1 Economic Models for Stable Chest Pain

1.1 Replicated Mowatt 2008 short-term diagnostic Economic Model with Revised Assumptions and Addition of Calcium Scoring Treatment Arms.

1.1.1 Introduction

The Mowatt et al HTA for 64-slice CT coronary angiography scanning included a short-term diagnostic economic model (Mowatt, G., Cummins, E., Waugh, N. et al, 2008). The model results were very favourable to 64-slice CT coronary angiography. The GDG felt that some of the modelled assumptions were over-optimistic in favour of 64-slice CT coronary angiography. Consequently, the guideline health economist was asked to replicate the model with a view to exploring the clinical and health economic implications of alternative model assumptions. We acknowledge the help of the developers of the HTA models who provided a template of their short-term model. Here we present some results from having replicated and revised the Mowatt et al model. The key revisions are to reduce the test sensitivity of 64-slice CT coronary angiography, and to add additional treatment arms which begin with calcium scoring using a 64-slice CT scanner. The latter was done because of concerns about radiation exposure for patients who might be subjected to repeat MSCT coronary angiography.

1.1.2 Methods and Model Assumptions

Using the model structure used by Mowatt and colleagues in their 2008 HTA (Mowatt, G., Cummins, E., Waugh, N. et al, 2008), their short term diagnostic model was rebuilt using Microsoft Excel™. The excel model was validated by replicating their base case results. The original HTA presented results for assumed CAD prevalence (pre-test likelihood) rates of 10%, 30%, 50% and 70%. In the following analyses model outputs are presented for a cohort of 1000 patients at assumed CAD prevalence of 5%, 20%, 40%, 60% and 80% respectively.

Ten diagnostic strategies have been modeled, the first eight of which represent the sequences presented by Mowatt and colleagues (Mowatt, G., Cummins, E., Waugh, N. et al, 2008). The two additional strategies incorporate calcium scoring as a rule out strategy prior to 64-slice CT coronary angiography.

Test	**Strategy 1**	**Strategy 2**	**Strategy 3**	**Strategy 4**	**Strategy 5**	**Strategy 6**	**Strategy 7**	**Strategy 8**	**Strategy 9**	**Strategy 10**
1st	ECG	ECG	ECG	MPS	CT	CA	ECG	CT	Ca Score	Ca Score
2nd	MPS	CT	CA	CA	CA	-	CT	-	CT	CT
3rd	CA	CA	-	-	-	-	-	-	-	CA

ECG=exercise ECG; MPS = MPS with SPECT; CA=invasive coronary angiography; CT=64-slice CT coronary angiography; Ca Score=calcium scoring with 64-slice CT scanner.

The treatment protocol assumptions are that patients only move on to subsequent tests if they test positive or indeterminate for the initial test(s). Patients who test negative are not subjected to further testing. For example, in strategy 1, exercise ECG is the first diagnostic test. Patients having an indeterminate or positive exercise test result move on to the second line MPS with SPECT. Patients having a positive or indeterminate MPS with SPECT result then have invasive coronary angiography as a final test. Strategies 6 and 8 assume that patients are sent straight to and only have invasive coronary angiography or 64-slice CT coronary angiography, respectively. In Strategies 1 to 6 and 10, patients testing positive always end up having an invasive coronary angiography as final confirmatory test. Strategies 7, 8 and 9 assume that only those patients who have an indeterminate result after 64-slice CT coronary angiography will go on to invasive coronary angiography in order to ensure that all patients end with a definitive diagnosis. The model assumes that invasive coronary angiography is the ‘gold standard’ and assigns 100% diagnostic sensitivity and specificity to this test.

The input assumptions required by the model for each of the 5 diagnostic technologies are the diagnostic sensitivity and specificity, a small risk of

immediate mortality induced by the test, the probability that the test is indeterminate and the estimated cost of the test. Table 1 summarises the model inputs used in the base case analysis.

Table 1: Base Case Model Parameters

Test	Value	Source
Exercise ECG		
Sensitivity	67%	(Mowatt, G., Cummins, E., Waugh, N. et al, 2008)
Specificity	69%	(Mowatt, G., Cummins, E., Waugh, N. et al, 2008)
Indeterminacy	24%	(Mowatt, G., Cummins, E., Waugh, N. et al, 2008)
Mortality Risk	0.005%	(Mowatt, G., Cummins, E., Waugh, N. et al, 2008)
Cost	£66	(Mowatt, G., Cummins, E., Waugh, N. et al, 2008)
MPS with SPECT		
Sensitivity	86%	(Mowatt, G., Cummins, E., Waugh, N. et al, 2008)
Specificity	64%	(Mowatt, G., Cummins, E., Waugh, N. et al, 2008)
Indeterminacy	6%	(Mowatt, G., Cummins, E., Waugh, N. et al, 2008)
Mortality Risk	0.005%	(Mowatt, G., Cummins, E., Waugh, N. et al, 2008)
Cost	£293	(Mowatt, G., Cummins, E., Waugh, N. et al, 2008)
Calcium Scoring (>0) with MSCT		
Sensitivity	89%	(Kitamura, A., Kobayashi, T., Ueda, K. et al, 2005)
Specificity	43%	(Kitamura, A., Kobayashi, T., Ueda, K. et al, 2005)
Indeterminacy	2%	(Dewey, M. and Hamm, B., 2007)
Mortality Risk	0.000%	(Dewey, M. and Hamm, B., 2007)
Cost	£103	Expert opinion
64-slice CT coronary angiography		
Sensitivity	80%	Expert opinion

Specificity	89%	(Mowatt, G., Cummins, E., Waugh, N. et al, 2008)
Indeterminacy	2%	(Mowatt, G., Cummins, E., Waugh, N. et al, 2008)
Mortality Risk	0.001%	Expert opinion
Cost CT alone	£206	(Mowatt, G., Cummins, E., Waugh, N. et al, 2008)
Cost after calcium scoring	£103	(Dewey, M. and Hamm, B., 2007); Expert opinion
Invasive coronary angiography		
Sensitivity	100%	Assumption
Specificity	100%	Assumption
Indeterminacy	0%	Assumption
Mortality Risk	0.020%	Expert opinion
Cost	£850	(Department of Health, 2008); (Sculpher, M., Smith, D., Clayton, T. et al, 2002)

1.1.3 Revisions to Mowatt base case assumptions

The base case model inputs used in this analysis include some key revisions from the Mowatt et al 2008 (Mowatt, G., Cummins, E., Waugh, N. et al, 2008) base case. Following discussions at the October 2008 GDG meeting, some GDG members indicated that they considered that the diagnostic sensitivity of 99%, attributed to 64-slice CT coronary angiography, was over-optimistic. This figure was derived from a systematic review, which primarily used a threshold of 50% stenosis to define presence of CAD. GDG members indicated that more recent papers, using a CAD threshold of 70% stenosis, showed 64-slice CT coronary angiography to have a test sensitivity of around 80%. (Expert opinion). The GDG also suggested revised estimates for the risk of immediate mortality from invasive coronary angiography which was subsequently reduced from the 0.15% used by Mowatt and colleagues to 0.02% in the new base case. Also, a 1 in 80,000 risk of mortality from reaction to contrast in patients undergoing 64-slice CT coronary angiography was introduced at the request of the GDG.

In their 2008 HTA, Mowatt and colleagues (Mowatt, G., Cummins, E., Waugh, N. et al, 2008) indicate that the cost of invasive coronary angiography may have been underestimated in their analysis. Indeed their base case estimate of £320 seems low compared with other published estimates. For example, an estimate close to £1,300 was used in the EMPIRE study (Underwood, S. R., Godman, B., Salyani, S. et al, 1999) and in the Mowatt 2004 HTA (Mowatt, G., Vale, L., Brazzelli, M. et al, 2004) evaluating the use of MPS with SPECT. More recent publications and the NHS reference costs suggest that the cost of invasive coronary angiography is £832 (Sculpher, M., Smith, D., Clayton, T. et al, 2002) or higher (2006/07 NHS reference costs (Department of Health, 2008) HRG code EA41z). For the revised model we have assumed a base case invasive coronary angiography cost of £850.

In addition to the above revisions, the Mowatt 2008 model was expanded to include two additional arms to evaluate calcium scoring as a rule out strategy prior to 64-slice CT coronary angiography. The inputs for calcium scoring were taken from two sources: indeterminacy was taken from an analysis by Dewey and Hamm (Dewey, M. and Hamm, B., 2007) and sensitivity and specificity were taken from a study identified in the clinical search, (Kitamura, A., Kobayashi, T., Ueda, K. et al, 2005)\which scored coronary calcification using 4-slice CT coronary angiography. In the base case, an Agatston score threshold of >0 was used to define a positive diagnosis of significant CAD. Dewey and Hamm (Dewey, M. and Hamm, B., 2007) calculate the cost of doing calcium scoring as roughly 54% of the cost of MSCT coronary angiography. This figure was confirmed by the GDG who stated that calcium scoring represents the first 50% of the cost of a complete 64-slice CT coronary angiography. Therefore, the cost of calcium scoring used in the model is £103 (50% of the cost of 64-slice CT coronary angiography as defined by Mowatt et al (Mowatt, G., Cummins, E., Waugh, N. et al, 2008)). The GDG also advised that the cost of doing 64-slice CT coronary angiography following calcium scoring is the remaining 50% of the total cost of 64-slice CT coronary angiography. For strategies where calcium scoring

is not a discrete step in the diagnostic pathway, the full cost of £206 is used for 64-slice CT coronary angiography.

1.1.4 Model Outputs

Like the 2008 HTA (Mowatt, G., Cummins, E., Waugh, N. et al, 2008) on 64-slice CT coronary angiography, this model calculates the short-term diagnostic cost for each of the defined strategies. Our model also presents the full two by two true-false, positive-negative matrix. We also presented an incremental economic analysis using the incremental cost per correctly diagnosed case. There is evidence from the 2004 HTA on MPS with SPECT that this ICER is a close proxy to the value of the longer-term cost per QALY ICER for higher levels of modelled CAD prevalence (Mowatt, G., Vale, L., Brazzelli, M. et al, 2004).

1.1.5 Base Case Results

Table 2 summarises the results of a 1000 patient cohort in the base case analysis at a range of modelled prevalence rates (5%, 20%, 40%, 60% and 80%). As prevalence increases, total costs increase and the proportion of accurate diagnoses decreases.

Table 2: Total costs and outcomes for 1000 patient cohort for each diagnostic strategy at each level of CAD prevalence modelled.

Prevalence	Strategy	Description	Total Cost	% Accurately Diagnosed	FP	FN	Total Deaths	CAD Negative Deaths
5%	9	Ca-CT	£164,211	92.66%	59.3	14.1	0.01	0.01
	7	ECG-CT	£175,104	93.14%	48.7	19.9	0.06	0.05
	8	CT	£223,000	88.78%	102.4	9.8	0.02	0.02
	2	ECG-CT-CA	£241,463	98.00%	0	19.9	0.07	0.06
	10	Ca-CT-CA	£254,407	98.58%	0	14.1	0.03	0.02
	5	CT-CA	£343,367	99.02%	0	9.8	0.04	0.04
	1	ECG-MPS-CA	£389,989	98.24%	0	17.5	0.12	0.11
	3	ECG-CA	£481,867	98.73%	0	12.5	0.15	0.14
	4	MPS-CA	£651,597	99.33%	0	6.6	0.13	0.12
	6	CA	£850,000	99.98%	0	0	0.2	0.19
20%	9	Ca-CT	£169,056	89.36%	49.9	56.5	0.01	0.01
	7	ECG-CT	£184,255	87.94%	41	79.5	0.06	0.05
	8	CT	£223,000	87.45%	86.2	39.2	0.02	0.01
	2	ECG-CT-CA	£318,964	92.04%	0	79.5	0.09	0.05
	10	Ca-CT-CA	£341,282	94.34%	0	56.5	0.05	0.02
	5	CT-CA	£429,581	96.07%	0	39.2	0.07	0.03
	1	ECG-MPS-CA	£460,801	93.00%	0	69.9	0.13	0.09
	3	ECG-CA	£516,749	94.97%	0	50.2	0.16	0.12
	4	MPS-CA	£711,519	97.35%	0	26.3	0.15	0.1
	6	CA	£850,000	99.98%	0	0	0.2	0.16
40%	9	Ca-CT	£175,516	84.95%	37.4	113.1	0.01	0
	7	ECG-CT	£196,457	81.01%	30.8	159	0.06	0.03
	8	CT	£223,000	85.69%	64.7	78.4	0.02	0.01
	2	ECG-CT-CA	£422,297	84.08%	0	159	0.11	0.04
	10	Ca-CT-CA	£457,116	88.69%	0	113.1	0.08	0.01

	5	CT-CA	£544,534	92.15%	0	78.4	0.09	0.02
	1	ECG-MPS-CA	£555,216	86.01%	0	139.7	0.15	0.07
	3	ECG-CA	£563,259	89.95%	0	100.3	0.17	0.09
	4	MPS-CA	£791,415	94.72%	0	52.6	0.17	0.08
	6	CA	£850,000	99.98%	0	0	0.2	0.12
60%	9	Ca-CT	£181,976	80.54%	24.9	169.6	0.01	0
	7	ECG-CT	£208,659	74.09%	20.5	238.6	0.06	0.02
	8	CT	£223,000	83.93%	43.1	117.6	0.02	0.01
	2	ECG-CT-CA	£525,631	76.13%	0	238.6	0.14	0.03
	10	Ca-CT-CA	£572,950	83.03%	0	169.6	0.1	0.01
	3	ECG-CA	£609,769	84.93%	0	150.5	0.18	0.06
	1	ECG-MPS-CA	£649,632	79.02%	0	209.6	0.18	0.04
	5	CT-CA	£659,486	88.23%	0	117.6	0.12	0.02
	6	CA	£850,000	99.98%	0	0	0.2	0.08
	4	MPS-CA	£871,311	92.09%	0	79	0.19	0.05
80%	9	Ca-CT	£188,436	76.14%	12.5	226.1	0.01	0
	7	ECG-CT	£220,861	67.16%	10.3	318.1	0.06	0.01
	8	CT	£223,000	82.16%	21.6	156.8	0.02	0
	2	ECG-CT-CA	£628,965	68.17%	0	318.1	0.16	0.01
	3	ECG-CA	£656,278	79.92%	0	200.6	0.19	0.03
	10	Ca-CT-CA	£688,784	77.37%	0	226.1	0.13	0
	1	ECG-MPS-CA	£744,048	72.03%	0	279.5	0.2	0.02
	5	CT-CA	£774,439	84.31%	0	156.8	0.15	0.01
	6	CA	£850,000	99.98%	0	0	0.2	0.04
	4	MPS-CA	£951,207	89.45%	0	105.3	0.2	0.03

Results of the incremental cost-effectiveness analysis are presented in Table 3. Diagnostic strategies are ranked in order of increasing cost and incremental cost-effectiveness ratios are calculated as the additional cost per additional accurate diagnosis. Table 3 does not include strategies that were excluded through dominance or extended dominance. At all levels of modelled CAD prevalence, MPS with SPECT is excluded through dominance or extended dominance, and therefore does not appear in the table of incremental results.

Table 3: Total costs, outcomes and incremental cost-effectiveness of each non-dominated and non-extendedly dominated diagnostic strategy for hypothetical cohort of 1000 patients

Prevalence	Strategy	Description	Total Cost	% Accurately Diagnosed	FP	FN	ICER (cost per correct diagnosis)
5%	9	Ca-CT	£164,211	92.66%	59.3	14.1	
	2	ECG-CT-CA	£241,463	98.00%	0	19.9	£1,466
	10	Ca-CT-CA	£254,407	98.58%	0	14.1	£2,234
	5	CT-CA	£343,367	99.02%	0	9.8	£20,605
	6	CA	£850,000	99.98%	0	0	£52,530
20%	9	Ca-CT	£169,056	89.36%	49.9	56.5	
	10	Ca-CT-CA	£341,282	94.34%	0	56.5	£3,454
	5	CT-CA	£429,581	96.07%	0	39.2	£5,099
	6	CA	£850,000	99.98%	0	0	£10,732
40%	9	Ca-CT	£175,516	84.95%	37.4	113.1	
	6	CA	£850,000	99.98%	0	0	£4,488
60%	9	Ca-CT	£181,976	80.54%	24.9	169.6	
	8	CT	£223,000	83.93%	43.1	117.6	£1,213
	6	CA	£850,000	99.98%	0	0	£3,906
80%	9	Ca-CT	£188,436	76.14%	12.5	226.1	
	8	CT	£223,000	82.16%	21.6	156.8	£574
	6	CA	£850,000	99.98%	0	0	£3,519

Results indicate that strategy 9 (Ca Score – CT) is the least cost option at all levels of CAD prevalence, but gives rise to a non-negligible number of false positives and false negatives. At 5% CAD prevalence, the move to strategy 2 (exercise ECG – CT – CA) from strategy 9 has a favourable incremental cost-effectiveness, but it is worth highlighting that while the number of false positive diagnoses falls to 0, the number of false negatives increases by 5.8. Strategy 10 (Ca Score – CT – CA) has a favourable incremental cost-effectiveness over

strategy 2. If, due to its increased number of false negatives, strategy 2 is removed from the incremental analysis, the incremental cost per correct diagnosis of strategy 10 compared to strategy 9 is £1,523. Strategies 5 (CT – CA) and 6 (CA only), though more effective, are considerably more expensive, with each additional correct diagnosis costing £20,605 and £52,530, respectively compared to the next most effective strategies.

At 20% CAD prevalence, the move to strategy 10 (Ca Score – CT – CA) from strategy 9 is likely to be considered cost-effective, as is the further move to strategy 5 (CT – CA). Strategy 6 is the most effective and most costly, with additional correct diagnoses costing £10,732 each compared to strategy 5.

At higher levels of prevalence (40%, 60% and 80%) the ICER for the move from strategy 9 (Ca Score – CT) to strategy 6 (CA only) is likely to be considered cost-effective. At 60% and 80%, strategy 8 (CT only) appears to have a favourable incremental cost-effectiveness compared to strategy 9, but it is worth pointing out the increased number of false positives arising from this move. These false positives are more than offset by a substantial decrease in the number of false negatives identified, but the most clinically and cost-effective option in this high prevalence population is likely to be strategy 6 (CA only).

1.1.6 Sensitivity Analysis

The following sensitivity analyses use the above base case assumptions, except that in each case one variable has been altered. The GDG was interested in looking at how further reducing the specificity of 64-slice CT coronary angiography would affect the relative cost-effectiveness of 64-slice CT coronary angiography based strategies. Additionally, there was interest in how increasing the calcium score threshold used to define positive diagnosis might affect calcium scoring based strategies' relative cost-effectiveness.

1.1.6.1 Reduced specificity of 64-slice CT coronary angiography

The following sensitivity analysis uses the above base case assumptions, except that the specificity of 64-slice CT coronary angiography is reduced from 89% to 67%. This reflects the less favourable results emerging from recent multi-centre studies. It is worth pointing out that the base case presented above had already reduced sensitivity of 64-slice CT coronary angiography from 99% in Mowatt 2008 (Mowatt, G., Cummins, E., Waugh, N. et al, 2008) to 80%.

Results of this sensitivity analysis compared with the base case are summarised in table 4. When specificity of 64-slice CT coronary angiography is reduced to 67%, strategy 9 (Ca score – CT) remains the least cost option, but gives rise to a substantial number of false positives. At 5% CAD prevalence, strategy 7 (exercise ECG – CT) was excluded through extended dominance in the base case, but emerges as a potentially cost-effective option in this sensitivity analysis. However, strategy 2 (exercise ECG – CT – CA) is likely to be a better option than strategy 7 given its incremental cost-effectiveness and dramatically reduced number of false positives. Strategy 10 (Ca score – CT – CA) is still likely to be cost-effective, although with a much higher incremental cost-effectiveness ratio at 5% CAD prevalence than in the base case. However, at 20% CAD prevalence, the ICER for strategy 10 over strategy 9 is much lower than in the base case, as the incremental benefit, in terms of correct diagnoses, between the strategies is much larger in the sensitivity analysis than the base case. Strategy 10 would ensure there are no false positive diagnoses and minimise the number of false negatives (14.1 and 56.5 at 5% and 20% CAD prevalence, respectively).

At 40% CAD prevalence and above, the most cost-effective strategy is still sending all patients directly for invasive coronary angiography.

Table 4: Incremental cost per accurate diagnosis and false positive and negative outcomes: reduced specificity value for CT.

Prevalence	Strategy	Description	ICER SA	ICER Base Case	SA FP	SA FN	Base Case FP	Base Case FN
5%								
	9	Ca Score - CT			177.8	14.1	59.3	14.1
	7	ECG - CT	£421	ext dom.	146.1	19.9	48.7	19.9
	2	ECG - CT - CA	£1,021	£1,466	0	19.9	0	19.9
	10	Ca Score - CT - CA	£5,335	£2,234	0	14.1	0	14.1
	5	CT-CA	ext dom.	£20,605	0	9.8	0	9.8
	6	CA	£35,383	£52,530	0	0	0	0
20%								
	9	Ca Score - CT			149.7	56.5	49.9	56.5
	10	Ca Score - CT - CA	£1,718	£3,454	0	56.5	0	56.5
	5	CT-CA	ext dom.	£5,099	0	39.2	0	39.2
	6	CA	£7,515	£10,732	0	0	0	0
40%								
	9	Ca Score - CT			112.3	113.1	37.4	113.1
	6	CA	£2,996	£4,488	0	0	0	0
60%								
	9	Ca Score - CT			74.8	169.6	24.9	169.6
	8	CT	dominated	£1,213	129.4	117.6	43.1	117.6
	6	CA	£2,735	£3,906	0	0	0	0
80%								
	9	Ca Score - CT			37.4	226.1	12.5	226.1
	8	CT	£821	£574	64.7	156.8	21.6	156.8
	6	CA	£2,833	£3,519	0	0	0	0

1.1.6.2 Increasing Calcium Score Threshold

The base case demonstrated that calcium scoring as an initial test in the low risk groups is very likely to be cost-effective. In the base case an Agatston score threshold of >0 was used to define a positive diagnosis warranting further testing with 64-slice CT coronary angiography. This threshold was chosen because diagnostic studies have shown it to have very high sensitivity and negative predictive value which makes it an excellent test for ruling out CAD. However, a

>0 threshold has a poor specificity which means that many people who do not have CAD will receive a false positive diagnosis and go on for further unnecessary testing. By increasing the threshold score for positive diagnosis to >100, the sensitivity of calcium scoring decreases to 72%, but the specificity increases to 81% (Kitamura, A., Kobayashi, T., Ueda, K. et al, 2005).

Table 6 summarises the results of this sensitivity analysis and compares them to those generated in the base case. When the calcification threshold is increased to a minimum score of 100, strategy 9 (Ca Score – CT) remains the least cost option at all levels of CAD prevalence, but strategy 10 (Ca Score – CT – CA) performs less favourably than in the base case. At 5% CAD prevalence, strategy 10 is still likely to be cost-effective, but with an increased ICER of £2,183 over strategy 9. In this scenario, strategy 2 (exercise ECG – CT – CA) is ruled out through extended dominance. At 20% CAD prevalence, strategy 10 is ruled out through extended dominance. Therefore, at 20% CAD prevalence, strategy 5 may be a cost-effective option (ICER = £4,764 compared to strategy 9). At 40% CAD prevalence and greater, a strategy of sending all patients directly to invasive coronary angiography is still likely to be cost-effective.

Table 5: Incremental cost per accurate diagnosis and false positive and negative outcomes: increased Agatston score threshold for coronary calcification (>100).

					SA		Base Case	
Prevalence	**Strategy**	**Description**	**ICER (Ca Score >100)**	**ICER Base Case**	**FP**	**FN**	**FP**	**FN**
5%	9	Ca Score - CT			21.1	20.8	59.3	14.1
	2	ECG-CT-CA	ext. dom	£1,466	0	19.9	0	19.9
	10	Ca Score - CT - CA	£2,183	£2,234	0	20.8	0	14.1
	5	CT-CA	£15,489	£20,605	0	9.8	0	9.8
	6	CA	£52,530	£52,530	0	0	0	0
20%	9	Ca Score - CT			17.8	83.3	49.9	56.5
	10	Ca Score - CT - CA	ext dom.	£3,454	0	83.3	0	56.5
	5	CT-CA	£4,764	£5,099	0	39.2	0	39.2
	6	CA	£10,762	£10,732	0	0	0	0
40%	9	Ca Score - CT			13.3	166.6	37.4	113.1

	8	CT	£2,097	ext dom.	64.7	78.4	64.7	78.4
	6	CA	£4,488	£4,488	0	0	0	0
60%	9	Ca Score - CT			8.9	250	24.9	169.6
	8	CT	£679	£1,213	43.1	117.6	43.1	117.6
	6	CA	£3,906	£3,906	0	0	0	0
80%	9	Ca Score - CT			4.4	333.3	12.5	226.1
	8	CT	£351	£574	21.6	156.8	21.6	156.8
	6	CA	£3,519	£3,519	0	0	0	0

1.1.7 Summary and Discussion

The analysis presented here represents a revision and expansion of the short term diagnostic model built for the Mowatt 2008 HTA (Mowatt, G., Cummins, E., Waugh, N. et al, 2008). Several adjustments were made to Mowatt et al's input assumptions, including a reduced diagnostic accuracy of 64-slice CT coronary angiography and an increased cost of invasive coronary angiography. In addition, two new arms which each include calcium scoring as a discrete step in the diagnostic pathway leading to 64-slice CT coronary angiography have been added and analysed. Finally, two one-way sensitivity analyses have been undertaken to test the sensitivity of results to assumptions made regarding 64-slice CT coronary angiography's specificity, and an alternative calcium score threshold for positive diagnosis.

Essentially this paper has presented a cost-consequence analysis, although an incremental analysis has been conducted with outcomes presented as the additional cost per accurate diagnosis. This is an enhancement on analyses previously presented to the GDG, in that other analyses involving key technologies do not undertake incremental analysis (Mowatt, G., Cummins, E., Waugh, N. et al, 2008) (Dewey, M. and Hamm, B., 2007) (Rumberger, J. A., Behrenbeck, T., Breen, J. F. et al, 1999) at all.

Results of the base case analysis presented here indicate that for lower risk groups (5% and 20%), the use of calcium scoring as a first line testing strategy is

likely to be cost-effective and should be followed by either 64-slice CT coronary angiography alone or with additional invasive coronary angiography as a confirmatory 3rd test. In higher risk populations (CAD prevalence greater than 40%), a strategy of sending all patients directly for invasive coronary angiography is likely to be cost-effective.

The model indicates that MPS with SPECT is excluded through dominance or extended dominance at every level of CAD prevalence. It also indicates that exercise ECG is only cost-effective as a first line investigation strategy at 5% CAD prevalence, but that even in this instance replacing exercise ECG with calcium scoring is likely to improve effectiveness at a reasonable level of additional cost.

All of the results analysed and presented here are based on assumptions about the diagnostic accuracy and costs of the five technologies included in the model. The validity of the outputs is clearly highly dependent on the appropriateness of the input assumptions.

The current model and results have several limitations worth mentioning. The model has the same structure as the short-term diagnostic model presented in Mowatt 2008 (Mowatt, G., Cummins, E., Waugh, N. et al, 2008) for the diagnosis of CAD, and no attempt has been made to extend the model to account for resource and health implications beyond the diagnosis timeframe. Thus, for example, any adverse health and resource implications of false negative diagnoses have not been accounted for in the current model. Similarly, the current model does not consider the prognostic value of the modelled technologies as these considerations were outside the scope of the guideline.

Although all of the short-term diagnostic costs and healthcare consequence outputs of the model are presented in this paper, the incremental economic evaluation focuses on the cost per correctly diagnosed patient. Although this is

more informative than previously published analyses presented to the GDG, it still has the disadvantage of not having a readily available NHS threshold for cost-effectiveness (e.g. £20,000 per QALY). However, evidence from the Mowatt 2004 HTA (Mowatt, G., Vale, L., Brazzelli, M. et al, 2004) indicated that for levels of modelled prevalence 30% and greater, the incremental cost per correct diagnosis values resulting from the short term model were similar to the incremental cost per QALY values estimated by the longer-term Markov model.

Finally, the GDG considered that the model did not adequately represent patients with an intermediate risk of disease for whom anatomical testing may not be sufficient to appropriately assess the functional significance of the CAD. In other words, it is possible that for some patients presenting with stable chest pain, doubt will remain as to whether the degree of stenosis observed on anatomical investigation is the cause of their chest pain. For this population, the GDG wanted to explore the cost-effectiveness of first line functional testing.

2 Cost-Effectiveness of First Line Functional Testing

2.1 Introduction

The economic model presented above has given support to use of anatomical imaging (64-slice CT coronary angiography preceded by calcium scoring in low risk CAD patients, and invasive coronary angiography in high risk patients) for patients presenting with stable chest pain respectively. The model indicated that functional testing, as represented by exercise ECG and MPS with SPECT, does not appear to cost-effective, (often dominated), for almost the full range of CAD prevalences modelled.

As discussed above, the GDG had reservations about the applicability of the model for patient with an intermediate risk of disease. Furthermore, they anticipated that this group of patients could constitute a relatively large group of patients in the context of the stable chest pain care pathway. The GDG believed

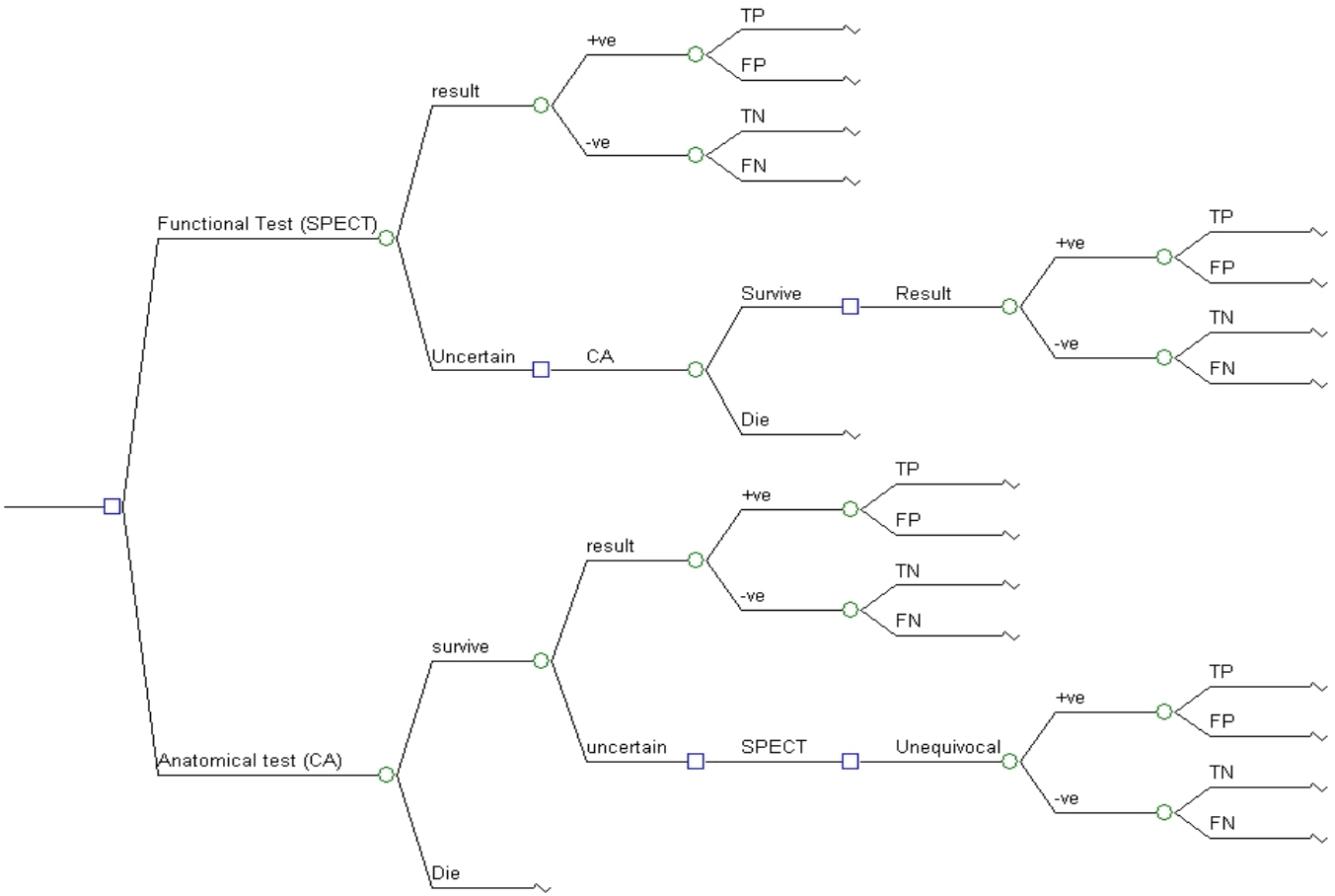
that there was likely to be a role for first line functional testing for this group of patients, and requested an alternative economic model appropriate for this patient group.

The model evaluates the cost-effectiveness of first line functional testing using MPS with SPECT, compared to first line anatomical testing, in patient populations presenting with stable chest pain, and a moderate pre-test likelihood of CAD (20% to 60%).

2.2 Model Structure and Input Assumptions

The model structure is illustrated in the decision tree presented in Figure 2.2.1.below.

Figure 2.2.1. First Line Functional Testing Model Structure



There are two alternative treatment arms in the model:

- First line functional testing using MPS with SPECT
- First line anatomical testing with invasive coronary angiography.

2.2.1 First Line Functional Testing

In line with the models presented in the Mowatt HTA for Angina (Mowatt, G., Vale, L., Brazzelli, M. et al, 2004), and CAD (Mowatt, G., Cummins, E., Waugh, N. et al, 2008), MPS with SPECT is used to represent first line functional testing. The first branch of the decision tree allows for the possibility of an equivocal (indeterminate) functional test result. The Mowatt 2004 (Mowatt, G., Vale, L., Brazzelli, M. et al, 2004) model used a figure of 9% to represent this proportion of uncertain results. Using results from their literature review, and including results from other reviews, Mowatt and colleagues used an uncertain proportion estimate of 6% for SPECT in their 2008 HTA model (Mowatt, G., Vale, L., Brazzelli, M. et al, 2004). The latter is used in the current base case model scenario. Patients with an equivocal first line functional test result, are assumed to go on to have a second line invasive coronary angiography, which is assumed to be 100% sensitive and specific, with no equivocal test results.

For a given prevalence (pre-test likelihood) of CAD in the modelled population, the model then calculates the expected number of true positive (TP), true negative (TN), false positive (FP), and false negative (FN) results based on the assumed test sensitivities and specificities. In the working base case it has been assumed that the sensitivity and specificity results for MPS with SPECT used in the Mowatt and colleagues 2008 (Mowatt, G., Cummins, E., Waugh, N. et al, 2008) model are appropriate (see table below for details of assumed parameter values).

2.2.2 First line Anatomical Testing

The structure of the first line anatomical testing arm is effectively a replica of the first line functional testing arm except that patients in this arm of the model have invasive coronary angiography as first line test (in a sensitivity analysis, invasive coronary angiography is replaced with 64-slice CT coronary angiography). The model allows for the possibility of a small proportion of patients having invasive coronary angiography to die from the procedure, (this risk is very small and has minimal impact on the model outputs). Patients with an equivocal invasive coronary angiography result for diagnosis of angina, are assumed to have a second line functional test (MPS with SPECT). Although the model structure allows for a proportion of second line functional tests producing an equivocal result, the base case assumes all second line test results are unequivocal. Again the model then calculates the outputs of the two by two true-false, positive-negative matrix.

2.2.3 Cost and Assumptions Summary

The cost of MPS with SPECT (£293) in the base case is taken from the Mowatt 2008 HTA(Mowatt, G., Cummins, E., Waugh, N. et al, 2008). Base case cost of invasive coronary angiography is assumed to be £850, based on the same estimates described previously. All base case input parameter values are presented in the table below.

Test characteristics	MPS	CA
Death Rate	0.000%	0.020%
Equivocal/Indeterminate	6.00%	Pt%
Sensitivity	86%	100%
Specificity	64%	100%
Cost	£293	£850

2.3 Analytical Methods

Our literature search did not identify the proportion of stable chest pain patients likely to have an equivocal/indeterminate invasive coronary angiography result for diagnosis of angina. As such, the model has been used to identify a threshold proportion (Pt) of equivocal invasive coronary angiography results. That is, the threshold at which decision makers are likely

to be indifferent between first line functional, and first line anatomical testing. In order to facilitate this, it is necessary to define a threshold willingness to pay (WTP). It is normal convention for NICE guidelines to use an incremental threshold willingness to pay of between £20,000 to £30,000 per QALY. In the absence of a QALY outcome from our diagnostic accuracy based cost-effectiveness model, we use anecdotal evidence from the, the analysis presented in the 2004 HTA for MPS SPECT,(Mowatt, G., Vale, L., Brazzelli, M. et al, 2004) which demonstrates incremental cost per proportion of patients correctly diagnosed values with very similar values to the modelled incremental cost per QALY, (see tables 38 and 39 in Mowatt 2004). That is, in the following analysis, we assumed a willingness to pay threshold of £20,000 per proportion of patients correctly diagnosed.

Having identified a threshold proportion of equivocal invasive coronary angiography results (Pt), if decision makers believe that the likely proportion of equivocal results (p) is higher than the identified threshold value (Pt) estimated by the model, then the model indicates that first line functional testing is cost-effective compared to first line anatomical testing. Conversely, if decision makers believe that the likely proportion of equivocal invasive coronary angiography results is lower than the identified threshold (Pt), the model indicates that first line anatomical testing is cost-effective compared to first line functional testing.

2.4 Results

2.4.1 Base Case

In the base case scenario the pre-test likelihood of CAD in the modelled patient population is assumed to be 50%. The model indicates that first line MPS with SPECT is the least cost of the two modelled options costing £344,000 per 1,000 patients and 76.5% of patients would get a correct diagnosis based on the MPS with SPECT test accuracy input assumptions presented in section 2.2.3. Assuming that coronary angiography is 100% accurate and unequivocal/determinate, the modelled cost of the first line coronary angiography treatment arm is £850,000. The incremental cost per

proportion of patients correctly diagnosed is therefore £21,549. Assuming a WTP threshold of £20,000, and given that we have presented an optimistic scenario for invasive coronary angiography (assumed that it is 100% accurate with no equivocal results), then our model indicates that it looks unlikely that use of first line coronary angiography for the modelled scenario is cost-effective compared with first line functional testing.

2.4.2 Sensitivity on Pre-test likelihood

In the following sensitivity analysis, the CAD prevalence (pre-test likelihood) in the modelled population is varied from 20% to 50%. Again assuming a threshold cost-effectiveness estimate of £20,000 per proportion of patients correctly diagnosed, the table below presents the estimated threshold of indifference values for the proportion of equivocal anatomical stenoses (Pt).

Pre-test Likelihood	20%	30%	40%	50%
Pt	9.5%	5.3%	0.6%	N/A

As the pre-test likelihood rises from 20% to 40%, the model indicates that the proportion of equivocal invasive coronary angiography results would have to be less than 9.5% (20% pre-test likelihood) and less than 0.6% (40% pre-test likelihood) for first line anatomical testing using invasive coronary angiography to have an ICER below £20,000. So, assuming a 40% population prevalence (pre-test likelihood) of 40%, invasive coronary angiography would have to be 100% sensitive and specific and have an equivocal result rate of less than 0.6%, (6 per 1,000), before it is likely to be considered cost-effective compared with first line functional testing using MPS with SPECT. It is not possible to find a positive Pt value in the 50% prevalence base case population discussed above, because it is not possible for invasive coronary angiography to achieve an ICER below £21,549.

2.4.3 Sensitivity replacing invasive coronary angiography with 64-slice CT coronary angiography

From the modelling results presented in section 1.1 above, first line 64-slice CT coronary angiography is the most cost-effective diagnostic testing strategy for low pre-test likelihood populations. A sensitivity analysis using the current model has been run, assuming a pre-test likelihood of 20%, and using the previously used test characteristic assumptions for 64-slice CT coronary angiography (presented in the following table).

Test characteristics	64CT
Death Rate	0.00125%
Indeterminacy	2%
Sensitivity	0.8
Specificity	0.89
Cost	£206

In this scenario, first line anatomical testing using 64-slice CT coronary angiography dominates first line functional testing. That is, 64-slice CT coronary angiography costs less than first line functional testing using MPS with SPECT, (£212,800 per thousand patients compared with £305,360 respectively) and produces a greater proportion of accurately diagnosed patients (86.9% c.f. 69.5%). For first line testing using 64-slice CT coronary angiography not to be considered cost-effective compared to first line functional testing in this scenario, (using a £20,000 per proportion of patients correctly diagnosed decision threshold), the model estimates that more than 74% of the 64-slice CT coronary angiography results would have to give an equivocal result.

2.4.4 Summary and Discussion

Previously published economic models (Mowatt, G., Vale, L., Brazzelli, M. et al, 2004) (Mowatt, G., Cummins, E., Waugh, N. et al, 2008) have been replicated, with modified assumptions for this guideline (section 1.1 of this Appendix). This was done to help inform recommendations for diagnosis of populations with either low or high pre-test likelihood of CAD and with stable chest pain. Because the guideline group had reservations about the applicability of the existing models for informing the diagnosis of angina in

stable chest pain patients with an intermediate pre-test likelihood, a new model was requested and developed and has been presented here. The model compares first line functional testing using MPS with SPECT with first line anatomical testing using invasive coronary angiography.

For a range of pre-test likelihoods of 30% to 50%, the model indicates that first line functional testing is the least cost of the two modelled testing strategies. Above 30% pre-test likelihood, invasive coronary angiography would have to provide 100% sensitivity and specificity and an equivocal result rate lower than 5.3% for it likely to be considered cost-effective compared to first line functional testing using a £20,000 WTP threshold. In a base case scenario using a pre-test likelihood of 50%, the model demonstrates that the incremental cost per proportion of patients correctly diagnosed from using first line invasive anatomical testing could never have an ICER below £21,500 compared to first line functional testing.

The model lends further to support to the use of 64-slice CT coronary angiography in low risk stable chest pain populations. For a pre-test likelihood of 20%, the model indicates that first line testing using 64-slice CT coronary angiography is more accurate, and costs less, than first line MPS with SPECT testing (dominant).

All models are simplifications of the real world, and our model and analysis has its limitations. Mainly because of the diagnostic focus of this guideline and time constraints, the de novo models developed for this guideline were restricted to assessing short term diagnostic outcomes, (discussed further below). The main drawback of having assessed the short term cost per proportion of patients correctly diagnosed is that there is no recognised WTP threshold for our effectiveness outcome variable. Based on the results of the model presented in the MPS HTA by Mowatt et al 2004, our model assumed that the short term diagnostic ICER is a close proxy to the cost per QALY ICER. This was demonstrated for modelled CAD prevalence at and above 30%, which is consistent with the range that we have modelled above. Admittedly this assumption is based on the results from a single study, and is therefore somewhat anecdotal, and our model, although similar, is not

structurally identical to the Mowatt model. Having said this, our results are not inconsistent with the results of the Mowatt 2004 QALY model, which indicated a role for functional testing in populations with a moderate pre-test likelihood of CAD. Furthermore, our model demonstrated dominance when 64TC angiography was compared to functional testing in a lower pre-test likelihood population, and as such there was no need to consider the size of the ICER.

The model has been subjected only to limited deterministic sensitivity analysis. Having said this, we believe that the model results presented are likely to be relatively insensitive to further analyses. We have used best case possible estimates for the diagnostic performance (sensitivity, specificity, equivocal result rate) of invasive coronary angiography, and as such, the model assumptions are weighted in favour of CA and against MPS). Also, we may have used a relatively conservative estimate for the cost of invasive CA. Finance and coding experts at an NHS hospital have indicated that based on OPCS codes, invasive coronary angiography for adults (>19 years) is likely to fall into HRG EA36Z, which has current estimated costs ranging from £792 to £2,490 depending on whether the procedure is done as a day case, or as an elective inpatient stay (personal communication). These figures are estimates of the mean cost. The inter-quartile ranges presented in the NHS reference costs database show an even wider range of costs, particularly at the upper end. Also, HRG EA36Z covers procedures other than invasive coronary angiography, and so it is not possible to get an accurate cost estimate for invasive coronary angiography from NHS reference costs(Department of Health, 2008). The evidence appears to indicate that our base case estimate of £850 may be at the lower end of the likely cost estimate distribution. Given this and the best case performance assumptions for CA, our ICER estimates may be very much on the low side thereby lending further support to our conclusions regarding the relative cost-effectiveness of functional imaging using MPS SPECT compared with invasive CA in patients with a moderate pre-test CAD likelihood (30% to 60%).

One sensitivity analysis that we did undertake compared 64-slice CT angiography with functional imaging for a pre-test CAD likelihood of 20%. With

relative conservative estimates regarding the performance of 64CT angiography, our model demonstrated dominance, and indicated that 64CT diagnostic performance would have to deteriorate to unrealistically low levels in terms of equivocal result rate to give us considerable confidence in this result.

We have only modelled MPS with SPECT to represent functional testing. The CECaT trial (Sharples, L., Hughes, V., Crean, A. et al, 2007) has indicated that in terms of both resource use and QALYs, MPS with SPECT, stress echocardiography and stress MR perfusion imaging were not significantly different from each other, in a population consistent with the patients modelled above (CAD prevalence greater than 20%). Also, other economic evaluations including these technologies demonstrated similar result, for example, dominance by CT angiography (Rumberger, J. A., Behrenbeck, T., Breen, J. F. et al, 1999). We may therefore have reached similar conclusions to those for MPS SPECT had we modelled stress echocardiography or stress MR perfusion imaging to represent functional testing.

Economic evaluation undertaken for this guideline has proved challenging from a number of respects. Not least, the fact that the technologies used to diagnose chest pain of suspected cardiac origin are numerous and improving rapidly. Ideally, economic evaluation involving NHS resources should take account of both the short-term diagnostic, and also the longer term prognostic implications on resource use and health outcomes. The scope of this guideline is focussed on diagnosis, and as such, the economic evaluation has also focused on the shorter term diagnostic costs and outcomes. Having said this, there is some evidence from previous economic modelling work in this area, longer term more speculative models may be subject to diminishing returns in terms of additional information for decision makers. In the 2008 HTA on 64-slice CT coronary angiography by Mowatt and colleagues (Mowatt, G., Cummins, E., Waugh, N. et al, 2008), their longer-term speculative Markov model, (which required assumptions to be made about the future risk of CAD events and how they would be treated), resulted in QALY differences which differed by less than one quarter of one percent for the testing strategies

assessed. Our additional analysis and revision of their model, also indicates that most treatment strategies (usually those including MPS and stress ECG) can be rejected through dominance, thereby negating the need to consider the ICER values for most strategies modelled. Also, there is a high degree of correlation of dominance between the short term and the longer term models. Comparison of the short and longer-term modelling output of the model presented in the 2004 HTA on MPS with SPECT (Mowatt, G., Vale, L., Brazzelli, M. et al, 2004) indicated that, for all but the lowest CAD prevalence groups, the estimated incremental cost per proportion of patients correctly diagnosed has a similar value to the longer-term incremental cost per QALY. Longer-term economic model evaluations, which have been published since the short term de novo models for this guideline have been developed, lend some support to the results of our modelling (e.g. that use of 64-slice CT coronary angiography is cost-effective or cost-saving in lower risk patients presenting with acute chest pain (Khare, R. K., Courtney, D. M., Powell, E. S. et al, 2008) (Min, J. K., Kang, N., Shaw, L. J. et al, 2008). Because of time constraints and the scoping boundary of this Guideline, further investigation of these issues, and research into the validity of our current assumptions, was not attempted, but could be considered in future work in this area.

Reference List

(1) Department of Health. NHS Reference Costs 2006-07. Website: www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_082571. 2008.

(2) Dewey M, Hamm B. Cost effectiveness of coronary angiography and calcium scoring using CT and stress MRI for diagnosis of coronary artery disease. Eur Radiol. 2007; 17 (5):1301-1309.

(3) Khare RK, Courtney DM, Powell ES, Venkatesh AK et al. Sixty-four-slice computed tomography of the coronary arteries: cost-effectiveness analysis of patients presenting to the emergency department with low-risk chest pain. Acad Emerg Med. 2008; 15 (7):623-632.

(4) Kitamura A, Kobayashi T, Ueda K, Okada T et al. Evaluation of coronary artery calcification by multi-detector row computed tomography for the detection of coronary artery stenosis in Japanese patients. J Epidemiol. 2005; 15 (5):187-193.

(5) Min JK, Kang N, Shaw LJ, Devereux RB et al. Costs and clinical outcomes after coronary multidetector CT angiography in patients without known coronary artery disease: comparison to myocardial perfusion SPECT. Radiology. 2008; 249 (1):62-70.

(6) Mowatt G, Cummins E, Waugh N, Walker S et al. Systematic review of the clinical effectiveness and cost-effectiveness of 64-slice or higher computed tomography angiography as an alternative to invasive coronary angiography in the investigation of coronary artery disease. Health Technol Assess. 2008; 12 (17):1-143.

(7) Mowatt G, Vale L, Brazzelli M, Hernandez R et al. Systematic review of the effectiveness and cost-effectiveness, and economic evaluation, of myocardial perfusion scintigraphy for the diagnosis and management of angina and myocardial infarction. Health Technol Assess. 2004; 8 (30):iii-89.

(8) Rumberger JA, Behrenbeck T, Breen JF, Sheedy PF. Coronary calcification by electron beam computed tomography and obstructive coronary artery disease: a model for costs and effectiveness of diagnosis as compared with conventional cardiac testing methods. J Am Coll Cardiol. 1999; 33 (2):453-462.

(9) Sculpher M, Smith D, Clayton T, Henderson R et al. Coronary angioplasty versus medical therapy for angina. Health service costs

based on the second Randomized Intervention Treatment of Angina (RITA-2) trial. Eur Heart J. 2002; 23 (16):1291-1300.

(10) Sharples L, Hughes V, Crean A, Dyer M et al. Cost-effectiveness of functional cardiac testing in the diagnosis and management of coronary artery disease: a randomised controlled trial. The CECaT trial. Health Technol Assess. 2007; 11 (49):1-115.

(11) Underwood SR, Godman B, Salyani S, Ogle JR et al. Economics of myocardial perfusion imaging in Europe--the EMPIRE Study. Eur Heart J. 1999; 20 (2):157-166.