The importance of model structure in the cost-effectiveness analysis of primary care interventions for the management of hypertension

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SUPPLEMENTARY MATERIAL

Appendix 1 Table 1 Model input parameters from the TASMIN-SR model (reproduced from Penaloza-Ramos et al (2015))

Parameter	Input	Sources
CVD risk in patients with DM		
Stroke		
60-69 years old	0.0196	NICE, Diabetes(37)
70-79 years old	0.0262	
80-89 years old	0.0298	
MI		
60-69 years old	0.0089	NICE, Diabetes(37)
70-79 years old	0.0100	
80-89 years old	0.0111	
UA		
60-69 years old	0.0041	NICE, Diabetes(37)
70-79 years old	0.0047	
80-89 years old	0.0052	
CVD risk in patients with CKD		
Stroke		
60-69 years old	0.0072	Kerr et al (2012)(38)
70-79 years old	0.0147	
80-89 years old	0.0189	
MI		
60-69 years old	0.0051	Kerr et al (2012)(38)
70-79 years old	0.0113	
80-89 years old	0.0171	
UA		
60-69 years old	0.0024	Kerr et al (2012)(38)
70-79 years old	0.0054	
80-89 years old	0.0081	
CVD risk in patients with stroke		
Stroke		
60-69 years old	0.0348	PROGRESS (1999) & NICE, Lipid modification guidelines(41, 42)
70-79 years old	0.0590	
80-89 years old	0.0715	
MI		
60-69 years old	0.0139	PROGRESS (1999) & NICE, Lipid modification guidelines(41, 42)
70-79 years old	0.0232	
80-89 years old	0.0232	
UA		
60-69 years old	0.0139	PROGRESS (1999) &

Parameter	Input	Sources
70-79 years old	0.0232	NICE, Lipid modification guidelines(41, 42)
80-89 years old	0.0232	
CVD risk in patients with CHD		
Stroke		
60-69 years old	0.0348	NICE, Lipid modification and Hypertension guidelines(3, 41)
70-79 years old	0.0590	
80-89 years old	0.0715	
MI		
60-69 years old	0.0666	NICE, Lipid modification and Hypertension guidelines(3, 41)
70-79 years old	0.1112	
80-89 years old	0.1112	
UA		
60-69 years old	0.0528	NICE, Lipid modification and Hypertension guidelines(3, 41)
70-79 years old	0.0882	
80-89 years old	0.0882	
Age-related relative risks		
MI, UA – self-management		
60-69 years old	0.63	TASMIN-SR trial & Law at al (2009)(6, 47)
70-79 years old	0.69	
80-89 years old	0.75	
Stroke – self-management		
60-69 years old	0.54	TASMIN-SR trial & Law at al (2009)(6, 47)
70-79 years old	0.59	
80-89 years old	0.75	
MI, UA - usual care		
60-69 years old	0.82	TASMIN-SR trial & Law at al (2009)(6, 47)
70-79 years old	0.85	
80-89 years old	0.88	
Stroke - usual care		
60-69 years old	0.76	TASMIN-SR trial & Law at al (2009)(6, 47)
70-79 years old	0.81	
80-89 years old	0.88	
Cost of death	0	By definition
Annual discount rate for costs	0.035	Gray et al (2011)(53)
Annual discount rate for utility	0.035	Gray et al (2011)(53)
Death utility	0	By definition
Average age of cohort at time of intervention (years)	70	TASMIN-SR trial(6)

Appendix 1 Table 2 Input parameters and their distributions from the TASMIN-SR model (reproduced from Penaloza-Ramos et al (2015)

Description	Input	Distribution	a	b
Probability of death from Stroke	0.23	Beta	125	420
Probability of death from MI	0.23	Beta	155	520
			alpha	lambda
Cost of well state self-monitoring	74	Gamma	1	0.0136
Cost of well state for Usual care arm	62	Gamma	1	0.0161
Cost acute angina	3292	Gamma	1	0.0003
Cost acute MI	5487	Gamma	1	0.0002
Cost acute Stroke	11020	Gamma	1	0.0001
Cost chronic angina	286	Gamma	1	0.0035
Cost chronic MI	286	Gamma	1	0.0035
Cost chronic Stroke	1361	Gamma	1	0.0007
Cost of intervention	35	Gamma	1	0.0286
			mean	s.d.
Multiplier used to adjust for initial health states by age	1	Normal	1	0.0125

Appendix 1 Table 3 Data extraction instrument for the assessment of structural uncertainty for the papers included in the review

Author, year	**Inclusion/exclusion of potentially relevant comparators**	**Health states included/excluded, recurrence of events; type of model**	**Inclusion/exclusion of other assumptions affecting the structure of the model**
Kaambwa et al. [38]	Yes	Yes	Yes
	Authors argued that self-monitoring of hypertension (as a means to lower blood pressure) has been largely evaluated; previous CE results found to be inconsistent plus not been extrapolated to the longer term. Their study examined the long-term cost-effectiveness of self-monitoring combined with self-titration (i.e., self-management) of blood pressure	Four acute health states (Stroke, MI, Angina, and HF) and death were considered. It was not mentioned how health states were identified; authors acknowledged to have made an assumption that CHD consisted of MI, HF and angina (this was reflected in the structure of their Markov model); the risk of secondary events, including progression of disease, was not modelled and was acknowledged as a weakness	Adverse effects such as anxiety or drug side effects were not modelled due to lack of data, however, trial data found minimal differences; effectiveness of the intervention after the year of the trial was unknown however the effect of various potential reductions in efficacy was tested in SA. Lifetime time horizon was tested in SA
Stevanovic et al. [71]	Yes	Yes	Yes
	Authors argued that health and economic consequences of newer anti-hypertensive agents such as ACEIs and ARBs were not available at the time of the study in Netherlands. As a result, authors compared HCT 25 mg (diuretics) versus HCT/ACEIs versus HCT/ARBs versus no treatment	One acute health state (Acute CVD), a chronic health state (Stable CVD) and death were considered. The inclusion of states in the Markov model was not justified. Risk of secondary events was assumed to be equal to the risk of a first non-fatal CVD event. This assumption was acknowledged to lead to an under-estimation of the CVD risk and compensated with the adoption of an increased risk of death in patients experiencing non-fatal CVD events	Adverse effect(s) from antihypertensive treatment was not considered; large uncertainty ranges around the expected values of the SCORE input parameters (model for ten year risk of fatal cardiovascular disease) used in the model for both 10-year and lifetime horizons, as tested through PSA and ANCOVA analyses
Wu et al. [72]	Yes	No	No

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Author, year	Inclusion/exclusion of potentially relevant comparators	Health states included/excluded, recurrence of events; type of model	Inclusion/exclusion of other assumptions affecting the structure of the model
	Comparators resulted from the results of a meta-analysis study indicating that Norvasc (Amlodipine) was superior to ARBs in the prevention of stroke and MI in hypertensive patients.	Two acute (Stroke and MI) and its corresponding chronic health states were considered. No justification was given for the inclusion of states in their Markov model; authors did not discuss the possibility of recurrent events, however they acknowledged as a weakness in the model not including the risk of patients having both stroke and MI due to lack of data	Even though an assumption was adopted that the risk of stroke or MI and the mortality risk during the lifetime of the model (5-years) will remain fixed, this assumption was not tested in SA
Kourlaba et al. [73]	Yes	No	No
	Comparators resulted from answering the research question in light of recent guidelines in Greece for the use of combined therapy to treat hypertension	Two acute (MI and Stroke) health states and its corresponding chronic health states were modelled. No movement from MI to stroke was assumed; it was acknowledged as a limitation; risk of secondary events in their Markov model was not considered; same risk of CVD death was assumed (independently of whether a patient has experienced a previous CVD). None of these assumptions was tested in SA	No evidence or discussion presented on this respect
Ekwunife et al. [74]	Yes	Yes	No
	Comparators were identified from hypertension guidelines in Nigeria	Two acute health states (Stroke and CHD) were modelled and two chronic post event health states. The model reflected the pathway of patients with hypertension starting in an asymptomatic health state, and then moving to a cardiovascular state (CHD or stroke) and death. The authors did not consider secondary events and this was not discussed. The authors used a Markov model	
Wisloff et al.	Yes	Yes	No

Author, year	Inclusion/exclusion of potentially relevant comparators	Health states included/excluded, recurrence of events; type of model	Inclusion/exclusion of other assumptions affecting the structure of the model
[75]	Alternatives were aimed at contribute towards the discussion around intervention thresholds and the choice of first-line drug and 'add on' drugs	Four acute health states (Stroke, AMI, Angina and HF) and two post event health states (Post-Stroke and Post-CVD) were considered. Health events in the Markov model reflected the asymptomatic stages, cardiovascular life and death of patients; the model allowed for secondary events after which the model assumed patients will move to the worst health state; some assumptions regarding risk of secondary events were based on expert opinion. These assumptions were not tested in SA	The authors used observed incidence rates to reflect risk factors using registry data; this was acknowledged as a limitation however was not tested in SA
Granstrom et al. [78]	Yes	Yes	No
	Justified on the grounds that no head to head randomised comparative studies were previously performed comparing Candesartan and Losartan; authors acknowledged as a limitation that there may be ARB comparators more relevant to Candesartan than Losartan in other health care setting	The authors considered health states (HF, PAD and Arrhythmia), post event health states (post-MI and post Stroke) and a chronic health state (IHD). Health states in the Markov model, including post MI and post stroke were based on CVD events measured in a registry study (authors commented and acknowledged a potential risk of confounding); after a CVD event an increased risk of mortality was applied (no SA to test for these assumptions)	
Baker et al. [79]	Yes	Yes	Yes
	Comparators were justified in view of the concerns surrounding non-medical ARB switching after Simvastatin became a generic product leading to a number of patients being switched from branded atorvastatin to generic Simvastatin for economic rather than medical reasons	Health states were designed to reflect the course and history of CVD events in a typical patient with hypertension (CVD event free, post CVD, and death). Although secondary CVD events were not explicitly considered in the model, patients in the post-event state were subject to an increased risk of death reflecting their disease state	The model assumed that Valsartan remained on patent for the first 2.75 years of the model time horizon and Losartan for only 4 months after which generic formulations would become available. No side effects were modelled, which was acknowledged as a weakness
Perman et al.	Yes	Yes	Yes

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Author, year	Inclusion/exclusion of potentially relevant comparators	Health states included/excluded, recurrence of events; type of model	Inclusion/exclusion of other assumptions affecting the structure of the model
[70]	Justified on the basis that previous evidence was favourable for hypertension programmes as compared to drug treatments	The health states were: an acute MI event, no event and death. The inclusion/exclusion of health states in the Markov model was not discussed but rather just introduced; an interesting assumption in the model was that patients presenting an acute CVD event could have or not have hospital attention? Risk of secondary events was considered. This was not tested in SA	The discount rate was considered as a structural variable and thus analyses were performed with different discount rates ranging from 0%-12%
Ekman et al. [76]	Yes	No	Yes
	The comparators corresponded to those found to have mild side effects as per previous clinical trials; it was acknowledged as a weakness not to include other comparators such as diuretics	Four acute health states (Angina, MI, CHF and stroke), a post MI, and post stroke health state were modelled. No particular explanation was given for the inclusion/exclusion of health states. The Markov model assumed that patients may undergo revascularization procedures while in the MI or angina health states; recurrence of events was modelled however acknowledged that data was limited to reflect how risks of recurrent strokes or MIs vary depending on various disease histories.	Treatment effects were supposed to last five years; SA tested the sensitivity of the model to changes in the duration of the antihypertensive treatment and variation of discount rate (between 0% to 8%) and measure of LYG instead of QALYs
Gandjour et al. [68]	Yes	No	No
	Comparators resulted from the research question which is whether the health service can reduce the underuse of hypertensive medication among the German population through a national programme	Three acute health states (MI, stroke and renal failure) were modelled. No particular reason argued for the inclusion/exclusion of health states in the Markov model; treatment and its effect were assumed to last a lifetime; secondary events were not modelled but captured through the mortality rates of patients after a CVD event. Model assumptions were not tested in SA	
Montgomery et al. [69]	Yes	No	No
	Comparators resulted from the research question which is whether incorporating patients' preferences into the decision-making process	A single acute CVD health state was considered with variations to account for the impact of side effects and treatment or lack of it. No explanation was given for the	

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Author, year	Inclusion/exclusion of potentially relevant comparators	Health states included/excluded, recurrence of events; type of model	Inclusion/exclusion of other assumptions affecting the structure of the model
	may have an important influence on treatment recommendations for individual patients	inclusion/exclusion of health states in the Markov model; secondary events were not modelled and the assumption that any second cardiovascular event was fatal was adopted. Model assumptions were not tested in SA	
Nordmann et al. [77]	Yes	No	No
	Comparators were chosen in line with hypertension guidelines for first-line antihypertensive therapy from both, the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure (JNC-VI) and the World Health Organization (WHO)	Three acute health states (CAD, CVD and CHF) were considered. Authors argued to have included the most common CVD outcomes as health states in the Markov model; the model allowed one opportunity to switch from conventional therapy to ACE inhibitors in response to adverse effects or lack of efficacy; recurrence of events was modelled	

Appendix 1 Table 4 Results of cost-effectiveness after increasing /decreasing total costs by 40%

Model structure	Costs	QALYs	Incremental cost	Incremental QALYs	ICER
TASMIN-SR					
Increasing costs					
Usual care	13,805	7.0946			
Self-management	12,596	7.4390	-1,209	0.3444	Dominant
Decreasing costs					
Usual care	5,917	7.0946			
Self-management	5,398	7.4390	-518	0.3444	Dominant
Model 1					
Increasing costs					
Usual care	13,234	6.9102			
Self-management	12,339	7.2311	-895	0.3210	Dominant
Decreasing costs					
Usual care	5,671	6.9102			
Self-management	5,287	7.2311	-384	0.3210	Dominant
Model 2					
Increasing costs					
Usual care	13,797	7.1612			
Self-management	12,402	7.5057	-1,394	0.3445	Dominant
Decreasing costs					
Usual care	5,913	7.1612			
Self-management	5,315	7.5057	-598	0.3445	Dominant
Model 3					
Increasing costs					

The importance of model structure in the CEA

Model structure	Costs	QALYs	Incremental cost	Incremental QALYs	ICER
Usual care	13,574	5.9274			
Self-management	12,819	6.2721	-755	0.3446	Dominant
Decreasing costs					
Usual care	7,069	5.9274			
Self-management	6,607	6.2721	-462	0.3446	Dominant
Model 4					
Increasing costs					
Usual care	16,097	7.0489			
Self-management	14,464	7.4085	-1,633	0.3596	Dominant
Decreasing costs					
Usual care	6,899	7.0489			
Self-management	6,199	7.4085	-700	0.3596	Dominant

Appendix 1 Table 5 Results of cost-effectiveness after increasing /decreasing total costs by 200% and 50% respectively

Model structure	Costs	QALYs	Incremental cost	Incremental QALYs	ICER
TASMIN-SR					
Increasing costs 200%					
Usual care	19,728	7.0946			
Self-management	17,899	7.4390	-1,829	0.3444	Dominant
Decreasing costs 50%					
Usual care	4,931	7.0946			
Self-management	4,550	7.4390	-382	0.3444	Dominant
Model 1					
Increasing costs 200%					
Usual care	18,905	6.9102			
Self-management	17,528	7.2311	-1,376	0.3210	Dominant
Decreasing costs 50%					
Usual care	4,726	6.9102			
Self-management	4,455	7.2311	-271	0.3210	Dominant
Model 2					
Increasing costs 200%					
Usual care	19,717	7.1612			
Self-management	17,626	7.5057	-2,091	0.3445	Dominant
Decreasing costs 50%					
Usual care	4,928	7.1612			
Self-management	4,479	7.5057	-449	0.3445	Dominant

The importance of model structure in the CEA

Model structure	Costs	QALYs	Incremental cost	Incremental QALYs	ICER
Model 3					
Increasing costs 200%					
Usual care	19,396	5.9274			
Self-management	18,218	6.2721	-1,179	0.3446	Dominant
Decreasing costs 50%					
Usual care	4,848	5.9274			
Self-management	4,628	6.2721	-220	0.3446	Dominant
Model 4					
Increasing costs 200%					
Usual care	31,071	7.0489			
Self-management	27,771	7.4085	-3,301	0.3596	Dominant
Decreasing costs 50%					
Usual care	7,766	7.0489			
Self-management	7,011	7.4085	-755	0.3596	Dominant

Appendix 1 Table 6 Results of cost-effectiveness after altering the time horizon

Model structure	Costs	QALYs	Incremental cost	Incremental QALYs	ICER
TASMIN-SR					
10 years					
Usual care	5,860	5.1741			
Self-management	5,237	5.3506	-623	0.1765	Dominant
5 years					
Usual care	3,109	3.2475			
Self-management	2,753	3.3079	-356	0.0605	Dominant
3 years					
Usual care	1,792	2.1372			
Self-management	1,626	2.1564	-166	0.0192	Dominant
2 years					
Usual care	1,173	1.4889			
Self-management	1,110	1.4957	-63	0.0068	Dominant
1 year					
Usual care	629	0.7791			
Self-management	652	0.7797	23	0.0006	35,391
Model 1					
10 years					
Usual care	5,729	5.1310			
Self-management	5,231	5.3029	-498	0.1719	Dominant
5 years					
Usual care					

The importance of model structure in the CEA

Model structure	Costs	QALYs	Incremental cost	Incremental QALYs	ICER
	3,066	3.2371			
Self-management	2,762	3.2955	-304	0.0584	Dominant
3 years					
Usual care	1,772	2.1331			
Self-management	1,630	2.1516	-141	0.0185	Dominant
2 years					
Usual care	1,162	1.4871			
Self-management	1,111	1.4937	-51	0.0066	Dominant
1 year					
Usual care	624	0.7788			
Self-management	650	0.7795	25	0.0006	40,799
Model 2					
10 years					
Usual care	5,738	5.2904			
Self-management	5,045	5.4608	-692	0.1704	Dominant
5 years					
Usual care	2,923	3.3047			
Self-management	2,565	3.3580	-357	0.0533	Dominant
3 years					
Usual care	1,644	2.1624			
Self-management	1,492	2.1786	-152	0.0161	Dominant
2 years					
Usual care	1,066	1.5018			
Self-management			-52	0.0056	

The importance of model structure in the CEA

Model structure	Costs	QALYs	Incremental cost	Incremental QALYs	ICER
	1,014	1.5075			Dominant
1 year					
Usual care	566	0.7830			
Self-management	593	0.7835	27	0.0005	50,960
Model 3					
10 years					
Usual care	6,114	4.4454			
Self-management	5,641	4.6811	-473	0.2357	Dominant
5 years					
Usual care	3,481	2.9515			
Self-management	3,132	3.0489	-348	0.0974	Dominant
3 years					
Usual care	2,100	2.0112			
Self-management	1,903	2.0448	-197	0.0336	Dominant
2 years					
Usual care	1,402	1.4255			
Self-management	1,314	1.4378	-89	0.0123	Dominant
1 year					
Usual care	771	0.7607			
Self-management	785	0.7619	14	0.0012	11,701
Model 4					
10 years					
Usual care	6,880	5.2107			
Self-management			-905	0.1696	

The importance of model structure in the CEA

Model structure	Costs	QALYs	Incremental cost	Incremental QALYs	ICER
	5,975	5.3803			Dominant
5 years					
Usual care	3,470	3.2711			
Self-management	2,985	3.3237	-485	0.0527	Dominant
3 years					
Usual care	1,889	2.1446			
Self-management	1,685	2.1611	-203	0.0165	Dominant
2 years					
Usual care	1,194	1.4907			
Self-management	1,123	1.4969	-71	0.0062	Dominant
1 year					
Usual care	629	0.7791			
Self-management	652	0.7797	23	0.0007	35,334

Appendix 1 Table 7 Results of cost-effectiveness in Model 4 after increasing/decreasing the probability of having a second event

Model structure	Costs	QALYs	Incremental cost	Incremental QALYs	ICER
Model 4					
Doubling the probability of having a second event					
Usual care	1,5528	6.0034			
Self-management	1,3925	6.3859	-1,603	0.3825	Dominant
Halving the probability of having a second event					
Usual care	8,213	7.9957			
Self-management	7,351	8.2767	-862	0.2810	Dominant