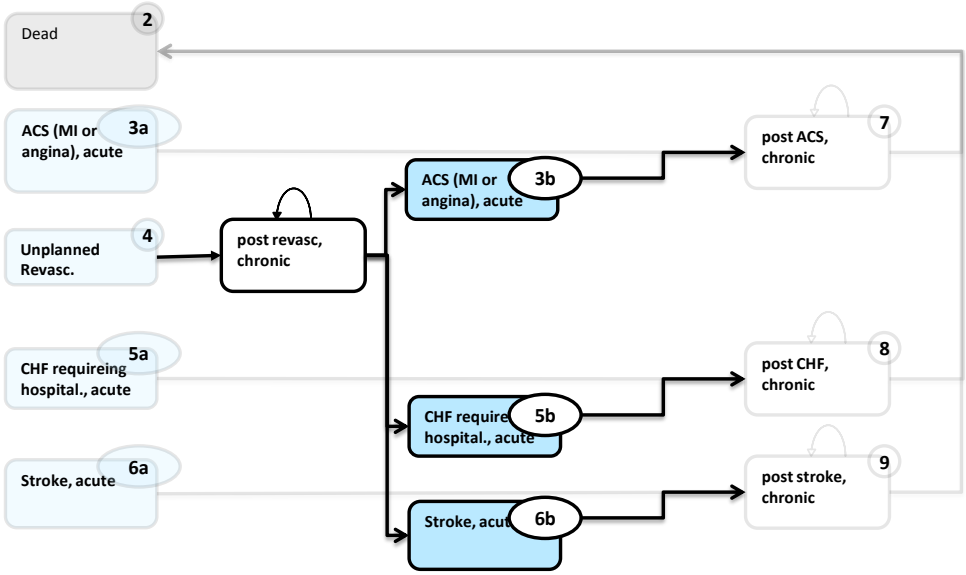
Appendix 1. Additional Model Structure, Assumptions, Equations and Inputs

The base-case model is shown in Figure 1 (in the main body of the manuscript). Additional post-revascularistion description and further model assumptions are provided below as part of this appendix. Patients who have survived a first MI and are eligible for secondary prevention with aspirin, statin and ACEI enter the model in health state 1, called the secondary prevention state. Therefore, all patients entering the model at time zero have already had one MI in their lifetime, and can have one of the five cardiovascular events or die from non-cardiovascular attributable death. In the model, patients having a non-fatal CV event progress to the acute stage (blue boxes corresponding to health states 3a, 4, 5a, 6a) where they remain for one model cycle after which they progress to post-ACS (health state 7), post-CHF (health state 8), or post-stroke (health state 9). Similarly, patients who have recently undergone revascularisation progress to a post-revascularisation state. In the model, patients may undergo revascularisation only once and may continue to have an ACS, CHF or stroke event. This submodel allows specification of a reduced risk of ACS, CHF or stroke among revascularised patients. Figure 1 below describes the flow of further CV events possible for revascularised patients.

Within a given 3-month model cycle, most patients will have no CV event and so remain in their current health state (white boxes).

Patients who experience CV-attributable mortality from chronic health states 1, 7, 8, or 9 progress to health state 2 where they remain until the end of the model. Patients may also experience non CV-attributable mortality; such deaths may also occur from states 1, 7, 8, or 9 and progress to state 2. Therefore, patients in state 2 represent all patients who die but who may have died of different CV attributable and non-attributable causes.

Figure 1. Zoom in for the Post-Revascularisation Part of the Secondary CV Prevention Model



ACS, acute coronary syndrome; CHF, congestive heart failure; CV, cardiovascular; ICER, incremental cost-effectiveness ratio; MI, myocardial infarction

Table 1. Additional Assumptions Made for Base–case and Sensitivity Analyses of the Model

	Model Definitions
1	Secondary Prevention State: MI patients who have survived an MI and are at risk of further CV events
2	ACS: having either non-fatal myocardial reinfarction (second MI of the patient in his lifetime) or unstable angina
3	Unplanned revascularisation: costly procedures such as percutaneous coronary interventions or coronary artery bypass grafts that are not performed at the time of another CV event like MI, CHF or stroke
4	CHF requiring hospitalisation: CHF that leads to hospitalisation, non-fatal
5	Stroke: ischemic or haemorrhagic stroke, non-fatal
6	CV death: death due to any CV event
	Model Structure and Analysis
7	Markov model defined by acute non-fatal CV disease states, chronic CV disease states which occur after the acute state, and CV attributable deaths and non-attributable deaths with fixed 3-month model cycles and half-cycle correction
8	For model simplicity, patients may not have a third CV event during their lifetime if they survive two prior CV events
9	Beta-blockers were assumed to be taken as appropriate by all patients so their effects were not modelled
10	Parameters included in one-way sensitivity analysis were varied between a minimum and maximum range, determined either directly from published data, or were assumed to be 20% above and below the base–case value when data was not available for the range
11	Distributions used in probabilistic sensitivity analysis: for probabilities and utilities, the beta distribution was used; for positively valued parameters such as costs, the chosen distribution was gamma; RRR followed a lognormal distribution
	Data and Assumptions on Risks, Efficacy, Resource Use, and Population
12	The baseline event risks were derived from the placebo arms of meta-analyses reported in the SLR, where Ward et al. (2007)[44] provided the most robust data. As it did not provide data on CHF as an event, the baseline risk of this event was derived from an alternative study by Saha et al. (2007),[46] which was the only study identified in the SLR that provided data on the placebo arm. To obtain the figures reported in Table 3, the annual risk, interpreted as an annual rate, is converted to a per cycle probability according to the equation risk per cycle = $1 - e^{\text{annual rate*time}}$, where time = 0.25, the duration of a model cycle
13	CV death baseline risk is the same after one, two or three events; from Ward et al. (2007)[44]
14	Non CV-attributable mortality is determined by UK-specific life tables (ONS, 2014) [51] which applies to the general population which is conservative given that CV patients have other comorbidities
15	The efficacy of the treatments is assumed to be constant over time and the same among adherents regardless of the comparator arm
16	Aspirin was assumed to have no benefit in reducing CHF with hospitalisation because no evidence was identified on this outcome

	Patients receiving secondary prevention were assumed stable. These stable patients therefore see their general practitioner (GP) biannually with biannual tests for liver function (LFT), renal function, full blood count (FBC), lipid profile, and thyroid function. GP visit costs are £45 (PSSRU 2013, Table 10.8b)[52]. Tests costs for LFT, lipid profile, renal function, thyroid function are each £1.25 (NHS ref costs 2012–13,[41] code DAPS04-Biochemistry).
17	FBC costs £3.01 (NHS ref costs 2012–13,[41] code DAPS05-hemotology). The acute events (ACS, Revasc, CHF, and stroke) consist of the cost of the event itself plus one cardiologist visit as a follow-up. Cardiologist visit cost £131.41 (NHS ref costs 2012–13) [41]. Patients in the chronic ACS, and CHF states are assumed symptomatic because they've had one MI plus a second event. Therefore, these patients see a cardiologist twice yearly with tests for LFT, renal function, FBC, lipid profile, thyroid function, and echocardiogram or other imaging test. Echocardiogram cost is £270 (NHS ref costs 2012–13, [41] code OPROC EA45Z)
18	Patient characteristics were: baseline proportion male 72.1% (SE: 0.56%) according to Zeymer et al. (2011).[22] The SE was inferred from the proportion p and sample size of n = 6260 according to the formula SE: sqrt [p (1 - p) / n]. Baseline mean age 64.7 years (SE: 0.158) according to Zeymer et al. (2011).[22] The SE is derived from the reported sample size n = 6260 and SD inferred from the 25–75% age range of 55.5–73.0
	Adherence
19	The maximum (starting) proportion adherent is assumed to be 0.9 (±20%) for both polypill and monocomponents. The minimum (long term) adherence value for polypill and monocomponents is 0.86 (0.011) and 0.65 (0.015), respectively, taken from Thom et al. 2013[24] Table 2. The sample size n = 1002 was used to derive the SE according to the formula (p*(1-p)/n)^(1/2)
20	In both comparator arms, adherence declines over a period of time and reaches a constant value. After suffering a non-fatal CV event, the patient's current adherence is not reset to the start of the adherence curve
21	Non-adherent patients receive no benefit of treatment and experience the baseline risk of CV events
22	For the scenario analysis that allows patients in the monocomponent to be adherent to 3, 2, 1 or 0 drugs, adherence assumptions are based on the UMPIRE study[24] aspirin and statin and from Bagnall et al (2010)[53] for ACEI. Since no data on ACE inhibitors was provided in this trial, these were taken from a prospective, multi-centre study of adherence to a range of cardiovascular drugs including ACEI in a population of patients with non-ST elevation MI (Bagnall et al 2010)[53]
23	Patients who are non-adherent incur the same full cost of their medication as adherent patients. In sensitivity analysis, this assumption is relaxed such that non-adherent patients do not incur the cost of unused medications

ACS, acute coronary syndrome; CHD, coronary heart disease; CHF, congestive heart failure; CV, cardiovascular; MI, myocardial infarction; ONS, United Kingdom Office of National Statistics; RRR, relative risk reduction; SLR, systematic literature review

The model incorporates a number of key equations that determine the rates at which CV events occur as a function of adherence to the polypill, aspirin, statin, and ACEI; and relative risk reductions of each of the three medications on specific CV event types for adherent and non-adherent patients. Furthermore, adherence in the monocomponents arm follows the same basic equation as the polypill arm. In other words, all patients are assumed to be adherent to all three drugs or adherent to none of the three.

The risk of acute coronary syndrome per 3-month cycle among patients in the monocomponents arm is given by:

Equation 1

$$Risk_{ACS} = BaselineRiskACS * [RRR_{ACS,ASA} * RRR_{ACS,ACEI} * RRR_{ACS,statin} * PropAdh_{Monocomponent}(t) + (1 - PropAdh_{Monocomponent}(t))]$$

Where, *BaselineRiskACS* is the 3-month probability of ACS amongst MI patients without any medication in health state 1; the three $RRR_{ACS,ASA}$, $RRR_{ACS,ACEI}$, $RRR_{ACS,statin}$ (all RRR<1) are the relative risk reductions of ACS amongst patients who are adherent to aspirin, ACEI and statin; the term $PropAdh_{Monocomponent}(t)$ is the proportion of patients who are adherent to all three of aspirin, ACEI and statin at time t. It can be seen from this equation that the benefit of adherence to all three drugs on ACS is given by $RRR_{ACS,ASA} * RRR_{ACS,ACEI} * RRR_{ACS,statin}$.

Five risk equations are constructed as described above, one for each CV outcome: ACS, stroke, unplanned revascularisation, CHF with hospitalisation, CV-attributable death. These equations explain the flow of patients from health state 1 to health states 2, 3a, 4, 5a, 6a.

This equation is similar for the polypill arm, where the risk of ACS per 3 month cycle is given by:

Equation 2

$$Risk_{ACS} = BaselineRiskACS * [RRR_{ACS,ASA} * RRR_{ACS,ACEI} * RRR_{ACS,statin} * PropAdh_{Polypill}(t) + (1 - PropAdh_{Polypill}(t))]$$

Where, $PropAdh_{Polypill}(t)$ is the proportion of patients who are adherent to the polypill at time t, and all other terms are as defined previously. In the base case, it is important to note that the relative risk reductions for the three drugs classes are the same for the polypill or its monocomponents among adherents. Therefore, patients who are adherent to the polypill have relative risk reduction to ACS of $RRR_{ACS,ASA} * RRR_{ACS,ACEI} * RRR_{ACS,statin}$ in both arms.

Five risk equations are constructed similarly for the polypill arm, one for each CV outcome: ACS, stroke, unplanned revascularisation, CHF with hospitalisation and CV-attributable death.

CV-attributable deaths in the model from health state 1 to 2 is as described above. Similarly, CV-attributable deaths from health states 7, 8, 9 and 11 to 2 occur according to this same type of risk equation. In the base case, the model assumes that these baseline risks of death are equal; hence, CV-attributable mortality does not depend on the history of prior number of CV events.

Patients may also die of non-CV attributable causes. This is based on UK-specific life tables and these patients experience the same non-CV mortality as the general UK population. This may underestimate non-CV attributable mortality in our model, given that our patients are less healthy due to comorbidities such as diabetes or renal dysfunction, which would increase risk of death by these causes, compared to the general population.

Adherence in the model is the proportion of subjects who are covered by their medication 80% of the time according to pill count or medication possession ratio (i.e., the most common way that adherence is reported in the SLR). Adherence is a time-dependent function that is initially decreasing from a maximum to a minimum value for a period of time, then constant thereafter, corresponding to an adherence function $PropAdh_{drug}(t)$ in model equations. There are two adherence functions, one each for the polypill and monocomponents arms. Each function requires specification of a maximum

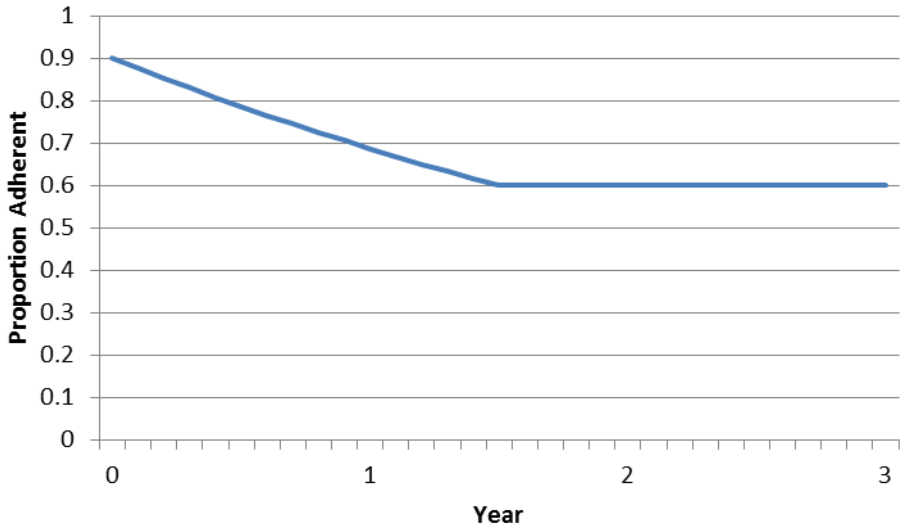
adherence (*MaxAdherence*), minimum adherence (*MinAdherence*) and time of decrease (*TimeToMin*). The adherence function takes the form:

Equation 3

$$PropAdh_{drug}(t) = MaxAdherence * e^{lambda*time}$$

Where, *lambda=ln(*$^{MinAdherence}/_{MaxAdherence}$*) / TimeToMin*. An example where *MaxAdherence=0.9, MinAdherence=0.6* and *TimeToMin*=1.5 years is given in Figure 2.

Figure 2. Sample Adherence Function for a Drug in Secondary Prevention Model



Updating Risk Equations to Include Individual Monocomponents in the 3-2-1-0 Model

The general model models all-or-nothing adherence in the monocomponents arm. Individual drug adherence can be modelled such that patients are adherent to 3, 2, 1 or 0 drugs using the equations described below. This equation for the polypill arm is unchanged and is as given previously.

Error! Reference source not found. is replaced by the equation below. The risk of acute coronary syndrome per 3-month cycle amongst patients in the monocomponents arm:

Equation 4

$$Risk_{ACS} = BaselineRiskACS *$$

$$* \left[RRR_{ACS,ASA} * PropAdh_{ASA}(t) + \left(1 - PropAdh_{ASA}(t)\right)\right]$$

$$* \left[RRR_{ACS,ACEI} * PropAdh_{ACEI}(t) + \left(1 - PropAdh_{ACEI}(t)\right)\right]$$

$$* \left[RRR_{ACS,statin} * PropAdh_{statin}(t) + \left(1 - PropAdh_{statin}(t)\right)\right]$$

Where, *BaselineRiskACS* is the 3-month probability of ACS amongst MI patients without any medication in health state 1; the three $RRR_{ACS,ASA}$, $RRR_{ACS,ACEI}$, $RRR_{ACS,statin}$ (all *RRR*<1) are the relative risk reductions of ACS amongst patients who are adherent to aspirin, ACEI and statin; and the three terms $PropAdh_{ASA}(t)$, $PropAdh_{ACEI}(t)$, $PropAdh_{statin}(t)$ are the proportion of patients who are adherent to aspirin, ACEI and statin at time t.

The equation can be expanded algebraically into eight terms: one that represents risk in patients who are adherent to all three drugs, three terms representing patients adherent to two drugs only, three terms for patients adherent to one drug and one term representing patients adherent to no drugs. Table 2 of this appendix lists these terms below. As an example of how proportions of patients are distributed on adherence to zero to three drugs, we assume adherence to all four drugs (polypill, aspirin, ACEI, statin) is 90%.

Table 2. Terms in CV Risk Equation Corresponding to Patients Adherent to 0 or 3 Drugs in the Polypill Arm And 0, 1, 2 or 3 Drugs in Monocomponents Arm with Examples for the Proportion of Patients Adherent to Each Combination of Drugs

	Proportion of Patients	Relative Risk Reduction for ACS Event	Proportion Assuming Adherence: 0.90 to all Pills
Patients adherent to polypill	$PropAdh_{Polypill}(t)$	$RRR_{ACS,ASA} * RRR_{ACS,ACEI} * RRR_{ACS,statin}$.	0.90
Patients not adherent to polypill	$1-PropAdh_{Polypill}(t)$	*1*	0.10
Patients adherent to 3 mono-components	$PropAdh_{ASA}(t)* PropAdh_{ACEI}(t)* PropAdh_{statin}(t)$	$RRR_{ACS,ASA} * RRR_{ACS,ACEI} * RRR_{ACS,statin}$	0.729
Patients adherent to 2 mono-components	$PropAdh_{ASA}(t)* PropAdh_{ACEI}(t)* (1-PropAdh_{statin}(t))$	$RRR_{ACS,ASA} * RRR_{ACS,ACEI}$	0.081
	$PropAdh_{ASA}(t)* (1-PropAdh_{ACEI}(t))* PropAdh_{statin}(t)$	$RRR_{ACS,ASA} * RRR_{ACS,statin}$	0.081
	$(1-PropAdh_{ASA}(t))* PropAdh_{ACEI}(t)* PropAdh_{statin}(t)$	$RRR_{ACS,ACEI} * RRR_{ACS,statin}$	0.081
Patients adherent to 1 mono-component	$PropAdh_{ASA}(t)* (1-PropAdh_{ACEI}(t))* (1-PropAdh_{statin}(t))$	$RRR_{ACS,ASA}$	0.009
	$(1-PropAdh_{ASA}(t))* PropAdh_{ACEI}(t)* (1-PropAdh_{statin}(t))$	$RRR_{ACS,ACEI}$	0.009
	$(1-PropAdh_{ASA}(t))* (1-PropAdh_{ACEI}(t))* PropAdh_{statin}(t)$	$RRR_{ACS,statin}$	0.009
Patients adherent to 0 mono-components	$(1-PropAdh_{ASA}(t))* (1-PropAdh_{ACEI}(t))* (1-PropAdh_{statin}(t))$	*1*	0.001

Adherence Inputs for the 3-2-1-0 Model

The 3-2-1-0 model requires specification of parameters for the proportion of the population with good adherence and poor adherence to each of the drugs in the monocomponents arm and polypill arm through time. In order to determine parameters for the proportion adherent and non-adherent data were taken from the UMPIRE study.[24] To allow for the change over time, the model requires parameters for the maximum or starting proportion adherent and the minimum or long-term proportion

adherent and the time over which the adherence has been observed changing. The first reported time point in the trial was 6 months after randomisation; the proportion of the population adherent at this time was taken to be the maximum adherence. The final point of follow-up was at 18 months, and adherence at this point was taken as the minimum proportion adherent. Time to go from maximum to minimum adherence was therefore 1 year.

No data on adherence to ACE inhibitors was provided in this trial. Therefore, adherence data for ACEI were taken from a prospective, multi-centre study of adherence to a range of cardiovascular drugs including ACEI in a population of patients after non-ST elevation MI.[53] This is a specific, high-risk subpopulation of patients, and therefore adherence in these patients may not be representative of the population included in the model. However, due to a lack of other suitable data sources on ACEI adherence it was decided to use this data. Data on proportion adherent to each drug over time in the 3-2-1-0 model are shown in Table 3.

Table 3. Proportion of Secondary Prevention Patients who are Adherent to Each Medication

	Value	Source/Explanation
Adherence		
Maximum proportion adherent to aspirin	0.947	Thom et al. (2013)[24]
Minimum proportion adherent to aspirin	0.910	Raw data used to derive model inputs were: 926/978 = 0.947; 475/522 = 0.910
Maximum proportion adherent to ACEI	0.650	Bagnall et al. (2010)[53]
Minimum proportion adherent to ACEI	0.603	
Maximum proportion adherent to statin	0.931	Thom et al. (2013)[24]
Minimum proportion adherent to statin	0.898	Raw data used to derive model inputs were:911/978 = 0.931; 469/522 = 0.898
Maximum proportion adherent to polypill	0.975	Thom et al. (2013)[24] Assume highest observed adherence from the polypill arm of the trial at 6 months and 18 months
Minimum proportion adherent to polypill	0.927	Raw data used to derive model inputs were: 953/977 = 0.975; 486/524 = 0.927

ACEI, Angiotensin Converting Enzyme Inhibitor

136 ***Appendix 2. Search Strategy***

137 **1. Efficacy and safety review**

138 **Embase**

139 Limits: Embase search, studies in humans with abstracts, in English published 2003–2013

Rationale	Search Criteria	Search Algorithm	Hits (18 July 2013)
CV disease	**1**	'cardiovascular disease'/exp OR 'heart infarction'/exp OR 'ischemic heart disease'/exp OR 'cerebrovascular accident'/exp OR 'heart failure'/exp OR 'st segment elevation myocardial infarction'/exp OR 'myocardial infarction':ab,ti OR stemi:ab,ti OR (heart:ab,ti OR cardiac:ab,ti OR coronary:ab,ti AND (failure:ab,ti OR insufficiency:ab,ti)) OR stroke:ab,ti OR 'acute coronary syndrome':ab,ti OR 'post-myocardial infarction outcomes':ab,ti	736,958
Secondary prevention	**2**	'secondary prevention'/exp OR 'secondary prevention':ab,ti OR recurrence:ab,ti OR reinfarction:ab,ti	100,833
Systematic review	**3**	'systematic review'/exp OR 'systematic review':ab,ti OR 'meta analysis'/exp OR 'meta analysis':ab,ti OR (systematic:ab,ti AND review:ab,ti)	79,300
Specific drugs	**4**	'acetylsalicylic acid'/exp OR aspirin:ab,ti OR 'antithrombocytic agent'/exp OR 'antiplatelet drug':ab,ti OR 'hydroxymethylglutaryl coenzyme a reductase inhibitor'/exp OR statin:ab,ti OR atorvastatin:ab,ti OR 'atorvastatin plus ramipril'/exp OR 'atorvastatin'/exp OR 'ramipril'/exp OR 'dipeptidyl carboxypeptidase inhibitor'/exp OR ramipril:ab,ti OR 'ACE inhibitor':ab,ti OR 'dipeptidyl carboxypeptidase inhibitor':ab,ti	133,706
Systematic reviews of polypill components in CV disease	**5**	1 AND 2 AND 3 AND 4	575
Fixed-dose combination therapy	**6**	'drug combination'/exp OR (combin*:ab,ti AND (therapy:ab,ti OR treatment:ab,ti OR tablet:ab,ti OR pill:ab,ti OR capsule:ab,ti)) OR comedication:ab,ti OR 'co medication':ab,ti OR 'fixed dose combination':ab,ti OR polypill:ab,ti	209,535

Rationale	Search Criteria	Search Algorithm	Hits (18 July 2013)
RCTs	**7**	random*:ab,ti OR 'placebo'/exp OR placebo*:ab,ti OR 'double blind':ab,ti OR ('phase ii' NEAR/4 trial):ab,ti OR ('phase ii' NEAR/4 study):ab,ti OR ('phase iii' NEAR/4 trial):ab,ti OR ('phase iii' NEAR/3 study):ab,ti OR (controlled NEAR/4 trial):ab,ti OR (controlled NEAR/4 study):ab,ti OR (random* NEAR/4 allocat*):ab,ti OR (randomized:ab,ti AND controlled:ab,ti AND trial:ab,ti) OR (randomised:ab,ti AND controlled:ab,ti AND trial:ab,ti) OR (clinical:ab,ti AND trial:ab,ti) OR (random:ab,ti AND allocation:ab,ti) OR (double:ab,ti AND blind:ab,ti) OR (double:ab,ti AND blinded:ab,ti) OR (double:ab,ti AND masked:ab,ti) OR (single:ab,ti AND blind:ab,ti) OR (single:ab,ti AND blinded:ab,ti) OR (single:ab,ti AND masked:ab,ti) OR 'clinical trial'/exp OR 'controlled clinical trial'/exp OR 'randomized controlled trial'/exp	558,440
RCTs of combination therapy in CV disease	**8**	1 AND 2 AND 6 AND 7	1,448
Combined SRs and RCTs	**9**	5 OR 8	1,890
Non-systematic reviews	**10**	review NOT (systematic OR 'meta analysis' OR (indirect OR mixed AND 'treatment comparison')) OR editorial:it OR letter:it OR note:it OR 'short survey':it	673,351
Studies for screening	**11**	**9 NOT 10**	**1,317**

MEDLINE

Limits: studies in humans with abstracts, in English published 2003–2013

Rationale	Search Criteria	Search Algorithm	Hits (19 July 2013)
CV disease	**1**	"cardiovascular diseases"[Mesh] OR "myocardial infarction"[Mesh] OR "myocardial ischemia"[Mesh] OR "coronary artery disease"[Mesh] OR "stroke"[Mesh] OR "heart failure"[Mesh] OR "acute coronary syndrome"[Mesh] OR "myocardial infarction"[TIAB] OR stemi[TIAB] OR (heart[TIAB] OR cardiac[TIAB] OR coronary[TIAB] AND (failure[TIAB] OR insufficiency[TIAB])) OR stroke[TIAB] OR "acute coronary syndrome"[TIAB] OR "post-myocardial infarction outcomes"[TIAB]	407,600
Secondary prevention	**2**	"secondary prevention"[Mesh] OR "secondary prevention"[TIAB] OR recurrence[TIAB] OR reinfarction[TIAB]	73,454

Rationale	Search Criteria	Search Algorithm	Hits (19 July 2013)
Systematic review	**3**	"Review" [Publication Type] OR "Meta-Analysis" [Publication Type] OR "systematic review"[TIAB] OR "meta analysis"[TIAB] OR (systematic[TIAB] AND review[TIAB])	589,932
Specific drugs	**4**	"aspirin"[Mesh] OR aspirin[TIAB] OR "Platelet Aggregation Inhibitors"[Mesh] OR "antiplatelet drug"[TIAB] OR "Hydroxymethylglutaryl-CoA Reductase Inhibitors"[Mesh] OR statin[TIAB] OR "atorvastatin" [Supplementary Concept] OR atorvastatin[TIAB] OR "ramipril"[Mesh] OR ramipril[TIAB] OR "ACE inhibitor"[TIAB] OR "Angiotensin-Converting Enzyme Inhibitors"[Mesh]	34,224
Systematic reviews of polypill components in CV disease	**5**	1 AND 2 AND 3 AND 4	855
Fixed-dose combination therapy	**6**	"drug combinations"[Mesh] OR (combin*[TIAB] AND (therapy[TIAB] OR treatment[TIAB] OR tablet[TIAB] OR pill[TIAB] OR capsule[TIAB])) OR comedication[TIAB] OR "co medication"[TIAB] OR 'fixed dose combination'[TIAB] OR polypill[TIAB]	136,470
RCTs	**7**	random*[TIAB] OR "placebos"[Mesh] OR placebo*[TIAB] OR "double blind"[TIAB] OR "phase ii"[TIAB] OR "phase iii"[TIAB] OR (controlled [TIAB] AND trial[TIAB]) OR (controlled[TIAB] AND study[TIAB]) OR (random*[TIAB] AND allocat*[TIAB]) OR (randomized[TIAB] AND controlled[TIAB] AND trial[TIAB]) OR (randomised[TIAB] AND controlled[TIAB] AND trial[TIAB]) OR (clinical[TIAB] AND trial[TIAB]) OR (random[TIAB] AND allocation[TIAB]) OR (double[TIAB] AND blind[TIAB]) OR (double[TIAB] AND blinded[TIAB]) OR (double[TIAB] AND masked[TIAB]) OR (single[TIAB] AND blind[TIAB]) OR (single[TIAB] AND blinded[TIAB]) OR (single[TIAB] AND masked[TIAB]) OR "clinical trial"[Publication Type] OR "controlled clinical trial"[Publication Type] OR "randomized controlled trial"[Publication Type]	498,043
RCTs of combination therapy in CV disease	**8**	1 AND 2 AND 6 AND 7	455
Combined SRs and RCTs	**9**	5 OR 8	1,209
Non-systematic reviews	**10**	review NOT (systematic OR "meta analysis" OR (indirect OR mixed AND "treatment comparison")) OR editorial[Publication Type] OR letter[Publication Type] OR comment[Publication Type]	622,636

Rationale	Search Criteria	Search Algorithm	Hits (19 July 2013)
Studies for screening	**11**	**9 NOT 10**	**509**

CENTRAL

Limits: search terms in title, abstract or keywords

Rationale	Search Criteria	Search Algorithm	Hits (4 August 2013)
Secondary prevention of CHD	**1**	(coronary heart disease OR myocardial infarction) and secondary prevention	**655**

149

150 **2. Humanistic Review**

151 **Embase**

152 Limits: Embase search, studies in humans with abstracts, in English published 2003–2013

Rationale	Search Criteria	Search Algorithm	Hits (18 July 2013)
CV disease	**1**	'cardiovascular disease'/exp OR 'heart infarction'/exp OR 'ischemic heart disease'/exp OR 'cerebrovascular accident'/exp OR 'heart failure'/exp OR 'st segment elevation myocardial infarction'/exp OR 'myocardial infarction':ab,ti OR stemi:ab,ti OR (heart:ab,ti OR cardiac:ab,ti OR coronary:ab,ti AND (failure:ab,ti OR insufficiency:ab,ti)) OR stroke:ab,ti OR 'acute coronary syndrome':ab,ti OR 'post-myocardial infarction outcomes':ab,ti	736,958
Secondary prevention	**2**	'secondary prevention'/exp OR 'secondary prevention':ab,ti OR recurrence:ab,ti OR reinfarction:ab,ti	100,833
Humanistic burden	**3**	'quality of life'/exp OR 'health related quality of life':ab,ti OR hrqol:ab,ti OR 'hqol':ab,ti OR 'hr qol':ab,ti OR 'quality of life':ab,ti OR qol:ab,ti OR 'eq-5d':ab,ti OR eq5d:ab,ti OR euroqol:ab,ti OR 'euro qol':ab,ti OR 'functional status':ab,ti OR 'health status':ab,ti OR 'patient reported':ab,ti OR 'patient-reported':ab,ti OR 'patients reported':ab,ti OR 'self reported':ab,ti OR patients NEAR/4 reported OR 'physical function':ab,ti OR 'time trade off':ab,ti OR disab*:ab,ti OR questionnaire:ab,ti OR satisfaction:ab,ti OR sexual:ab,ti OR sleep:ab,ti OR utility:ab,ti OR utilities:ab,ti OR 'sickness impact profile':ab,ti OR sip:ab,ti OR 'nottingham health profile':ab,ti OR nhp:ab,ti OR sf12:ab,ti OR 'sf 12':ab,ti OR 'short form 12':ab,ti OR 'shortform 12':ab,ti OR 'sf twelve':ab,ti OR sftwelve:ab,ti OR 'shortform twelve':ab,ti OR 'short form twelve':ab,ti OR sf36:ab,ti OR 'sf 36':ab,ti OR 'short form 36':ab,ti OR 'shortform 36':ab,ti OR 'sf thirtysix':ab,ti OR 'sf thirty six':ab,ti OR 'shortform thirtysix':ab,ti OR 'shortform thirty six':ab,ti OR 'short form thirtysix':ab,ti OR 'short form thirty six':ab,ti OR EQ-VAS:ab,ti OR HUI3:ab,ti OR WHOQOL-BREF:ab,ti OR MIDAS:ab,ti OR 'myocardial infarction dimensional assessment scale':ab,ti OR 'Kansas city cardiomyopathy questionnaire':ab,ti OR 'macnew heart disease health related quality of life questionnaire':ab,ti OR 'burden of disease':ab,ti OR 'burden':ab,ti	495,764
Humanistic burden in secondary prevention of CV disease	**4**	1 AND 2 AND 3	3,226
Not non-systematic reviews	**5**	review NOT (systematic OR 'meta analysis' OR (indirect OR mixed AND 'treatment comparison')) OR editorial:it OR letter:it OR note:it OR 'short survey':it	673,351

Rationale	Search Criteria	Search Algorithm	Hits (18 July 2013)
Studies for screening		**4 NOT 5**	**2,249**

153

154 **MEDLINE**

155 Limits: studies in humans with abstracts, in English published 2003–2013

Rationale	Search Criteria	Search Algorithm	Hits (18 July 2013)
CV disease	1	"cardiovascular diseases"[Mesh] OR "myocardial infarction"[Mesh] OR "myocardial ischemia"[Mesh] OR "coronary artery disease"[Mesh] OR "stroke"[Mesh] OR "heart failure"[Mesh] OR "acute coronary syndrome"[Mesh] OR "myocardial infarction"[TIAB] OR stemi[TIAB] OR (heart[TIAB] OR cardiac[TIAB] OR coronary[TIAB] AND (failure[TIAB] OR insufficiency[TIAB])) OR stroke[TIAB] OR "acute coronary syndrome"[TIAB] OR "post-myocardial infarction outcomes"[TIAB]	407,600
Secondary prevention	**2**	"secondary prevention"[Mesh] OR "secondary prevention"[TIAB] OR recurrence[TIAB] OR reinfarction[TIAB]	73,454
Humanistic burden	**3**	"quality of life"[Mesh] OR "health related quality of life"[TIAB] OR hrqol[TIAB] OR hqol[TIAB] OR "hr qol"[TIAB] OR "quality of life"[TIAB] OR qol[TIAB] OR eq-5d[TIAB] OR eq5d[TIAB] OR euroqol[TIAB] OR "euro qol"[TIAB] OR "functional status"[TIAB] OR "health status"[TIAB] OR "patient reported"[TIAB] OR "patient-reported"[TIAB] OR "patients reported"[TIAB] OR "self reported"[TIAB] OR (patients[TIAB] AND reported[TIAB]) OR "physical function"[TIAB] OR "time trade off"[TIAB] OR disab*[TIAB] OR questionnaire[TIAB] OR satisfaction[TIAB] OR sexual[TIAB] OR sleep[TIAB] OR utility[TIAB] OR utilities[TIAB] OR "sickness impact profile"[TIAB] OR sip[TIAB] OR "nottingham health profile"[TIAB] OR nhp[TIAB] OR sf12[TIAB] OR "sf 12"[TIAB] OR "short form 12"[TIAB] OR "sf twelve"[TIAB] OR sftwelve[TIAB] OR "short form twelve"[TIAB] OR sf36[TIAB] OR "sf 36"[TIAB] OR "short form 36"[TIAB] OR "sf thirty six"[TIAB] OR "shortform thirtysix"[TIAB] OR "shortform thirty six"[TIAB] OR "short form thirtysix"[TIAB] OR "short form thirty six"[TIAB] OR EQ-VAS[TIAB] OR HUI3[TIAB] OR WHOQOL-BREF[TIAB] OR MIDAS[TIAB] OR "myocardial infarction dimensional assessment scale"[TIAB] OR "kansas city cardiomyopathy questionnaire"[TIAB] OR "macnew heart disease health related quality of life questionnaire"[TIAB] OR "burden of disease"[TIAB] OR burden[TIAB]	522,554

Rationale	Search Criteria	Search Algorithm	Hits (18 July 2013)
Humanistic burden in secondary prevention of CV disease	**4**	1 AND 2 AND 3	2,178
Not non-systematic reviews	**5**	review NOT (systematic OR "meta analysis" OR (indirect OR mixed AND "treatment comparison")) OR editorial[Publication Type] OR letter[Publication Type] OR comment[Publication Type]	622,636
Studies for screening		**4 NOT 5**	**1,602**

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157 **3. Economic Burden Review**

158 **Embase**

159 Limits: Embase search, studies in humans with abstracts, in English published 2003–2013

Rationale	Search Criteria	Search Algorithm	Hits (18 July 2013)
CV disease	**1**	'cardiovascular disease'/exp OR 'heart infarction'/exp OR 'ischemic heart disease'/exp OR 'cerebrovascular accident'/exp OR 'heart failure'/exp OR 'st segment elevation myocardial infarction'/exp OR 'myocardial infarction':ab,ti OR stemi:ab,ti OR (heart:ab,ti OR cardiac:ab,ti OR coronary:ab,ti AND (failure:ab,ti OR insufficiency:ab,ti)) OR stroke:ab,ti OR 'acute coronary syndrome':ab,ti OR 'post-myocardial infarction outcomes':ab,ti	736,958
Secondary prevention	**2**	'secondary prevention'/exp OR 'secondary prevention':ab,ti OR recurrence:ab,ti OR reinfarction:ab,ti	100,833

Rationale	Search Criteria	Search Algorithm	Hits (18 July 2013)
Economic burden	**3**	cost*:ab,ti OR costs:ab,ti OR budget*:ab,ti OR expenditure*:ab,ti OR economic*:ab,ti OR pharmacoeconomic*:ab,ti OR productivity:ab,ti OR burden*:ab,ti OR cost* NEAR/3 (hospital OR hospitalization OR hospitalisation) OR (hospital* AND cost*) OR 'resource utilization':ab,ti OR 'resource utilisation':ab,ti OR (('health resources' OR 'health care' OR 'medical resources') NEAR/3 (use OR utilisation OR utilization OR service OR consumption)):ab,ti OR 'direct cost':ab,ti OR 'direct costs':ab,ti OR 'direct medical cost':ab,ti OR 'direct medical costs':ab,ti OR 'medical direct cost':ab,ti OR 'medical direct costs':ab,ti OR 'direct non medical cost':ab,ti OR 'direct non medical costs':ab,ti OR 'non medical direct cost':ab,ti OR 'non medical direct costs':ab,ti OR 'indirect cost':ab,ti OR 'indirect costs':ab,ti OR 'total cost':ab,ti OR 'total costs':ab,ti OR 'cost per patient treated':ab,ti OR 'health economics'/exp OR 'health economics':ab,ti OR 'medical leave':ab,ti OR (work NEAR/8 disability):ab,ti OR 'work disability':ab,ti OR 'absenteeism':ab,ti OR 'sick leave':ab,ti OR 'sick day':ab,ti OR 'cost of illness':ab,ti	272,782
Economic burden in secondary prevention of CV disease	**4**	1 AND 2 AND 3	2,365
Not non-systematic reviews	**5**	review NOT (systematic OR 'meta analysis' OR (indirect OR mixed AND 'treatment comparison')) OR editorial:it OR letter:it OR note:it OR 'short survey':it	673,351
Primary research studies only	**6**	4 NOT 5	1,542
EU5	**7**	uk:ab,ti OR 'united kingdom':ab,ti OR 'great britain':ab,ti OR england:ab,ti OR wales:ab,ti OR scotland:ab,ti OR 'northern ireland':ab,ti OR france:ab,ti OR germany:ab,ti OR french:ab,ti OR german:ab,ti OR italy:ab,ti OR italian:ab,ti OR spain:ab,ti OR spanish:ab,ti OR british:ab,ti OR english:ab,ti OR welsh:ab,ti OR scottish:ab,ti OR irish:ab,ti OR eu5:ab,ti	223,684
Spain	**8**	spain:ab,ti OR espagne:ab,ti OR espana:ab,ti OR spagna:ab,ti OR spain:ad OR espagne:ad OR espana:ad OR spanien:ad OR spagna:ad OR catalunya:ad OR catalonia:ad OR catalogne:ad OR cataluna:ad OR catala:ad OR barcelon*:ad OR tarragona:ad OR lleida:ad OR lerida:ad OR girona:ad OR gerona:ad OR sabadell:ad OR hospitalet:ad OR lhospitalet:ad OR valencia*:ad OR castello*:ad OR alacant:ad OR alicant*:ad OR murcia*:ad OR (cartagen*:ad NOT indias:ad) OR andalu*:ad OR sevill*:ad OR granad*:ad	110,699

Rationale	Search Criteria	Search Algorithm	Hits (18 July 2013)
	9	7 or 8	315,585
Studies for screening: economic burden in EU5	**10**	**6 AND 9**	**219**

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161 **MEDLINE**

162 Limits: studies in humans with abstracts, in English published 2003–2013

Rationale	Search Criteria	Search Algorithm	Hits (19 July 2013)
CV disease	**1**	"cardiovascular diseases"[Mesh] OR "myocardial infarction"[Mesh] OR "myocardial ischemia"[Mesh] OR "coronary artery disease"[Mesh] OR "stroke"[Mesh] OR "heart failure"[Mesh] OR "acute coronary syndrome"[Mesh] OR "myocardial infarction"[TIAB] OR stemi[TIAB] OR (heart[TIAB] OR cardiac[TIAB] OR coronary[TIAB] AND (failure[TIAB] OR insufficiency[TIAB])) OR stroke[TIAB] OR "acute coronary syndrome"[TIAB] OR "post-myocardial infarction outcomes"[TIAB]	407,600
Secondary prevention	**2**	"secondary prevention"[Mesh] OR "secondary prevention"[TIAB] OR recurrence[TIAB] OR reinfarction[TIAB]	73,454
Economic burden	**3**	"Cost of illness"[Mesh] OR cost*[TIAB] OR costs[TIAB] OR budget*[TIAB] OR expenditure*[TIAB] OR economic*[TIAB] OR pharmacoeconomic*[TIAB] OR productivity[TIAB] OR ((burden*[TIAB] OR cost*[TIAB]) AND (hospital[TIAB] OR hospitalisation[TIAB] OR hospitalization[TIAB])) OR (hospital*[TIAB] AND cost*[TIAB]) OR "resource utilization"[TIAB] OR "resource utilisation"[TIAB] OR (("health resources"[TIAB] OR "health care"[TIAB] OR "medical resources"[TIAB]) AND (use[TIAB] OR utilization[TIAB] OR utilization[TIAB] OR service[TIAB] OR consumption[TIAB])) OR "direct cost"[TIAB] OR "direct costs"[TIAB] OR "direct medical cost"[TIAB] OR "direct medical costs"[TIAB] OR "medical direct cost"[TIAB] OR "medical direct costs"[TIAB] OR "direct non medical cost"[TIAB] OR "direct non medical costs"[TIAB] OR "non medical direct cost"[TIAB] OR "non medical direct costs"[TIAB] OR "indirect cost"[TIAB] OR "indirect costs"[TIAB] OR "total cost"[TIAB] OR "total costs"[TIAB] OR "cost per patient treated"[TIAB] OR "health economics"[Mesh] OR "health economics"[TIAB] OR "medical leave"[TIAB] OR "work disability"[TIAB] OR "absenteeism"[TIAB] OR "sick leave"[TIAB] OR "sick day"[TIAB] OR "cost of illness"[TIAB]	166,798

Rationale	Search Criteria	Search Algorithm	Hits (19 July 2013)
Economic burden in secondary prevention of CV disease	**4**	1 AND 2 AND 3	638
Not non-systematic reviews	**5**	review NOT (systematic OR "meta analysis" OR (indirect OR mixed AND "treatment comparison")) OR editorial[Publication Type] OR letter[Publication Type] OR comment[Publication Type]	622,636
Primary research studies only	**6**	4 NOT 5	418
EU5	**7**	uk[TIAB] OR "united kingdom"[TIAB] OR "great britain"[TIAB] OR england[TIAB] OR wales[TIAB] OR scotland[TIAB] OR "northern ireland"[TIAB] OR france[TIAB] OR germany[TIAB] OR french[TIAB] OR german[TIAB] OR italy[TIAB] OR italian[TIAB] OR spain[TIAB] OR spanish[TIAB] OR british[TIAB] OR english[TIAB] OR welsh[TIAB] OR scottish[TIAB] OR irish[TIAB] OR eu5[TIAB]	147,501
Spain	**8**	spain[TIAB] OR espagne[TIAB] OR espana[TIAB] OR spagna[TIAB] OR spain[ad] OR espagne[ad] OR espana[ad] OR spanien[ad] OR spagna[ad] OR catalunya[ad] OR catalonia[ad] OR catalogne[ad] OR cataluna[ad] OR catala[ad] OR barcelon*[ad] OR tarragona[ad] OR lleida[ad] OR lerida[ad] OR girona[ad] OR Gerona[ad] OR sabadell[ad] OR hospitalet[ad] OR l'hospitalet[ad] OR valencia*[ad] OR castello*[ad] OR alacant[ad] OR alicant*[ad] OR murcia*[ad] OR (cartagen*[ad] NOT indias[ad]) OR andalu*[ad] OR sevill*[ad] OR granad*[ad]	73,140
	9	7 or 8	207,006
Studies for screening: economic burden in EU5	**10**	**6 AND 9**	**68**

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164 **4. Economic Models Review**

165 **Embase**

166 Limits: Embase search, studies in humans with abstracts, in English published 2003–2013

Rationale	Search Criteria	Search Algorithm	Hits (18 July 2013)

Rationale	Search Criteria	Search Algorithm	Hits (18 July 2013)
CV disease	**1**	'cardiovascular disease'/exp OR 'heart infarction'/exp OR 'ischemic heart disease'/exp OR 'cerebrovascular accident'/exp OR 'heart failure'/exp OR 'st segment elevation myocardial infarction'/exp OR 'myocardial infarction':ab,ti OR stemi:ab,ti OR (heart:ab,ti OR cardiac:ab,ti OR coronary:ab,ti AND (failure:ab,ti OR insufficiency:ab,ti)) OR stroke:ab,ti OR 'acute coronary syndrome':ab,ti OR 'post-myocardial infarction outcomes':ab,ti	736,958
Secondary prevention	**2**	'secondary prevention'/exp OR 'secondary prevention':ab,ti OR recurrence:ab,ti OR reinfarction:ab,ti	100,833
Economic evaluation studies	**3**	'economic evaluation':ab,ti OR 'cost-benefit analysis':ab,ti OR 'cost benefit':ab,ti OR 'cost-effectiveness':ab,ti OR 'cost effectiveness':ab,ti OR 'cost utility':ab,ti OR 'cost-utility':ab,ti OR 'cost-minimisation':ab,ti OR 'cost-minimization':ab,ti OR 'cost minimisation':ab,ti OR 'cost minimization':ab,ti OR 'cost savings':ab,ti OR 'cost saving':ab,ti OR 'cost-saving':ab,ti OR 'cost-savings':ab,ti OR 'pharmaceutical economics':ab,ti OR 'budget impact':ab,ti OR 'econometric':ab,ti OR 'markov':ab,ti OR 'decision analysis':ab,ti OR ('model':ab,ti OR 'models':ab,ti OR 'modeling':ab,ti OR 'modelling':ab,ti AND ('cost':ab,ti OR 'costs':ab,ti OR 'economic':ab,ti OR 'economics':ab,ti)) OR efficiency:ab,ti	84,539
Economic evaluations of secondary prevention in CV disease	**4**	1 AND 2 AND 3	514
Not non-systematic reviews	**5**	review NOT (systematic OR 'meta analysis' OR (indirect OR mixed AND 'treatment comparison')) OR editorial:it OR letter:it OR note:it OR 'short survey':it	673,351
Studies for screening	**6**	**4 NOT 5**	**380**

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170 **MEDLINE**Limits: studies in humans with abstracts, in English published 2003–2013

Rationale	Search Criteria	Search Algorithm	Hits (19 July 2013)
CV disease	**1**	"cardiovascular diseases"[Mesh] OR "myocardial infarction"[Mesh] OR "myocardial ischemia"[Mesh] OR "coronary artery disease"[Mesh] OR "stroke"[Mesh] OR "heart failure"[Mesh] OR "acute coronary syndrome"[Mesh] OR "myocardial infarction"[TIAB] OR stemi[TIAB] OR (heart[TIAB] OR cardiac[TIAB] OR coronary[TIAB] AND (failure[TIAB] OR insufficiency[TIAB])) OR stroke[TIAB] OR "acute coronary syndrome"[TIAB] OR "post-myocardial infarction outcomes"[TIAB]	407,600
Secondary prevention	**2**	"secondary prevention"[Mesh] OR "secondary prevention"[TIAB] OR recurrence[TIAB] OR reinfarction[TIAB]	73,454
Economic evaluation studies	**3**	"economic evaluation"[TIAB] OR "Cost-Benefit Analysis"[Mesh] OR "cost-benefit analysis"[TIAB] OR "cost benefit"[TIAB] OR "cost-effectiveness"[TIAB] OR "cost effectiveness"[TIAB] OR "cost utility"[TIAB] OR "cost-utility"[TIAB] OR "cost-minimisation"[TIAB] OR "cost-minimization"[TIAB] OR "cost minimisation"[TIAB] OR "cost minimization"[TIAB] OR "cost savings"[TIAB] OR "cost saving"[TIAB] OR "cost-saving"[TIAB] OR "cost-savings"[TIAB] OR "pharmaceutical economics"[TIAB] OR "budget impact"[TIAB] OR "econometric"[TIAB] OR "markov"[TIAB] OR "decision analysis"[TIAB] OR ((model[TIAB] OR models[TIAB] OR modeling[TIAB] OR modelling[TIAB]) AND ("cost"[TIAB] OR "costs"[TIAB] OR "economic"[TIAB] OR "economics"[TIAB])) OR efficiency[TIAB]	86,822
Economic evaluations of secondary prevention in CV disease	**4**	1 AND 2 AND 3	309
Not non-systematic reviews	**5**	review NOT (systematic OR "meta analysis" OR (indirect OR mixed AND "treatment comparison")) OR editorial[Publication Type] OR letter[Publication Type] OR comment[Publication Type]	622,636
Studies for screening	**6**	**4 NOT 5**	**220**

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NHSEED

Limits: NHSEED Search, in English published 2003–2013

Search Algorithm	Hits (18 July 2013)
(“ace inhibitors” AND aspirin) OR (“fixed dose” AND “cardiovascular disease”) OR polypill OR “myocardial infarction" OR “transient ischaemic attacks” OR stroke OR (“cardiovascular disease” AND stroke) OR (“cardiovascular disease” AND “myocardial infarction”) OR (“cardiovascular disease” AND “transient ischaemic attacks”) OR (“cardiovascular disease” AND polypill) OR (“cardiovascular disease” AND “fixed dose”)	275

5. Adherence Review

Embase

Limits: Embase search, studies in humans with abstracts, in English published 2003–2013

Rationale	Search Criteria	Search Algorithm	Hits (18 July 2013)
CV disease	**1**	‘cardiovascular disease’/exp OR ‘heart infarction’/exp OR ‘ischemic heart disease’/exp OR ‘cerebrovascular accident’/exp OR ‘heart failure’/exp OR ‘st segment elevation myocardial infarction’/exp OR ‘myocardial infarction’:ab,ti OR stemi:ab,ti OR (heart:ab,ti OR cardiac:ab,ti OR coronary:ab,ti AND (failure:ab,ti OR insufficiency:ab,ti)) OR stroke:ab,ti OR ‘acute coronary syndrome’:ab,ti OR ‘post-myocardial infarction outcomes’:ab,ti	736,958
Secondary prevention	**2**	‘secondary prevention’/exp OR ‘secondary prevention’:ab,ti OR recurrence:ab,ti OR reinfarction:ab,ti	100,833
Adherence	**3**	persisten*:ab,ti OR discontin*:ab,ti OR adheren*:ab,ti OR complian*:ab,ti OR intermittent*:ab,ti OR ‘medication possession ratio’:ab,ti OR ‘proportion of days covered’:ab,ti OR ‘pill count’:ab,ti	195,899
Adherence to secondary prevention in CV disease	**4**	1 AND 2 AND 3	3,010
Polypill components	**5**	‘acetylsalicylic acid’/exp OR aspirin:ab,ti OR ‘antithrombocytic agent’/exp OR ‘antiplatelet drug’:ab,ti OR ‘hydroxymethylglutaryl coenzyme a reductase inhibitor’/exp OR statin:ab,ti OR atorvastatin:ab,ti OR ‘atorvastatin plus ramipril’/exp OR ‘atorvastatin’/exp OR ‘ramipril’/exp OR ‘dipeptidyl carboxypeptidase inhibitor’/exp OR ramipril:ab,ti OR ‘ACE inhibitor’:ab,ti	133,706

Rationale	Search Criteria	Search Algorithm	Hits (18 July 2013)
	6	'drug combination'/exp OR (combin*:ab,ti AND (therapy:ab,ti OR treatment:ab,ti OR tablet:ab,ti OR pill:ab,ti OR capsule:ab,ti)) OR comedication:ab,ti OR 'co medication':ab,ti OR 'fixed dose combination':ab,ti OR polypill:ab,ti OR education:ab,ti OR support:ab,ti OR information:ab,ti	678,676
	7	5 or 6	783,705
Adherence to polypill components	**8**	4 AND 7	1,192
Not non-systematic reviews	**9**	review NOT (systematic OR 'meta analysis' OR (indirect OR mixed AND 'treatment comparison')) OR editorial:it OR letter:it OR note:it OR 'short survey':it	673,351
Studies for screening	**10**	8 NOT 9	**881**

MEDLINE

Limits: studies in humans with abstracts, in English published 2003–2013

Rationale	Search Criteria	Search Algorithm	Hits (19 July 2013)
CV disease	**1**	"cardiovascular diseases"[Mesh] OR "myocardial infarction"[Mesh] OR "myocardial ischemia"[Mesh] OR "coronary artery disease"[Mesh] OR "stroke"[Mesh] OR "heart failure"[Mesh] OR "acute coronary syndrome"[Mesh] OR "myocardial infarction"[TIAB] OR stemi[TIAB] OR (heart[TIAB] OR cardiac[TIAB] OR coronary[TIAB] AND (failure[TIAB] OR insufficiency[TIAB])) OR stroke[TIAB] OR "acute coronary syndrome"[TIAB] OR "post-myocardial infarction outcomes"[TIAB]	407,600
Secondary prevention	**2**	"secondary prevention"[Mesh] OR "secondary prevention"[TIAB] OR recurrence[TIAB] OR reinfarction[TIAB]	73,454
Adherence	**3**	"Medication Adherence"[Mesh] OR "Patient Compliance"[Mesh] OR persisten*[TIAB] OR discontin*[TIAB] OR adheren*[TIAB] OR complian*[TIAB] OR intermittent*[TIAB] OR "medication possession ratio"[TIAB] OR "proportion of days covered"[TIAB] OR "pill count"[TIAB]	162,741
Adherence to secondary prevention in CV disease	**4**	1 AND 2 AND 3	1571

Rationale	Search Criteria	Search Algorithm	Hits (19 July 2013)
Polypill components	**5**	"aspirin"[Mesh] OR aspirin[TIAB] OR "Platelet Aggregation Inhibitors"[Mesh] OR "antiplatelet drug"[TIAB] OR "Hydroxymethylglutaryl-CoA Reductase Inhibitors"[Mesh] OR statin[TIAB] OR "atorvastatin"[Supplementary Concept] OR atorvastatin[TIAB] OR "ramipril"[Mesh] OR ramipril[TIAB] OR "ACE inhibitor"[TIAB] OR "Angiotensin-Converting Enzyme Inhibitors"[Mesh]	34,224
	6	"drug combinations"[Mesh] OR (combin*[TIAB] AND (therapy[TIAB] OR treatment[TIAB] OR tablet[TIAB] OR pill[TIAB] OR capsule[TIAB])) OR comedication[TIAB] OR "co medication"[TIAB] OR "fixed dose combination"[TIAB] OR polypill[TIAB] OR education[TIAB] OR support[TIAB] OR information[TIAB]	609,724
	7	5 or 6	636,053
Adherence to polypill components	**8**	4 AND 7	540
Not non-systematic reviews	**9**	review NOT (systematic OR "meta analysis" OR (indirect OR mixed AND "treatment comparison")) OR editorial[Publication Type] OR letter[Publication Type] OR comment[Publication Type]	622,636
Studies for screening	**10**	8 NOT 9	**392**

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184 ***Appendix 3. Inclusion/Exclusion Criteria***

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Criteria	Efficacy review	Humanistic burden review	Economic burden review	Adherence review	Economic models review
Population	People who have had one or more myocardial infarctions at any time and who are eligible for secondary prevention with aspirin or a statin or an ACEI. If unclear: include participants stated to have existing cardiovascular disease and not stated to be ineligible for secondary prevention	As for efficacy review	As for efficacy review	As for efficacy review	As for efficacy review
Intervention	Priority 1: RCTs or SLRs of fixed-dose combination products containing 2 or more of: aspirin or other antiplatelet agent, atorvastatin or other statin, and/or ramipril or other ACEI; or SRs of multiple monotherapy with aspirin, atorvastatin, and/or ramipril Priority 2: SLRs on monotherapy or dual therapy with aspirin, atorvastatin or ramipril Priority 3: SLRs on monotherapy or dual therapy with other antiplatelet agents, other statins, or other ACEIs	Specific interventions for secondary prevention may not be reported in the abstract. If reported, we are interested in QoL in patients receiving the following interventions: Priority 1: fixed-dose combination products containing 2 or more of: aspirin or other antiplatelet agent, atorvastatin or other statin, and/or ramipril or other ACEI; or	Priority 1: Include studies assessing costs or resource use of secondary prevention with multiple monotherapies or fixed-dose combination therapy with antiplatelet drugs, statins or ACEIs Priority 2: studies assessing costs or resource use with other secondary prevention strategies If unclear: include studies reporting costs or resource use in people with existing	Priority 1: fixed-dose combination products containing 2 or more of: aspirin or other antiplatelet agent, atorvastatin or other statin, and/or ramipril or other ACEI; or aspirin, atorvastatin and/or ramipril as monotherapy or combination therapy Priority 2: other antiplatelet agents, other statins, and/or other ACEI as monotherapy or combination therapy	Priority 1: fixed-dose combination products containing 2 or more of: aspirin or other antiplatelet agent, atorvastatin or other statin, and/or ramipril or other ACEI; or aspirin, atorvastatin and/or ramipril as monotherapy or combination therapy Priority 2: other antiplatelet agents, other statins, and/or other ACEI as monotherapy or combination therapy

Criteria	Efficacy review	Humanistic burden review	Economic burden review	Adherence review	Economic models review
		aspirin, atorvastatin and/or ramipril as monotherapy or combination therapy Priority 2: other antiplatelet agents, other statins, and/or other ACEIs as monotherapy or combination therapy	CV disease who are not stated to be ineligible for secondary prevention		
Comparators	Multiple monotherapy with aspirin or other antiplatelet drugs, atorvastatin or other statins, ramipril or other ACEIs Other oral secondary prevention drugs, as monotherapy or combination therapy; Placebo or usual care	Studies may or may not report a comparator group– this may be patients on other secondary prevention therapies, or patients with other diseases (or healthy controls)	Any comparator for secondary prevention No comparator	Multiple monotherapy with aspirin or other antiplatelet drugs, atorvastatin or other statins, ramipril or other ACEIs Educational interventions or healthcare provider support and advice	Multiple monotherapy with aspirin or other antiplatelet drugs, atorvastatin or other statins, ramipril or other ACEIs; Other oral secondary prevention drugs, as monotherapy or combination therapy placebo or usual care
Outcomes	Do not exclude on outcomes at abstract screening stage. At full-text screening: outcomes include: mortality repeat myocardial infarction stroke planned revascularisation for coronary ischaemia/stenosis/angina	Do not exclude on outcomes at abstract screening stage. At full-text screening: outcomes include: Priority 1: Utility values associated with having CV	Do not exclude on outcomes at abstract screening stage. At full-text screening: outcomes include: Direct medical costs of drug treatment Direct medical costs of hospitalisation or other interventions for CV	Do not exclude on outcomes at abstract screening stage. At full-text screening: outcomes include: Objective measures of adherence with treatment eg pill count, prescription refill rates, electronic	Do not exclude on outcomes at abstract screening stage. At full-text screening: outcomes include: ICERs Cost per quality-adjusted life-year Other measures of

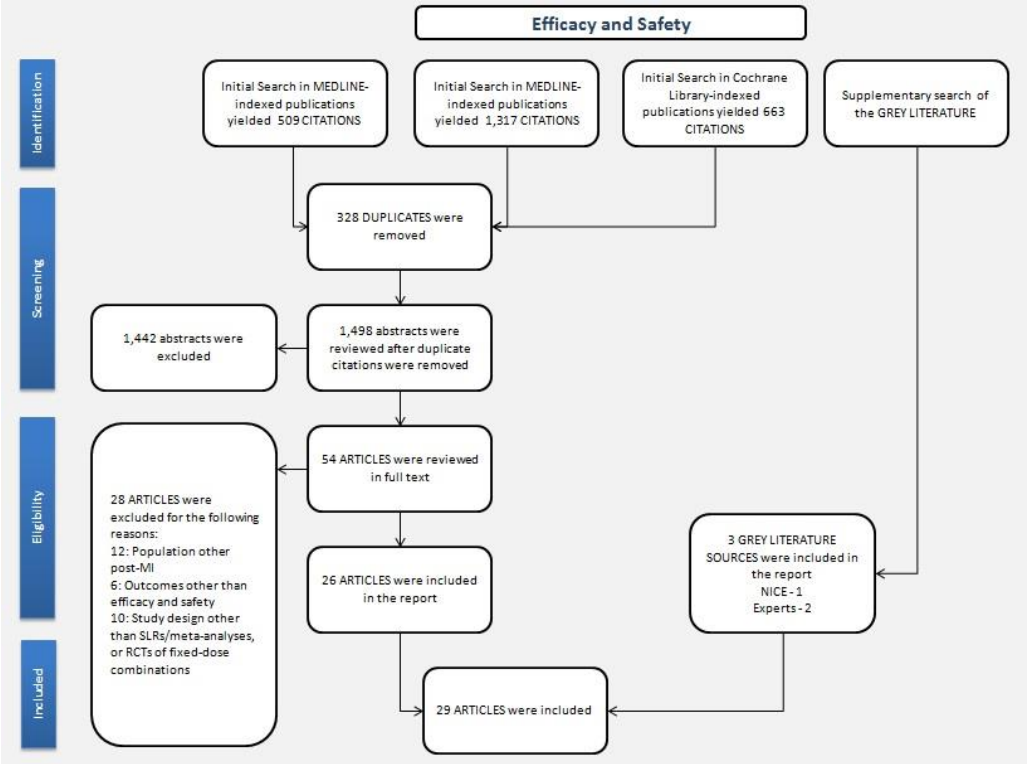
Criteria	Efficacy review	Humanistic burden review	Economic burden review	Adherence review	Economic models review
	admission for heart failure or other CV disease event or intervention	disease or experiencing a CV disease event Priority 2: Other quality-of-life scores in people with CV disease Priority 3: Burden on caregivers of patients with CV disease	disease Resource use by providers, patients and carers including duration of hospital admission Indirect costs including lost productivity Informal costs of caregiving	devices to record opening of container, blood medication levels Patient-reported adherence rates CV disease event rates associated with different levels of adherence with secondary prevention medication	cost-effectiveness
Timepoints/ follow-up	Any	Any	Any	Any	Any
Study type	RCTs (fixed-dose combination products only) SLRs (other interventions)	Primary observational or cohort studies Comparative studies	Primary observational or cohort studies Comparative studies SLRs of these study types	Comparative studies Observational or cohort studies	Cost-effectiveness, cost-benefit or cost-utility studies SLRs of these types of economic model
Publication date	2003–2013 (note: this is publication date of SLR, not the RCTs included in the SLR. At full-text screening we will exclude SLRs that only include RCTs published before 2000, or where >80% of participants in the SLR were from RCTs published before 2000)	2003–2013	2003–2013	2003–2013	2003–2013

Criteria	Efficacy review	Humanistic burden review	Economic burden review	Adherence review	Economic models review
Publication language	English	English	English	English	English
Setting	Any country Primary, secondary or tertiary care as initiator of preventive therapy or follow-up setting	Priority 1: EU5 (France, Germany, Italy, Spain, UK) Priority 2: Other countries	Priority 1: EU5 (France, Germany, Italy, Spain, UK) Priority 2: Other countries	Priority 1: EU5 (France, Germany, Italy, Spain, UK) Priority 2: Other countries	EU5 (France, Germany, Italy, Spain, UK), US, South America

ACEI, angiotensin-converting enzyme inhibitor; ACS, acute coronary syndrome; CV, cardiovascular; ICER, incremental cost-effectiveness ratio; MI, myocardial infarction; QoL, quality of life; RCT, randomized controlled trial; SLR, systematic literature review

Appendix 4. PRISMA Flow of Literature Diagram

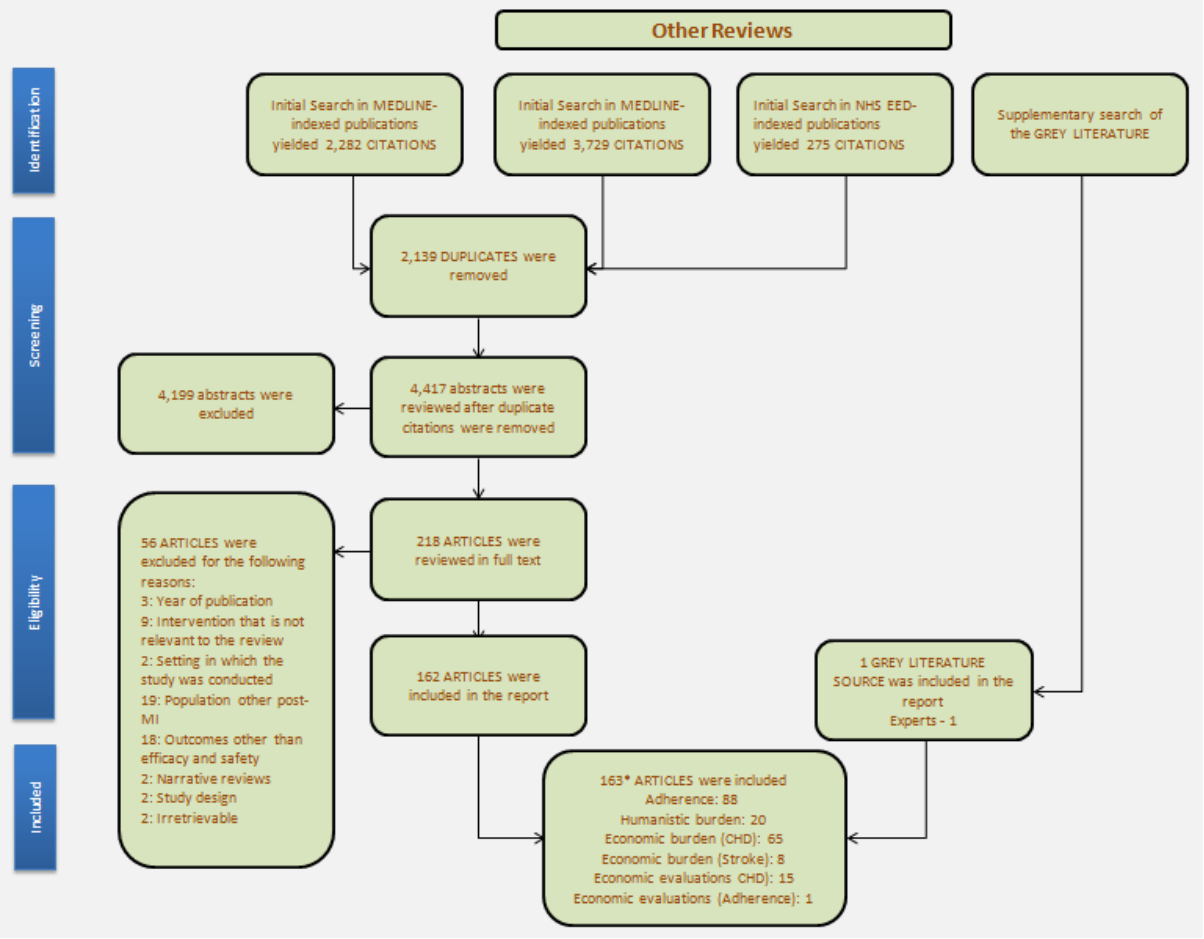
Figure 1. Flow of Literature for Efficacy Review



*Final number of articles is different from the total number of included studies per review topic due to some publications reporting multiple outcomes.

NICE, National Institute for Health and Care Excellence; RCT, Randomised Controlled Trial

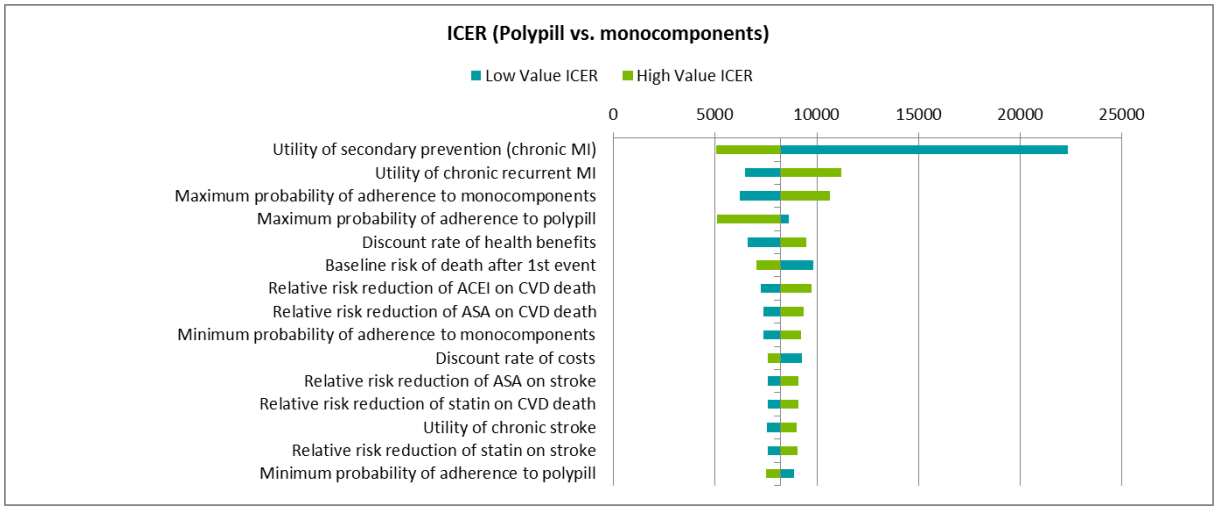
Figure 2. PRISMA Flow of Literature for Other Review Topics

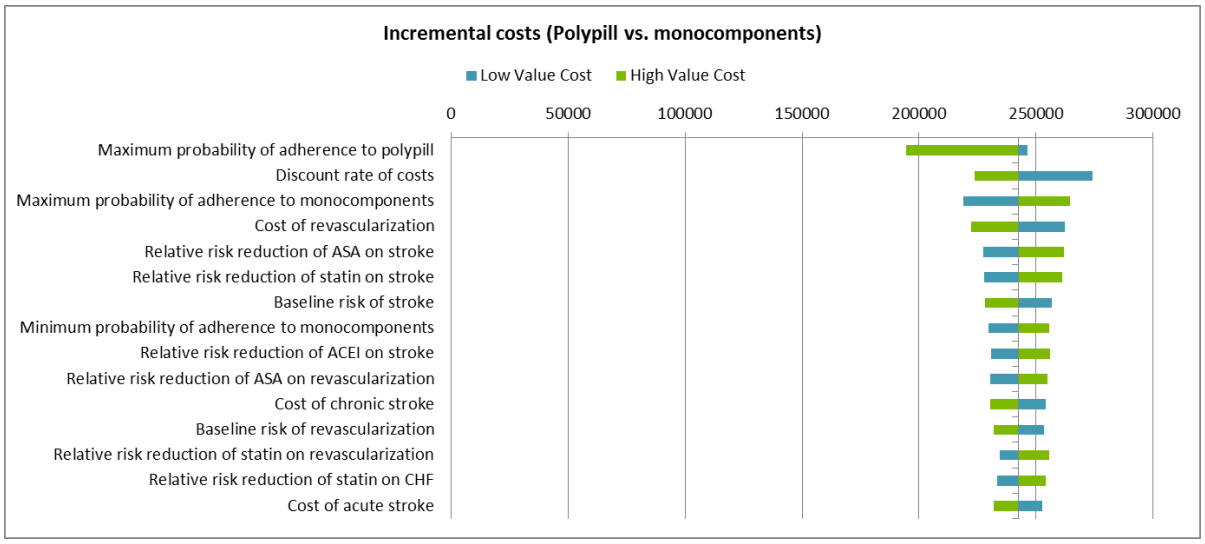


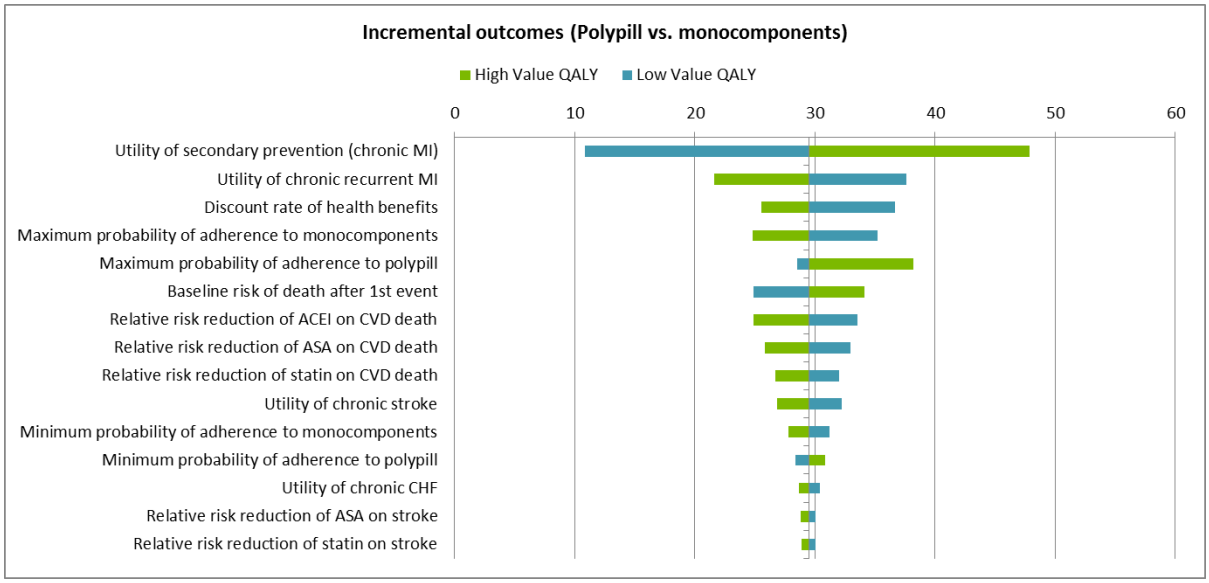
CHD, congestive heart failure

Appendix 5. Additional Model Results for Sensitivity Analysis

Figure 1. Tornado Diagrams from One-way Sensitivity Analysis Showing Variables Most Influential on ICER, Incremental Costs and QALYs







ACEI, angiotensin-converting enzyme inhibitor; ASA, Acetylsalicylic acid; CHF, congestive heart failure; CVD, cardiovascular disease; ICER, incremental cost-effectiveness ratio; MI, myocardial infarction; QoL, quality of life

Figure 2. Cost-effectiveness Plane for Probabilistic Sensitivity Analysis where Incremental Costs and QALYs are per 1000 Patients

QALY, quality-adjusted life-year

Figure 3. Cost-effectiveness Acceptability Curve

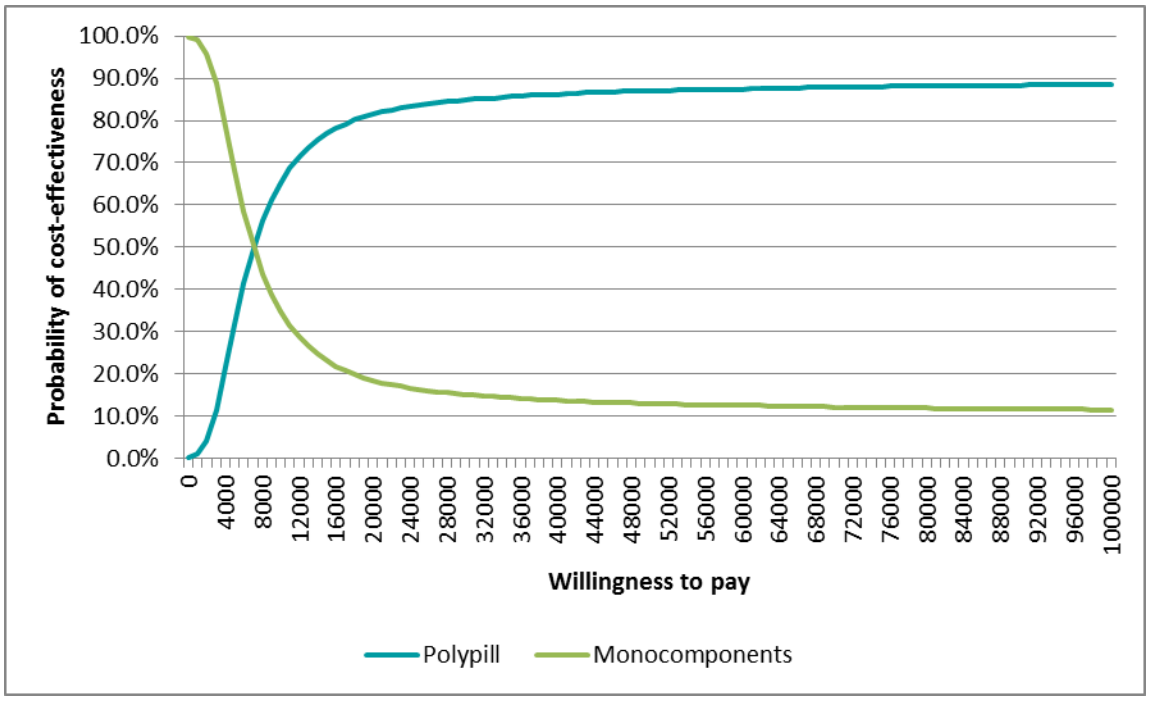
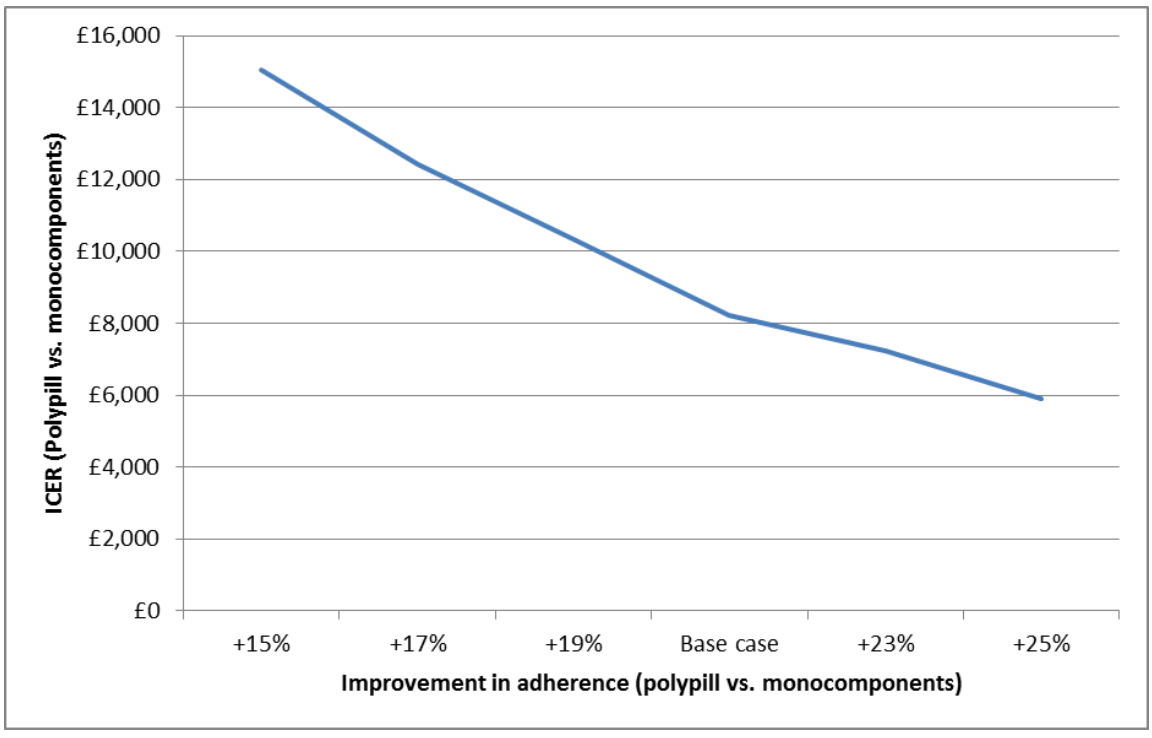
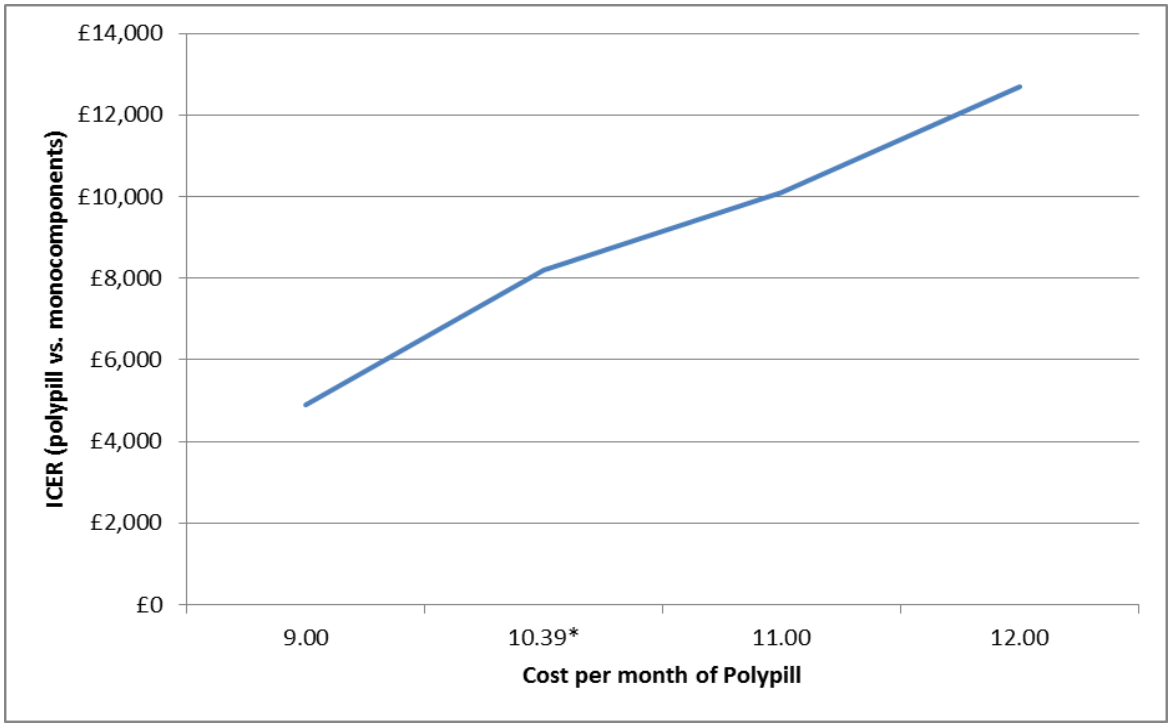


Figure 4. Relationship between ICER and Improvement in Adherence of Polypill over Monocomponents



ICER, incremental cost-effectiveness ratio

Figure 5. Relationship between ICER and Polypill Unit Cost (£) per Month



* - Base case value

ICER, incremental cost-effectiveness ratio